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A Phase II Study of High-Dose Medroxyprogesterone Acetate in Advanced Breast Cancer

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Summary. *Twenty-three evaluable patients with advanced breast cancer were treated with MPA, 1,400 mg/m² daily PO for the first 6 months, and 500 mg/m² daily PO thereafter. The median total dose was 191,400 mg in 88 days, with the maximum dose given to date 522,600 mg in 282 days. Most patients tolerated high-dose MPA well. Side-effects were minimal and reversible. The commonest side-effects were tremor or edema. The CR plus PR rate was five of 23 (22%). All responding patients were over 50 years of age and had a good performance status. Hormone receptor status was known in four patients only, so that no correlation between receptor status and response could be drawn. MPA appears to be a useful hormone for use in the management of breast cancer. Optimal dosage remains to be determined.*

Introduction

6α-Methyl-17α-hydroxyprogesterone acetate (medroxyprogesterone acetate, MPA) is a well-known synthetic progestogen whose action against hormone-dependent tumors has been recognized since the early 1960s. Interest in this hormone has recently been revived because clinical trials conducted in Italy suggested that MPA's effectiveness in advanced breast cancer is enhanced if it is used in high daily doses [2–4]. Significantly improved response rates (40%–46%) have been reported with the use of high-dose parenteral MPA. Studies on the bioavailability of the hormone when given IM or PO have been published by this Italian group [5, 6], and it has been reported that improved response rates can also be achieved with high-dose MPA when it is given by the oral route [1, 7].

We undertook a trial to determine whether these improved response rates in advanced breast cancer were reproducible, and further to evaluate the incidence of side-effects with high-dose oral MPA.

Materials and Methods

Twenty-six women with histologically documented breast cancer with recurrent and/or metastatic disease received high-dose oral MPA. The following clinical measurements and follow-up studies were done: prior to treatment, complete history and physical examination, full blood count, urinalysis, serum electrolytes, calcium, urea, uric acid, creatinine, alkaline phosphatase, serum electrophoresis, bilirubin, SGOT, LDH, gamma-GT, and plasma CEA, chest X-rays and tomograms when indicated, bone scan, skeletal survey, and liver and brain scan if indicated. These studies were repeated at regular intervals. Response criteria were as follows: complete remission (CR), disappearance of all evidence of disease; partial remission (PR), ≥ 50% reduction in size of bidimensionally measurable lesions; no change (NC), failure of a patient's status to qualify for either response or progressive disease over a period of 8 weeks of therapy; progressive disease (PD), appearance of new lesions or an increase of ≥ 25% in existing lesions.

The median age of the patients was 57 years (range 33–75 years). The ECOG performance status was used and the coding is as follows: PS 0 = normal activity; PS 1 = symptoms but ambulatory; PS 2 = in bed < 50% of the time; and PS 3 = in bed > 50% of the time. There were 18 patients with PS 0–1 and eight patients with 2–3. Dominant disease sites were: soft tissue, eight patients; bone, six patients; bone and visceral, four patients; bone and soft tissue, two patients; liver, three patients; abdominal metastases, one patient; central nervous system, one patient; and pleura and skin, one patient. Hormone receptor status was known in four patients (three were estrogen-receptor-positive and one estrogen-receptor-negative). Seventeen patients had received previous chemo- and hormono- or hormone therapy, and only six had no prior treatment. The six patients who received MPA as first-line treatment were all older women (median age 69).

MPA was given in a dose of 1,400 mg/m² daily PO for the first 6 months, followed by 500 mg/m² daily PO thereafter.

Results

Of 26 patients entered on study, two refused treatment shortly after entry on study and a third received an inadequate trial because she died at day 14. Twenty-three patients are therefore evaluable. The total median dose given was 191,400 mg in 88 days (range 54,600–522,600 mg in 37–282 days).

Toxic Effects

No hematopoietic or renal toxicity occurred; increasing LDH occurred in 10 patients. The incidence of side-effects was very low and most patients tolerated high-dose MPA well. The following side-effects were recorded: tremor (3 patients); edema (3 patients); skin rash or hirsutism (3 patients); nausea

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Table 1. Characteristics of responding patients

Age	PS[a]	Prior CT and response	Dominant disease	MPA total dose (mg)	Response	TTF[c] (days)
59	0	CMFP – PD DAVTH – PD	Subcutaneous/skin	> 499,400	CR	> 372
62	0	None	Subcutaneous/skin	485,400	PR	248
57	1	CMFAV – PR MitoT – PR Pala – NC FIVB – NC CAF – NC	Subcutaneous/skin	352,500	PR	168
66	1	None	Lung and bone	> 452,600	PR	> 326
73	0	None	Mamma and bone	> 398,500	PR	> 250
51	1	CAF – PR Spiro – NC	Bone	246,600	IMP	138
62	1	DAVTH/CMFP – PD Spiro – PR	Bone	384,800	IMP	245
71	1	None	Bone	> 522,600	IMP	> 282

[a] PS, performance status. 0, no symptoms; 1, symptomatic
[b] C, cyclophosphamide; M, methotrexate; F, fluorouracil; D, dibromodulcitol; A, adriamycin; V, vincristine; I, imidazole carboxamide; B, bischloroethyl nitrosourea; Mito, mitomycin C; Spiro, spirogermanium; Pala, phosphonacetyl-L-aspartate; T, tamoxifen; H, fluoxymesterone; P, prednisone
[c] TTF, time to treatment failure

(2 patients); thrombophlebitis (1 patient); moon facies (1 patient); and vaginal bleeding (1 patient). Side-effects were reversible when the dosage of MPA was reduced.

Therapeutic Results

Twenty-three patients are evaluable for therapeutic efficacy: one CR occurred and four PRs. A CR was documented in a 59-year-old woman with subcutaneous metastases who had received two different chemotherapeutic regimens previously. Her hormonal status was estrogen receptor-positive (148 fm/mg) and progesterone receptor-negative. She is still in CR at 372 days and has already received a total of 499,400 mg MPA. Partial remissions occurred in four patients. Data for responding patients are outlined in Table 1. In a further three patients, who all had bone metastases, no change was documented radiologically but there was a significant decrease in analgesic requirements accompanied by improvement in performance score. These patients would be better classified as improvement than NC (see Table 1). The total response could therefore be eight of 23 (35%), and the 95% confidence interval for this response rate is 15%–54%. Of the eight responding patients, four had had no prior chemotherapy or chemohormonotherapy.

NC occurred in four patients, while 11 had PD. Hormone receptor status was known in four patients. In one of these, in whom CR occurred, the estrogen receptor level recorded was 148 fm/mg, and that of progesterone receptors, nil, while in three patients who had PD the hormone receptor levels were: estrogen receptor 79 fm/mg, progesterone receptor 13 fm/mg; estrogen receptor 120 fm/mg, progesterone receptor nil; estrogen receptor nil, progesterone receptor 32 fm/mg.

Discussion

MPA has been used in the treatment of endometrial cancer, renal carcinoma, and breast cancer for the past 20 years. The initial therapeutic dosages in advanced breast cancer varied from 100 to 300 mg/day given PO. In the phase II trial reported here our CR plus PR rate of 22% (5/23) (the 95% confidence interval for this is 5%–39%) was lower than was expected from the results obtained with high-dose MPA by Italian workers. These workers reported response rates of 40%–46% with high-dose parenteral MPA (1,500 mg/day IV for 30 days) [2, 3] and response rates of 30%–38% with oral MPA, 500–1,000 mg/day [1, 7]. Their best responses were noted in cases with osseous and soft tissue metastases. If those of our patients with bone metastases in whom no change was documented radiologically but who experienced a significant decrease in analgesic requirements accompanied by improvement in performance score are added to the responding patients, our total response is eight of 23 (35%) (95% confidence interval 15%–54%). All our responses occurred in patients over 50 years of age who had a good performance status. The majority of patients in the study received MPA as third-line therapy, as can be seen in Table 1; one of the responding patients had had three and another, five prior treatment regimens. All patients tolerated high-dose MPA well with minimal side-effects; the absence of serious side-effects makes MPA a useful hormone to consider for combination regimens. Furthermore, the drug is a useful hormone even in third-line treatment. However, further studies are needed to determine optimal therapeutic dosage.

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