High- Versus Standard-Dose Megestrol Acetate in Women With Advanced Breast Cancer: A Phase III Trial of the Piedmont Oncology Association

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One hundred seventy-two patients with advanced breast cancer were randomized to receive oral standard-dose megestrol acetate (MA), 160 mg/d or high-dose MA, 800 mg/d. All but two patients had one prior trial of tamoxifen therapy for either metastatic disease (74%) or as adjuvant treatment (26%). Pretreatment characteristics were similar for both arms. High-dose MA resulted in a superior complete plus partial response rate (27% *v* 10%, $P = .005$), time to treatment failure (median, 8.0 *v* 3.2 months, $P = .019$), and survival (median, 22.4 *v* 16.5 months, $P = .04$) when compared with standard-dose therapy. These differences remained significant after adjustment for other covariates. Thirty-four patients were given high-dose MA after failure of standard-dose MA treatment, and none responded. Weight gain was the most distressing side effect, with 13% of standard-dose and 43% of high-dose patients gaining more than 20 lbs. Four major cardiovascular events occurred in patients receiving high-dose treatment and one in patients given standard doses. Other toxicity was modest. High-dose MA may represent a significant improvement in secondary endocrine therapy for advanced breast cancer patients refractory to initial endocrine treatment, but its use on a regular basis should be reserved until these results are confirmed by other clinical trials.

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ENDOCRINE therapy represents a major modality for the treatment of metastatic breast cancer. Historically, ablative procedures, including oophorectomy, adrenalectomy, and hypophysectomy, provided objective remissions in 20% to 50% of patients. Later, estrogens, androgens, progestins, and corticosteroids were added with similar results.[1,2] Currently, tamoxifen, an antiestrogen represents the most commonly used first-line endocrine therapy because of its ease of administration, minimal toxicity, and similar efficacy to older agents.[3]

Unfortunately, almost all patients treated with tamoxifen will ultimately progress and require salvage treatment with either further endocrine therapy or chemotherapy. Both medroxyprogesterone acetate (MPA) and megestrol acetate (MA) have been extensively used as salvage treatments.[4,5] In randomized trials, both MPA and MA have had similar response rates to tamoxifen when used as first-line therapy. MA has demonstrated response rates ranging from 14% to 56% when used as primary treatment and from 6% to 23% when used as secondary therapy.[5] These salvage response rates with MA are similar to those achieved with other agents including aromatase inhibitors, androgens, and estrogens.

Two phase III trials of high-dose MPA have demonstrated higher response rates than those using standard doses.[6,7] Cavalli et al[6] compared 1,000 mg/d intramuscularly (IM) with 500 mg IM twice weekly. In 184 assessable patients, there was a 33% response rate to high-dose therapy and a 15% response to the low-dose therapy ($P < .01$). However, time to progression and survival did not differ significantly between the two arms. Pannuti et al[7] compared 1,500 mg IM daily with 500 mg IM daily. The proportion of patients with complete or partial response or

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stable disease was significantly greater for the high-dose regimen. Other investigators,[8,9] however, have not shown superiority of high-dose MPA compared with lower dosages. The development of MA, a potent and well-absorbed oral progestin, has led to renewed interest in clinical trials using oral progestins.[10] Serum levels of progestin activity are substantially higher for MA than for equivalent doses of MPA.[11,12] MA has also been extremely well tolerated, with the major toxicity being weight gain. The suggestion that high-dose MPA might be associated with higher response rates coupled with the superior oral availability of MA compared with MPA led to the development of a phase III trial by the Piedmont Oncology Association (POA) comparing high-dose with standard-dose MA therapy. A preliminary report of this trial has been presented.[13]

PATIENTS AND METHODS

The study was designed as a phase III, randomized five-stage group sequential trial and was based on the assumption that the response rate to standard-dose MA as salvage therapy would be 20%. A maximum of 150 evaluable patients (75 per arm) was necessary to allow detection of an increase in the response rate to 40% in the high-dose arm with 80% power at the 5% one-sided level of significance. Patients were stratified into three groups prior to randomization: group 1 had received prior hormonal therapy and responded, group 2 had received prior hormonal therapy without response, and group 3 had received prior adjuvant hormonal therapy and relapsed. Patients relapsing after adjuvant therapy were eligible for the trial at time of relapse.

Eligibility required that patients be at least 18 years of age, have histologically confirmed breast cancer with progressive metastatic disease, have one previous trial of hormonal therapy other than a progestin, have measurable or evaluable disease, and have less than three prior chemotherapy regimens. Either the estrogen or progesterone receptor from the primary tumor or a metastatic site had to be positive or both had to be unknown with the exception that patients who had receptor-negative tumors but had responded to prior hormonal therapy were eligible. Those receiving concurrent progestin therapy for nonmalignant disease or those with brain metastasis as the only evidence of tumor recurrence were excluded. Patients were allowed on trial if they had any prior malignancy regardless of type without evidence of recurrence for longer than 5 years, skin malignancy excluding melanoma, or cancer of the cervix treated greater than 3 years prior to protocol entry without evidence of recurrence. Prior concomitant radiation therapy was permissible provided there was evaluable or measurable disease outside the treatment field. Informed consent meeting Cancer Center, institutional, and federal guidelines was required.

Patients were randomized to either MA, a 160 mg tablet (Megace; Bristol-Myers, Evansville, IN), once daily or high-dose MA, five 160 mg tablets (800 mg) daily. For patients receiving high-dose therapy, two tablets of the drug were administered in the morning, and one tablet at lunch, dinner, and bedtime. The bioequivalence of the 160 mg investigational tablet has been shown to be 97% of the 40 mg four times a day dosage.[14] Patients were maintained on therapy unless removed for toxicity or disease progression. Dose modifications were made only for excessive weight gain (generally an increase in 10% of prestudy body weight) on the high-dose arm; such patients were continued on therapy at 160 mg daily. Patients randomized to the standard treatment arm were allowed to cross over to the high-dose arm following progression. Patients were removed from study for grade 3 or 4 granulocyte or platelet suppression, nausea and vomiting not easily controlled with antiemetics, persistent vaginal bleeding, uncontrolled hypertension, or hypercalcemia for longer than 3 weeks.

Patients were seen every 4 weeks for follow-up. Palpable lesions and chest x-rays showing metastatic disease were reevaluated every 4 weeks to assess response. For patients with disease on bone scan, bone survey, liver scan, or other imaging modality, studies were required to be repeated every 12 weeks for two separate time periods and then every 6 months. Patients who had stable disease in one disease site were not required to have repeat follow-up studies unless disease progression was clinically suggested. Strict International Union Against Cancer criteria were used to document response.[15] In order to qualify for complete or partial response, patients must have had repeat evaluation of all previously documented metastatic sites, with changes meeting complete and partial regression criteria.

Differences in pretreatment characteristics and response outcomes between treatment groups were assessed using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. Logistic regression was used to determine which variables were significantly associated with response and to assess the effect of treatment regimen adjusted for other covariates. Log-rank tests were used to compare unadjusted survival and time to treatment failure distributions between regimens. Cox's proportional hazards regression model was used to determine which variables were significantly associated with survival or time to treatment failure and to assess the effect of treatment regimen adjusted for other covariables. Estimates of median follow-up time were calculated using the Korn method.[16] Analysis of weight gain changes over time was done using methods described by Espeland[17] and Espeland et al.[18]

RESULTS

Between September 1985 and October 1988, 172 patients were accrued to this study. Of these patients, two were ineligible: one had estrogen and progesterone receptor (ER/PR)-negative disease without prior response to endocrine therapy and a second did not have histologically confirmed breast cancer, leaving 170 qualified patients available for analysis. The final update of these data was completed in November 1989. Follow-up ranged from 0.1 to 47+ months with

an estimated median of 21.3 months.[16] Except for two patients who had received prior diethylstilbestrol, all patients had received tamoxifen.

Descriptive statistics for the pretreatment characteristics are shown in Table 1. Most of these characteristics are fairly evenly balanced between the two arms. However, more patients who were black were randomized to the standard-dose regimen ($P = .072$), and all six patients with poor performance status (three) received standard-dose MA initially ($P = .029$). Disease site data are shown in Table 2. For purposes of coding dominant site, breast, soft tissue, and lymph node metastasis were considered soft tissue; bone and bone marrow metastasis (with or without soft tissue involvement) were considered bone; and other sites (with or without soft tissue or bone involvement) were considered viscera. There were no significant differences in disease sites, number of sites, or dominant site between arms.

Table 1. Pretreatment Characteristics

Characteristic	Standard-Dose		High-Dose	
	No.	%	No.	%
Total patients	86	100	84	100
Median age, years	63		62	
Range	37-84		38-82	
Age ≥ 50	75	87	68	81
Race				
White	70	81	77	92
Black	16	19	7	8
Performance status				
0	24	28	26	31
1	47	55	46	55
2	9	10	12	14
3	6	7	0	0
DFI				
0	16	19	10	12
0-2 years	22	26	27	32
> 2 years	48	56	47	56
ER/PR status				
+/+	31	36	39	46
+/−	24	29	14	17
+/?	11	13	9	11
−/+	6	7	5	6
−/−	0	0	1	1
Unknown	14	16	16	19
Hormonal strata				
Prior Rx − response	34	40	31	37
Prior Rx − no response	30	35	30	36
Prior hormone − adjuvant	22	26	23	27
Prior treatment				
Radiation	43	50	42	50
Chemotherapy	44	51	48	57

Abbreviations: Rx, treatment; DFI, disease-free interval.

Table 2. Disease Sites

	Standard-Dose		High-Dose	
	No.	%	No.	%
Total	86	100	84	100
Site				
Breast (contralateral)	10	12	9	11
Soft tissue*	32	37	20	24
Lymph nodes	9	10	15	18
Bone	65	76	60	71
Bone marrow	5	6	1	1
Liver	13	15	10	12
Lung parenchyma	20	23	12	14
Pleural effusion	10	12	7	8
Brain	1	1	1	1
Other	3	3	3	4
No. sites/patient				
1	35	41	43	51
2	26	30	30	36
3	19	22	9	11
4	6	7	2	2
Dominant site				
Soft tissue	7	8	11	13
Bone	40	47	47	56
Viscera	39	45	26	31

*Includes skin, subcutaneous, and muscle involvement.

Response data are presented in Table 3. Twenty-two of 80 evaluable patients on high-dose MA (28%) responded compared with eight of 81 evaluable standard-dose patients (10%) ($P = .005$). There were two complete responders to high-dose MA and one to the standard-dose regimen. Logistic regression was used to assess treatment effect after adjustment for other covariables. Age, race, performance status, disease-free interval (DFI), ER/PR status, physician group (POA *v* medical school), prior therapy, dominant site, and number of sites were included in the analysis. ER and PR were initially excluded due to the substantial number of missing values. Treatment regimen, adjusted for these variables, was significantly associated with re-

Table 3. Response Versus Initial Treatment

	Standard-Dose		High-Dose	
	No.	%	No.	%
No. evaluable	81	100	80	100
Response				
Complete response	1	1	2	2
Partial response	7	9	20	25
Stable disease	31	38	37	46
Progression	42	52	21	26
95% CI for response		4-19		18-39

NOTE. 95% CI for response overall, 13%-26%.
Abbreviation: CI, confidence interval.

sponse ($P = .0102$). A backward-stepping algorithm was used to remove nonsignificant covariates from the model. DFI ($P = .0008$) was the only covariate significantly associated with response. Performance status was of borderline significance ($P = .0943$). Treatment regimen, adjusted for DFI, was significantly associated with response ($P = .0011$). The odds of responding to treatment were approximately 4.2 times greater for high-dose patients. ER and PR were then included, thus reducing the number of observations available in the analysis. DFI ($P = .004$) and ER were significant ($P = .0180$); treatment regimen, adjusted for these variables, was still significant ($P = .0155$).

Only 16 of the 170 qualified patients remain on their initial treatment regimen, six patients on standard dose and 10 on high dose. Of those removed from the standard-dose regimen, 74% had disease progression, 15% died while on treatment, 2% were removed for toxicity, and 1% refused further treatment. Of those removed from the high-dose regimen, 71% had disease progression, 5% were removed for toxicity, 4% were removed per decision of the treating physician, 4% died while on study, 1% refused further treatment, and 2% were removed for other reasons. Three of the deaths on the low-dose regimen and one of the three deaths on the high-dose regimen were due to causes other than cancer.

Time to treatment failure was calculated as the time from initial therapy to failure on the initial arm or to the last date of contact. Patients were considered treatment failures if removed from the study for any reason above. Time to failure estimates are shown in Fig 1. The overall estimated median time to failure was 5.1 months; the estimated median was 3.2 months for the standard-dose regimen and 8.0 months for the high-dose regimen ($P = .0185$). Cox's proportional hazards regression model was used to determine which covariates were significantly associated with time to treatment failure and to assess treatment effect after adjustment for other variables. Treatment regimen, adjusted for all the other covariates except receptor status, was significantly associated with time to failure ($P = .0088$). The same backward-stepping strategy described previously was used for this analysis. Dominant site of disease ($P = .0001$), prior chemotherapy ($P = .0005$), and strata ($P = .0434$) were all significantly associated with time to failure. Patients with bone-dominant disease have the longest times to treatment failure. Treatment regimen, adjusted for these variables, was also significantly associated with time to failure ($P = .0078$). Standard-dose patients are at approximately 1.56 times the risk of failure per unit time as compared to the high-dose patients. ER and PR were then included in the analysis, but neither was significantly associated with time to failure. Time to failure estimates are

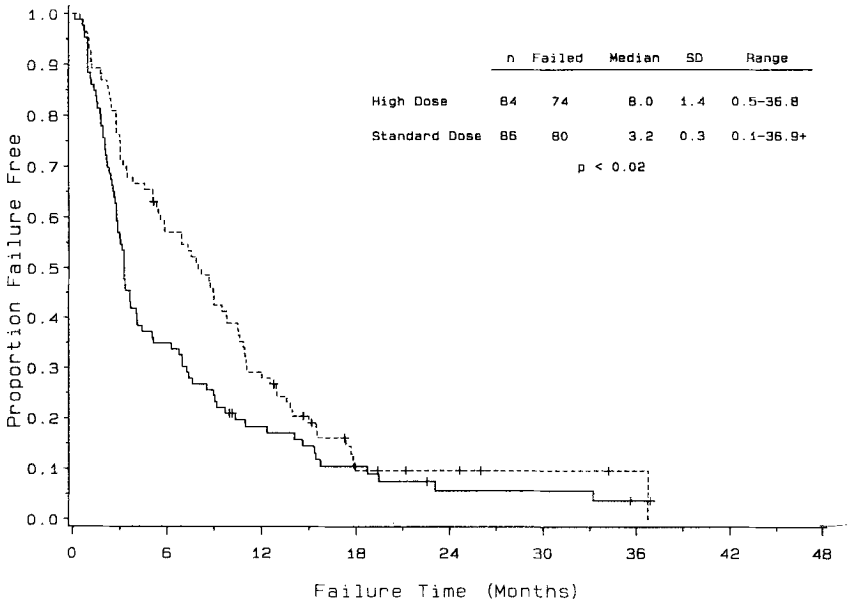

Fig 1. Time to treatment failure v time. (---) high dose; (—) standard dose.

Table 4. Time To Treatment Failure in Months

	Standard-Dose				High-Dose			
	n	Fail	Median	SD	n	Fail	Median	SD
Total	86	80	3.2	0.3	84	74	8.0	1.4
Site								
Skin	7	7	3.6	1.0	11	11	5.1	1.6
Bone	40	36	4.0	1.4	47	39	9.5	1.1
Visceral	39	37	2.7	0.4	26	24	3.0	1.9
Strata								
Prior Rx, response	34	31	4.1	1.4	31	25	11.0	2.5
Prior Rx, no response	30	28	3.2	0.4	30	28	6.9	2.3
Prior Rx, adjuvant	22	21	2.7	0.4	23	21	7.5	3.2
Chemotherapy								
No	42	37	4.4	1.7	36	31	8.9	2.1
Yes	44	43	2.8	0.2	48	43	7.3	1.9

shown in Table 4 for the significant covariates noted above.

Thus far, 89 of the 170 qualified patients have died. Survival data are plotted in Fig 2. The overall estimated median survival time was 18.5 months; the estimated median was 16.5 months for the standard-dose patients and 22.4 months for the high-dose patients ($P = .0388$). Cox's proportional hazards regression model was used to determine which covariates were significantly associated with survival and to assess the effect of treatment regimen after adjustment for covariates. The same variables used in response assessment were included in this analysis. Treatment regimen, adjusted for all these covariates except receptor status, was of borderline significance ($P = .0903$). A backward-stepping algorithm was used to remove nonsignificant variables from the model. Prior chemotherapy ($P = .0061$), dominant site of disease ($P = .0381$), DFI ($P = .0174$), and physician location ($P = .0290$) were the significant covariates. No prior chemotherapy, soft tissue disease, a DFI of greater than 2 years, and being treated in the community were the favorable characteristics. Treatment regimen, adjusted for these covariates, was significantly associated with survival ($P = .0190$). Standard-dose patients were at approximately 1.68 times the risk of death per unit time compared with high-dose patients. ER and PR were then included in the analysis, but neither was significantly associated with survival. Survival esti-

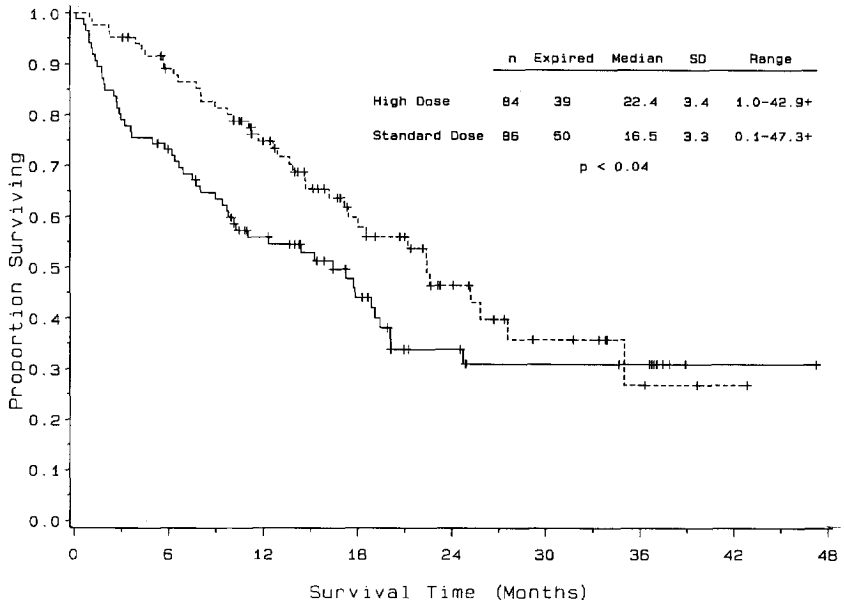

Fig 2. Survival *v* time. (---) high dose; (—) standard dose.

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