Dose-Response Trial of Megestrol Acetate in Advanced Breast Cancer: Cancer and Leukemia Group B Phase III Study 8741

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Purpose: To investigate whether dose escalation of megestrol acetate (MA) improves response rate and survival in comparison with standard doses of MA.

Patients and Methods: Three hundred sixty-eight patients with metastatic breast cancer, positive and/or unknown estrogen and progesterone receptors, zero or one prior trial of hormonal therapy, and no prior chemotherapy for metastatic disease were prospectively randomized into three groups. The groups of patients received either MA 160 mg/d (one tablet per day), MA 800 mg/d (five tablets per day), or MA 1,600 mg/d (10 tablets per day).

Results: Patient characteristics were well balanced in the three treatment groups. Three hundred sixty-six patients received treatment and were included in the analyses. The response rates were 23%, 27%, and 27% for the 160-mg, 800-mg, and 1,600-mg arms, respectively. Response duration correlated inversely with dose.

Median durations of response were 17 months, 14 months, and 8 months for the 160-mg, 800-mg, and 1,600-mg arms, respectively. No significant differences in the treatment arms were noted for time to disease progression or for survival; survival medians were 28 months (low dose), 24 months (mid dose) and 29 months (high dose). The most frequent and troublesome toxicity, weight gain, was dose-related, with approximately 20% of patients on the two higher-dose arms reporting weight gain of more than 20% of their prestudy weight, compared with only 2% in the 160-mg dose arm.

Conclusion: With a median follow-up of 8 years, these results demonstrate no advantage for dose escalation of MA in the treatment of metastatic breast cancer.

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MEGESTROL ACETATE (MA), a semisynthetic, oral progestin with excellent gastrointestinal absorption, has demonstrated efficacy comparable to that of tamoxifen as first-line treatment in women with advanced breast cancer.[1] At the standard dose of 160 mg daily, side effects from MA are minimal and include nausea, vaginal bleeding and discharge, weight gain, and fluid retention. In a series of 908 patients treated at this dose, the only serious toxicities possibly attributable to MA were three cases of congestive heart failure, one case of pulmonary embolism, and one case of acute left-ventricular failure.[2]

Efforts to improve the activity of MA focused on dose escalation, an approach that has been widely pursued for cytotoxic agents but less so for hormonal therapies. Potential mechanisms that could explain improved antitumor effects from high-dose progestins include an enhancement of the direct cytotoxic effect of the hormone via the progestin receptor,[3] additional direct cytotoxic effects on other related and important corticosteroid receptors,[4] and an increase in the indirect effects of progestins by further suppression of the hypothalamo-pituitary-adrenal axis.[5] Two phase III trials compared high versus standard doses of another progestin, medroxyprogesterone acetate, administered by intramuscular injection, and demonstrated improved response rates.[6,7] These encouraging results provided the impetus to initiate further trials to explore the dose-response effect of MA. However, not all investigators found higher doses to be more effective.[8,9]

The superior oral availability of MA compared with medroxyprogesterone acetate led the Piedmont Oncology Association (POA) to perform a phase III trial in patients with metastatic breast cancer comparing high-dose (800 mg/d) with standard-dose (160 mg/d) MA. All but two of the 172 patients entered had one prior trial of tamoxifen therapy for either metastatic (74%) or adjuvant (26%) treatment. 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.[10]

A phase I/II trial demonstrated that the dose of MA could be further escalated to 1,600 mg daily.[11,12] Although dose-limiting toxicity was not reached, substantial weight gain (median, 5.0 kg; range, 5.6 to 44 kg) occurred in 71% of patients at the 1,600-mg dose level, making further escalation difficult. Responses occurred at all dose levels in this trial, but the most promising results occurred in a subset of 27 patients who had progressed after treatment with standard doses of MA (160 mg/d). A 15% response rate (one complete response, three partial responses) was noted in this subset, and 10 patients (37%) had stable disease lasting a median of 5.4 months. Two of the objective responses occurred in women whose tumors had not previously responded to the standard MA dose.

These provocative results provided the rationale for the Cancer and Leukemia Group B (CALGB) to develop a randomized, three-arm, phase III trial design in which women with metastatic breast cancer received either standard-dose MA (160 mg/d), five times the standard dose (800 mg/d), or 10 times the standard dose (1,600 mg/d). A preliminary report of this trial has been presented.[13]

PATIENTS AND METHODS

Patient Selection

Women at least 18 years of age and with histologically documented breast carcinoma and progressive metastatic disease were eligible. Other requirements included a performance status of 0 to 3, positive and/or unknown estrogen and progesterone receptors, and no prior or concomitant malignancy other than curatively treated in situ cancer of the cervix or basal cell carcinoma of the skin. Patients with metastatic disease that was either bidimensionally measurable or assessable were entered, but they were assessed separately. Only one prior hormonal therapy (drug or surgical manipulation) for adjuvant or metastatic treatment was permitted, excepting progestins, which were not allowed. Patients who responded to their initial hormonal therapy were required to wait 6 weeks off all therapy before entering the study to avoid confusion with a withdrawal response. This did not apply to surgical manipulations. Prior adjuvant chemotherapy was acceptable if the disease-free period off treatment was more than 1 year, but chemotherapy for metastatic disease was not permitted.

Brain, leptomeningeal, lymphangitic, lung, and extensive liver and bone marrow metastases were all causes for exclusion. Evidence of normal kidney, liver, and bone marrow function was required, and patients with serious medical problems (especially congestive heart failure, uncontrolled hypertension, or diabetes mellitus) and those with a history of thrombophlebitis or stroke were excluded. All participants had to sign an informed consent that had been approved by institutional review boards.

Treatment Evaluation

Before beginning treatment with MA, all patients had a chest x-ray, electrocardiogram, bone scan, and a liver/spleen scan or abdominal computed tomogram. Additional studies were performed as necessary to measure indicator lesions. Patients were initially evaluated for response and toxicity every 4 weeks, but this was changed to every 8 weeks for responding patients who were on treatment for long periods of time.

Treatment and Dose Modification

Patients were stratified according to prior hormone therapy (yes v no), prior adjuvant therapy (yes v no), and receptor status (estrogen- and/or progesterone-positive v both unknown). They were then randomized within each stratification subgroup to one of the following three treatment arms: (1) MA at 160 mg/d, one tablet per day; (2) MA at 800 mg/d, five tablets per day; and (3) MA at 1,600 mg/d, 10 tablets per day. To facilitate oral administration, Bristol-Myers Squibb Co (Princeton, NJ) provided specially prepared 160-mg tablets for this trial. A prior study in normal volunteers compared the pharmacokinetic profile of the 40-mg four-times-a-day dosage with the 160-mg investigational tablet. It demonstrated that the peak plasma concentrations, the extent of absorption (area under the curve), and the half-life (t 1/2) showed no significant differences. The bioequivalence of the 160-mg investigational tablet was 97% of the 40-mg four-times-a-day dosage.[14] The recommended administration schedule was as follows: arm 1, one tablet at 8 AM; arm 2, one tablet at 8 AM, 12 PM, and 6 PM, and two tablets at 10 PM; and arm 3, two tablets at 8 AM and 12 PM and three tablets at 6 PM and 10 PM. No dose modifications were allowed for toxicity. Uncontrolled arterial hypertension, congestive heart failure, and thrombophlebitis were all causes for discontinuation of MA. Patients with weight gain and minor vaginal bleeding were encouraged to continue their treatment. If unacceptable side effects occurred in a responding patient, the patient was taken off the study drug and could then be treated with additional hormonal agents at the physician's discretion. After disease progression, patients were to be removed from MA and treated at the physician's discretion. For patients with rapidly progressive or life-threatening disease, chemotherapy was usually initiated, whereas further hormonal manipulations were considered for those with slower progression.

Study Design

The objective of this trial was to compare the response rates of the three treatment arms. The response rates were hypothesized to fall between 25% and 55%. A sample size of 100 patients per arm would yield at least an 80% power to detect a 17% additive difference, such as 30% versus 47%, between any two arms. Thus, with 123 patients randomized to the 160-mg arm, 124 to the 800-mg arm, and 119 to the 1,600-mg arm, there is better than 80% probability of detecting a 17% difference in response between any two arms.

Variables of Interest

We examined several demographic, pretreatment clinical, and treatment-related variables. These included: patient age, menopausal status, receptor status, performance status, measurability of disease, sites of involvement, number of involved sites, prior treatment, and time from initial diagnosis of breast cancer to first recurrence.

End Points

The study end points were response rate, response duration, time to disease progression, and overall survival. Definitions of response were assessed according to standard response criteria for patients with bidimensionally measurable disease.[15] Briefly, a complete response was defined as the complete disappearance of all signs and symptoms of disease, including reossification of osteolytic lesions, for at least 30 days. A partial response was defined as a decrease of at least 50% in the

product of the cross-perpendicular dimensions of all measurable indicator lesions, and no worsening of any existing lesion or the appearance of any new lesions, for at least 30 days. Stable was defined as less than a 50% reduction or less than a 25% increase in the product of the cross-perpendicular dimensions of all measurable lesions, with no new lesions for at least 60 days. For patients with assessable disease, symptomatic benefit but continued presence of lesions without the appearance of new lesions for at least 60 days qualified as stable disease. Progression was defined as an increase of at least 25% in the product of the cross-perpendicular dimensions of any measured lesion over the size present at entry, or for responders, the size at the time of maximum regression or the appearance of any new lesion. Those with only assessable disease were excluded from the assessment of partial responses.

Duration of MA response was measured from the date of complete or partial response, whichever occurred first, on MA until disease progression. Responders who were alive and disease-free were censored at their last follow-up visit. Time to disease progression was the date of study entry until the date of first disease progression or the date of last follow-up for patients who were alive and disease-free. Overall survival was the date of study entry until death due to any cause, or until date of last follow-up for survivors.

Statistical Methods

Survival curves were estimated by the Kaplan-Meier product limit method, whereas the log-rank test was used to compare two or more survival distributions. We used the Cox proportional hazards model initially to screen for individual variables potentially related to survival and time to disease progression. Subsequently, this method was used to identify sets of prognostic variables while controlling for the effect of other variables in the model.[16]

Comparisons between categorical variables were performed by the χ^2 test. The Mantel-Haenszel χ^2 test measures whether tumor response increases with increased MA dose (treatment arm). All P values are two-sided. We define statistical significance as $P \le .05$. We included data available as of February 1997. The median follow-up was 8.2 years.

Comparison with POA Trial

The POA kindly provided us with data from their previously published study.[10] We included in analysis only variables that both our study and the POA study measured. We defined variables identically in the two studies, both pretreatment characteristics and end point measures.

RESULTS

Patient Characteristics

A total of 368 patients were enrolled from 23 CALGB main member institutions and their affiliates between June 1, 1987, and March 22, 1991. Of these, 124 patients were randomly assigned with equal probability to the 160-mg arm, 124 were assigned to the 800-mg arm, and 120 were assigned to the 1,600-mg arm. Two patients, one on the 160-mg arm and the other on the 1,600-mg arm, never received treatment. Twenty-eight patients did not meet the eligibility criteria. For the 160-mg arm (n = 7), reasons for ineligibility included the following: two prior hormone regimens (three patients), laboratory values out of range (one patient), less than 1 year from end of adjuvant treatment

(one patient), visceral crisis (one patient), and prior chemotherapy for metastatic disease (one patient). For the 800-mg arm (n = 9), reasons for ineligibility included the following: two prior hormone regimens (3 patients), laboratory values out of range (one patient), less than 1 year from end of adjuvant treatment (three patients), and visceral crisis (two patients). For the 1,600-mg arm (n = 12), reasons for ineligibility included the following: less than 1 year from end of adjuvant treatment (two patients), visceral crisis (seven patients), prior chemotherapy for metastatic disease (one patient), estrogen- and progesterone-negative (one patient), and prior cancer (one patient).

In keeping with an intent-to-treat analysis, all treated patients (n = 366) were included in analyses. One patient received radiotherapy (RT) concurrent with MA therapy. She is excluded from analyses of MA response but included in analyses of other end points. Analyses (not shown) of all major study end points were recalculated using only eligible patients. No significant differences were found between these results and those based on the intent-to-treat principle.

Table 1 lists the pretreatment characteristics of participants by treatment arm. Patients on the three arms were well matched at pretreatment. Examination of baseline characteristics between white and nonwhite patients revealed no significant differences. The relatively small size of the nonwhite populations did not allow us to perform a separate analysis of outcome according to race.

Tumor Response and Duration of Response

Table 2 lists the maximum tumor response to MA therapy. Of the 365 total patients, 19 were missing follow-up tumor assessments. The most common reason for missing assessments was treatment termination before the scheduled 8-week follow-up evaluation. Reasons for early treatment termination included early death, toxicity, withdrawn consent, physician decision, and other complicating illness. Patients without repeat tumor assessments due to early death or MA toxicity were considered nonresponders and were included in response rate calculations. Other patients were considered to have nonassessable tumors and were excluded from response rates. Thus, response evaluation is based on 357 patients.

Ninety-one patients achieved a tumor response, that is, either a complete or partial response, while on MA. The response rates were 23%, 27%, and 27% for the 160-mg, 800-mg, and 1,600-mg arms, respectively. Results of the Mantel-Haenszel test show that response rate did not significantly rise with increasing doses of MA. The overlapping 95% confidence intervals indicate that treatment did not correlate with tumor response. Note that including nonassessable patients in response rates gave similar results as did excluding them.

Table 1. Patient Demographics and Pretreatment Characteristics

| | Megestrol Acetate Treatment Arm | | | | | | | |
| | 160 mg | | 800 mg | | 1,600 mg | | Total | |
Variable	No.	%	No.	%	No.	%	No.	%
Total patients	123	100	124	100	119	100	366	100
Age, years								
< 40	5	4	2	2	1	1	8	2
40-49	9	7	19	15	12	10	42	11
50-59	25	20	26	21	32	27	82	22
60-60	53	43	42	34	37	31	131	36
70+	31	25	35	28	37	31	103	28
Median	65		63		65		64	
Range	35-88		37-90		38-89		35-90	
Menopausal status								
Pre-	9	7	12	10	8	7	29	8
Peri-/ post-	114	93	111	90	110	92	335	92
Unknown	0	0	1	< 1	1	1	2	< 1
Estrogen receptor status								
Negative	4	3	7	6	6	5	17	4
Positive, borderline	95	77	88	71	90	76	273	75
Unknown	24	20	29	23	23	19	76	21
Progesterone receptor status								
Negative	18	15	16	13	20	17	54	15
Positive, borderline	67	54	74	60	68	57	209	57
Unknown	38	31	34	27	31	26	103	28
CALGB performance score								
0	66	54	65	53	70	59	201	55
1	48	39	45	36	41	34	134	37
2	4	3	10	8	5	4	19	5
3	4	3	3	2	2	2	9	2
Unknown	1	1	1	1	1	1	3	1
Disease type								
All assessable	50	41	47	38	43	36	140	38
Any measurable	73	59	77	62	76	64	226	62
Disease-free interval (diagnosis to 1st recurrence)								
0	13	11	15	12	9	8	37	10
0-2 years	27	22	47	38	26	22	100	27
≥ 2 years	83	67	62	50	84	71	229	63
Metastatic involvement*								
Visceral metastases								
No	76	62	72	58	68	57	216	59
Yes	47	38	52	42	51	43	150	41
Bone metastases								
No	43	35	46	37	48	40	137	37
Yes	80	65	78	63	71	60	229	63
Soft tissue metastases								
No	69	56	65	52	65	55	199	54
Yes	54	44	59	48	54	45	167	46
No. of metastatic sites at study entry								
1	14	11	13	10	11	9	38	10
2	70	57	69	56	74	62	213	58
3+	39	32	42	34	34	29	115	31
Median	2		2		2		2	
Range	1-5		1-5		1-5		1-5	

Table 1. Patient Demographics and Pretreatment Characteristics (Cont'd)

| | Megestrol Acetate Treatment Arm | | | | | | | |
| | 160 mg | | 800 mg | | 1,600 mg | | Total | |
Variable	No.	%	No.	%	No.	%	No.	%
Prior therapy								
Prior chemotherapy								
No	74	60	76	61	73	61	223	61
Yes	48	39	48	39	45	38	141	39
Unknown	1	1	0	0	1	1	2	< 1
Prior radiation therapy								
No	66	54	58	47	65	55	189	52
Yes	56	46	66	53	54	45	176	48
Unknown	1	< 1	0	0	0	0	1	< 1
Prior hormone therapy								
No	48	39	49	40	44	37	141	39
Yes	75	61	75	60	74	63	224	61
Unknown	0	0	0	0	1	< 1	1	< 1
Prior tamoxifen†								
No	2	3	2	3	3	4	7	3
Yes	73	97	72	96	71	96	216	96
Unknown	0	0	1	1	0	0	1	1

*Visceral metastases: lung, pleura, pleural effusion, liver, brain, adrenal, kidney, spleen, pancreas, brachial, malignant ascites, pericardium, mesentary, hilar mass. Bone metastases: bone, bone marrow. Soft tissue metastases: recurrent primary, inoperable primary, contralateral breast, chest wall, nodes, axilla, skin, scalp, shoulder.

†Among patients who received prior hormonal therapy.

Figure 1 shows the duration of response on MA for the 91 patients whose tumors responded to MA treatment. Dose did not correlate with achieving a response; however, dose did correlate with length of time in response. Of interest, the correlation was negative ($P < .003$), that is, the higher the MA dose, the shorter the time in response. Specifically, the median response duration was 17 months for patients on the 160-mg arm, 14 months for patients on the 800-mg arm, and 8 months for patients on the 1,600-mg arm.

Time to Disease Progression

Figure 2 shows time to disease progression by treatment arm. Two patients from the mid-dose arm discontinued MA therapy before documented disease progression and subsequently received chemotherapy. Their disease progressed subsequent to chemotherapy. We censored these patients at the start of chemotherapy.

Higher doses of MA did not prolong the time until disease progression. The median time to disease progression was 8 months for patients on the 160-mg arm, 7 months for patients on the 800-mg arm, and 8 months for patients on the 1,600-mg arm. These differences were not of statistical significance.

Table 2. Maximum Response to Megestrol Acetate

| | Treatment Arm | | | | | | | |
| | 160 mg | | 800 mg | | 1,600 mg | | Total | |
Response	No.	%	No.	%	No.	%	No.	%
Total patients	123	100	123	100	119	100	365	100
Not assessable	2	2	3	2	3	3	8	2
Total assessable	121	100	120	100	116	100	357	100
Complete response	13	11	7	6	13	11	33	9
Partial response	15	12	25	21	18	16	58	16
Stable disease	67	55	61	51	59	51	187	52
Disease progression	23	19	25	20	20	17	68	20
Early death	2	2	2	2	1	1	5	1
Toxicity failure	1	1	0	0	5	4	6	2
Response (complete + partial)	28	23	32	27	31	27	91	25
95% confidence interval	16-32%		19-36%		19-36%		21-30%	

*χ^2 = 0.532, 2 df, not significant; Mantel-Haenszel χ^2 = 0.405, 1 df, not significant.

Univariate analysis of multiple pretreatment characteristics showed that age at study entry (P = .0001) and presence or absence of bone metastases (P = .007) correlated most highly with time until disease progression. Younger patients were at a greater risk of progressing compared with older patients (risk ratio = 1.03). Patients who had bone metastases had a risk of progressing that was 37% greater than the risk for those patients who did not have bone involvement (risk ratio = 1.37).

Other variables in this univariate analysis that also correlated, although weakly, with time until disease progres-
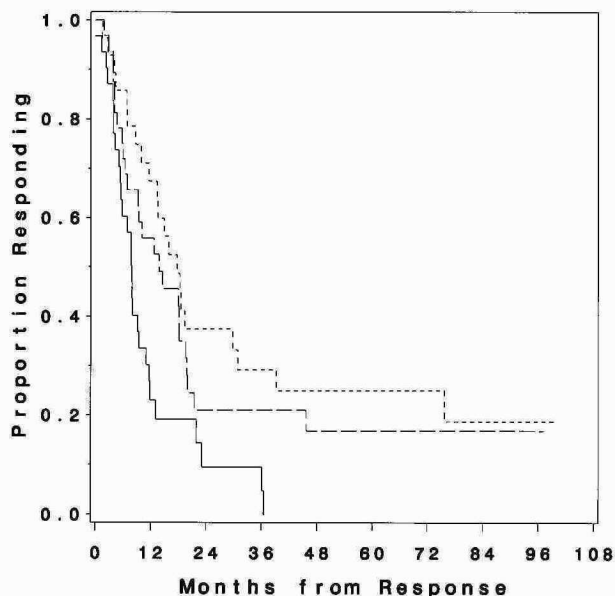

Fig 1. Response duration by treatment arm (160-mg arm: - - -, n = 28, median = 17.1; 800-mg arm: — —, n = 32, median = 13.5; 1,600-mg arm: —, n = 31, median = 7.8; P = .0028).
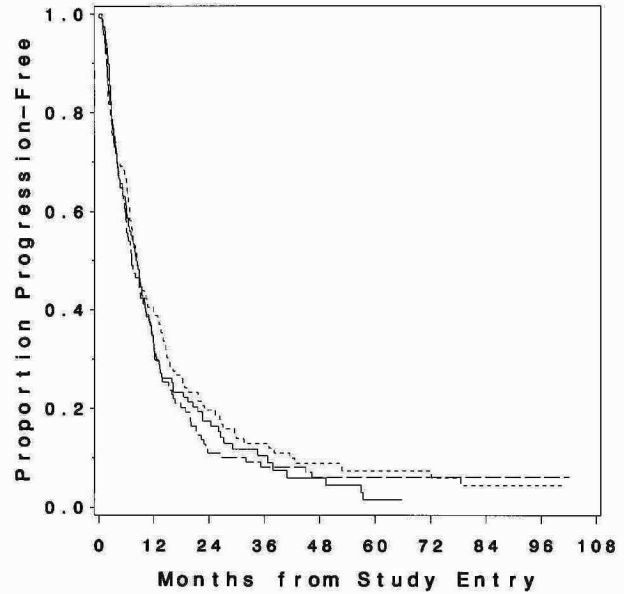

Fig 2. Time to disease progression by treatment arm (160-mg arm: - - -, n = 123, median = 8.3; 800-mg arm: — —, n = 124, median = 7.0; 1,600-mg arm: —, n = 119, median = 8.1; P = .57).

sion were prior hormone therapy (P = .01), total number of metastatic sites (P = .04), estrogen receptor status (P = .04), disease-free interval (P = .04), and patient race (P = .03). Variables that correlated with better prognoses included no prior hormone treatment, fewer metastatic sites, estrogen receptor-positive tumors, longer disease-free interval, and white race.

The following did not correlate univariately with time to disease progression: treatment arm; whether or not the patient received prior chemotherapy, RT, or tamoxifen; presence or absence of visceral metastases; progesterone receptor status; and performance score.

Table 3. Results of Multivariate Cox Regression Analysis

| | Overall Survival (N = 361) | | | Time to Progression (N = 361) | | |
Variable	RR	P	Better Prognosis	RR	P	Better Prognosis
Prior HT	1.56	.0002	No prior HT	1.46	.0015	No prior HT
Age, years	1.02	.0001	Older	1.03	.0001	Older
No. of mets	1.31	.0001	Fewer mets	1.10	.13	Fewer mets
Performance score	1.46	.0001	Lower score	1.16	.10	Lower score
DFI, years	1.17	.05	Longer DFI	1.14	.11	Longer DFI

NOTE. Prior Ht = no versus yes; age at study entry = continuous scale; No. of mets = total number of metastatic sites at study entry; performance score = continuous scale; DFI (diagnosis to first recurrence) = at presentation versus within 2 years versus ≥ 2 years after diagnosis.

Abbreviations: RR, risk ratio; HT, hormone therapy; DFI, disease-free interval (diagnosis to first recurrence).

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