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Oral medroxyprogesterone acetate in the treatment of metastatic breast cancer

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Summary

Thirty-nine evaluable, postmenopausal patients with metastatic breast carcinoma were treated with medroxyprogesterone acetate administered orally at daily doses of 800 mg/day in 29 patients and 400 mg/day in 10 patients. One patient experienced a complete remission and 16 had partial remissions for an objective remission rate of 44%. There was no apparent difference in response between the two dose levels. Median remission duration was 8 months, and median survival for the whole group is expected to exceed 18 months. Increased appetite (66%) and weight gain (97%) were the most common side effects, followed by fluid retention, muscle cramps, and increased blood pressure. Performance status improved and white blood cell and platelet counts increased in the majority of patients. Medroxyprogesterone acetate is an effective hormonal agent in the treatment of metastatic breast cancer.

Endocrine therapy is effective in patients with recurrent or metastatic breast cancer (1); 20% to 40% of unselected patients respond to some form of hormonal manipulation. The presence of steroid hormonal receptors, specifically estrogen and progesterone receptors, within the tumor correlates with a 50% to 60% response rate to hormonal therapy. Conversely, receptor-negative tumors are unlikely to respond to these agents (2). Medroxyprogesterone acetate, a synthetic steroid molecule endowed with a specific progestational action, is one hormonal agent that has been demonstrated to be effective against breast cancer (3). It can be administered both orally and intramuscularly (4). Early experience with low dose (40 to 260 mg/day) medroxyprogesterone acetate given orally produced objective responses in up to 25% of patients. When administered parenterally at doses of 500 to 1,500 mg/day, this drug brought about responses in up to 40% of treated patients, with responses lasting between 7 and 13 months. Intramuscular administration has been complicated by significant local reactions, such as sterile abscesses, in 16% to 60% of patients (5,6). In addition, daily intramuscular administration is inconvenient. In this study, we evaluated the therapeutic efficacy of oral administration of meroxyprogesterone acetate in high doses in patients with advanced breast cancer.

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Materials and methods

Patients who had histologically documented breast cancer and clearly measurable disease, who were one or more years postmenopausal, and whose performance status was ≤3 (Zubrod scale) were eligible for this study. Patients with known estrogen receptor-negative tumor or those who had received prior progestational therapy were not eligible. Also excluded were patients with other concurrent or past malignancies, central nervous system metastases, or extensive liver metastases.

Medroxyprogesterone acetate, 800 mg/day, was administered orally in four divided doses. The drug was provided in 50 mg tablets. To decrease side effects, after the initial six months of therapy, the maintenance dose of medroxyprogesterone acetate was decreased to 400 mg/day. Subsequently, the last 10 patients entered in this study were started at 400 mg/day.

An adequate trial was defined as 12 weeks of therapy unless clear-cut evidence of significant progressive disease was detected before that date.

Evaluation included a complete history and physical examination, complete blood count, biochemical survey (SMA 12), plasma carcinoembryonic antigen level, and the appropriate x-rays and scans to determine and measure the extent of metastatic disease. These assessments were made prior to initiation of therapy and repeated monthly for the first 3 months and every 2 months thereafter.

The disappearance of all measurable lesions and complete recalcification of osteolytic lesions without the appearance of new lesions was considered a complete response. A partial response was defined as a 50% to 99% decrease in the sum of the products of the two largest perpendicular diameters of all measurable lesions and partial recalcification of osteolytic lesions. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% in the original measurements of all lesions for a period in excess of 8 weeks. Progressive disease was considered an increase in tumor burden of greater than 25% or the appearance of any new lesions. Time to progression was measured from the initiation of therapy until the time of relapse or last contact. Survival time was measured from the initiation of treatment until death or the last follow-up visit. Survival times were plotted using the Kaplan and Meier method (7), and the modified Wilcoxon test (8) was used to test the differences between pairs of curves for statistical significance.

Results

Forty-two patients seen between February 1981 and October 1982 were selected for the trial. One was considered ineligible because of a history of soft tissue sarcoma. Two were inevaluable for response due to inadequate trial. All patients were assessable for toxicity. The pretreatment characteristics of the 41 eligible patients included the following. Thirty-nine patients were female and 2 were male. The median age was 62 years (range 32 to 80). The disease-free interval was <12 months in 4 patients, 12 to 36 months in 20, and >36 months in 17. Thirty-six patients were Caucasian, 4 were black and 1 was Mexican-American. Twenty-nine (71%) patients had a performance status between 0 and 1, 9 (22%) had a performance status of 2, and 3 had a performance status of 3. Other pretreatment characteristics are shown in Table 1.

Of the 39 evaluable patients, complete remission was achieved in 1 (3%), partial remission in 16 (41%), 14 had stable disease, and 9 (23%) continued to have clear-cut progressive disease. Four patients included in the stable category achieved objective responses that did not meet the criteria for a partial remission. The overall major objective response rate was 44%. Of 30 patients treated at 800 mg/day, 11 (37%) had a complete or partial response. Six of the 9 patients (67%) treated from the beginning at 400 mg/day achieved a partial response. The difference between these two response rates is not statistically significant. Univariate analysis was performed to search for correlations between response to medroxyprogesterone acetate and standard prognostic factors (Table 2). Response rates were higher in patients over 60 years old, those with soft tissue or osseous dominant disease, those who achieved responses with prior hormone therapy, and those with estrogen

Table 1. Pretreatment characteristics.

	No. of patients	(%)
Eligible patients	41	
Performance status (Zubrod)		
0	11	(27)
1	18	(44)
2	9	(22)
3	3	(7)
Number of sites		
1	20	(49)
2	11	(27)
≥3	10	(24)
Dominant site of disease		
Soft tissue	7	(17)
Osseous	19	(46)
Visceral	15	(37)
Estrogen receptor		
Positive	20	(49)
Not done	21	(51)
Progesterone receptor		
Positive	4	(10)
Negative	2	(5)
Not done	35	(85)

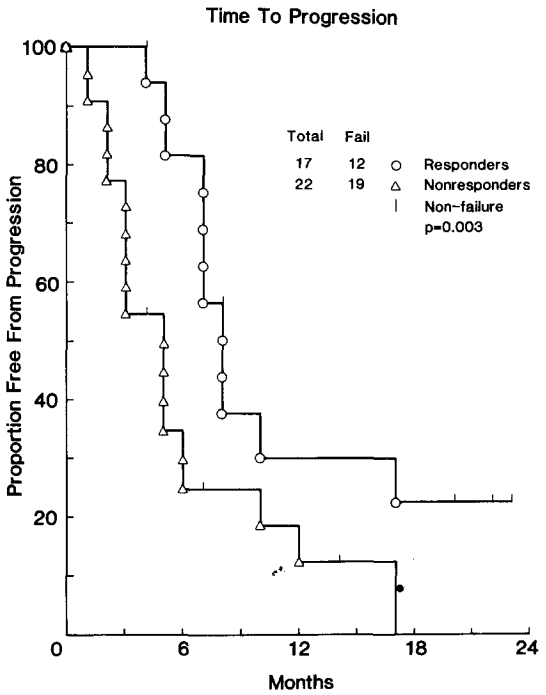

Fig. 1. Progression-free curves for responders and nonresponders.

and/or progesterone receptor-positive tumors. One 68-year-old male patient with an estrogen receptor-positive, progesterone receptor-unknown tumor achieved a partial remission on this regimen, while the other patient, a 47-year-old male, with a borderline estrogen receptor, progesterone receptor-negative tumor did not respond. The median time to progression for all patients was 7 months (range 1 to 23+), for responders 8 months (range 4 to 23+), and for nonresponders 5 months (range 1 to 17) ($P = 0.003$) (Figure 1). Median survival has not been reached, but this interval is estimated to be in excess of 18 months for the whole group.

In 19 patients (16 treated with 800 mg/day and 3 with 400 mg/day) there was clear-cut improvement of at least 1 point in performance status rating. Twenty-seven (66%) had a noticeable increase in appetite. In 29 patients the white blood cell count increased more than 2,000/mm^3. These hematologic changes occurred within the first month after initiation of treatment.

The toxicities that occurred in these patients are listed in table 3. The most common side effect was excessive weight gain with or without fluid retention. While it occurred at both dose levels, an increase of more than 20 lbs took place only in patients receiving 800 mg/day of the drug and was a gradual process over many months. This side effect was also analyzed relative to body weight: weight increase of 5% or less was observed in 40% of patients, a 6–10% increase in 25% of patients, and a greater than 10% weight increase in 35% of them. The median weight gain for the entire group was 6% and the maximal increase observed was 30%. Only patients treated with 800 mg/day of medroxyprogesterone acetate had weight gains exceeding 10% of their body weight. Thirteen patients had mild hypertension (11 treated at 800 mg/day and 2 treated at 400 mg/day), and 3 others required antihypertensive medical treatment. Congestive heart failure developed in 4 patients, probably as a result of fluid retention. Treatment with medroxyprogesterone acetate was discontinued in 3 of them, and their cardiac funtion returned to normal. In 1 patient diuretics resulted in improved cardiac function, while medroxyprogesterone acetate, 400 mg/day, was continued.

Ten patients experienced mild to moderate fa-

Table 2. Analysis of response by prognostic factors

	No. of patients	No. of responses	(%)
Age (years)			
≤60	16	6	(38)
>60	23	11	(48)
Disease-free interval			
<12 months	4	3	(75)
12–36 months	19	7	(37)
>36 months	16	7	(44)
No. of sites			
1–2	30	12	(40)
≥3	9	5	(55)
Dominant site			
Soft tissue	7	4	(57)
Bone	18	9	(50)
Visceral	14	4	(29)
Performance status			
0–1	29	13	(45)
2	7	2	(29)
3	3	2	(67)
Prior hormonal therapy			
Response	26	14	(54)
No response	4	1	(25)
Prior chemotherapy			
Yes	25	11	(44)
No	14	6	(43)
Estrogen receptor			
Positive	19	10	(53)
Unknown	20	7	(35)
Progesterone receptor			
Positive	3	2	(67)
Negative	1	–	(0)
Unknown	35	15	(43)

The differences observed in response rate were not statistically significant. The p value calculated for the differences in response rate according to dominant site of disease was 0.07.

tigue (8 treated at 800 mg/day and 2 at 400 mg/day). One patient who was treated with 800 mg/day of the drug for 7 months developed a severe Cushingoid syndrome and congestive heart failure. Two patients treated with 800 mg/day developed nonfatal pulmonary embolism during treatment. One patient treated at 400 mg/day developed moderately severe vaginal bleeding which precluded continuation of therapy after the first month.

Discussion

Medroxyprogesterone acetate given at the two dose levels used in this study consistently produced objective responses in patients with metastatic breast cancer. Only 10 patients were treated at the lower dose, but no apparent difference in the response rate was observed between the two dose schedules; however, at the higher dose the incidence and severity of side effects, especially weight gain, were increased. The therapeutic results achieved with the oral administration of medroxyprogesterone acetate are similar to those obtained with parenteral administration (4), and the response rate is also in keeping with reports of other investigators who have prescribed similar doses of orally administered medroxyprogesterone acetate

Table 3. Toxicity.

	No. of patients	(%)
Common side effects		
Increased appetite	27	(66)
Weight gain (lbs)	40	(97)
0–10	21	(51)
11–20	8	(20)
21–30	6	(15)
>30	5	(12)
Weight gain (% body weight)		
< 5%	16	(40)
6–10%	10	(25)
11–20%	8	(20)
>20%	6	(15)
Fluid retention	15	(37)
Mild	9	(22)
Moderate	2	(5)
Severe	4	(10)
Muscle cramps	17	(41)
Increased blood pressure	16	(39)
Increased perspiration	14	(34)
Fatigue (mild)	10	(24)
Nervousness	9	(22)
Tremor	7	(17)
Facial fullness	9	(22)
Uncommon side effects		
Hair loss (slight)	4	(10)
Vaginal bleeding	4	(10)
Headache	4	(10)
Hot flashes	4	(10)
Irritability	4	(10)
Insomnia	3	(7)
Facial hair	3	(7)
Congestive heart failure	4	(10)
Pulmonary embolism	2	(5)
Thrombophlebitis	1	(2)
Cushingoid syndrome	1	(2)
Hypercalcemia	1	(2)
Diabetes	1	(2)

therapy (500 to 1,500 mg/day). Though doses of at least 400 mg/day appear to be more effective than low doses of the drug (20 to 400 mg/day), it is unclear whether doses in excess of 500 mg/day produce an additional therapeutic benefit (4). It appears, however, that the higher doses are associated with more toxicity by either route of administration.

Several other favorable biological effects were observed during this study. Increased appetite and weight gain occurred in a few patients who experienced anorexia and weight loss as a result of previous cytotoxic therapies. Increased white blood cell and platelet counts suggested that the combination of medroxyprogesterone acetate and chemotherapy may be an aid in decreasing the myelosuppressive toxicity of the latter form of therapy. Indeed, some investigators have reported that medroxyprogesterone acetate reduces toxicity of combination chemotherapy (11).

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