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High-dose Medroxyprogesterone Acetate in Combination with Vindesine in Advanced Breast Cancer*

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Abstract—*Forty-three evaluable women with metastatic breast cancer received treatment with high-dose medroxyprogesterone acetate (MPA) plus vindesine. Patients tolerated treatment well, no lethal toxicities occurred. The commonest side-effects were hemopoietic, with leukopenia documented in 22 patients. Symptoms of peripheral neuritis occurred in 10 patients. A response rate of 28% (12 out of 43 patients) was seen. Ten of the responding patients had multiple prior chemotherapeutic agents. These results indicate that the combination of MPA and vindesine is not of value in patients with advanced breast cancer.*

INTRODUCTION

MEDROXYPROGESTERONE acetate (MPA) and vindesine have shown some activity when used as single agents in patients with advanced breast cancer who had received prior chemotherapy. We reported the following response rates with these agents used as single drugs in phase II trials: a 35% response rate in 23 patients treated with high-dose MPA [1] and a 19% response rate in 31 patients treated with vindesine [2].

Since these agents had not yet been evaluated when used in combination, and since none of them are presently being used in first line regimens for breast cancer, a study was undertaken to evaluate the therapeutic efficacy of combining these two agents in the treatment of pretreated patients with advanced breast cancer.

MATERIALS AND METHODS

Forty-five women with histologically documented breast cancer with recurrent and/or metastatic disease were entered on the study. MPA was given in a dose of 650 mg/m^2 per os per day for 30 days and then 400 mg/m^2 per os per day continuously, vindesine was given as a bolus intravenous injection of 3 mg/m^2 on days 1, 8 and 15, the vindesine was repeated every month.

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If the white blood count was < 4000/mm^3 or platelets were < 100 000/mm^3 at the beginning of a cycle, vindesine treatment was delayed until white blood cells were > 4000/mm^3 and platelets were > 100 000/mm^3 or until 2 weeks had elapsed. If leukopenia or thrombocytopenia persisted for 2 weeks then the vindesine dosage was reduced to 50% for white blood cells < 4000 or platelets <100 000 and omitted for white blood cells < 3000/mm^3 or platelets < 75 000/mm^3.

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. This response had to be maintained for at least 8 weeks for it to count as a PR; 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 54 yr (range 29–74 yr). The ECOG (Eastern Cooperative

Oncology Group) performance status (PS) 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 25 patients with a PS 0–1 and 20 patients with PS 2–3 (patients who were completely bedridden, e.g. PS 4, were not eligible for the study). Dominant disease sites were bone, 13 patients; liver, five patients; lung, five patients; soft tissue, six patients; abdominal, one patient; and 15 patients with multiple involvement of bone, and/or lung and/or soft tissue. Hormone receptor status was known in 17 patients, 10 were ER positive, seven were ER negative. Progesterone receptors were only determined in eight of these: five ER positive patients had positive PgR receptors, two ER-negative patients had PgR positive receptors, and one patient had both ER and PgR negative receptors. Forty-one patients were heavily pretreated with multiple combination chemo-hormonotherapy. Only four patients had not received prior chemo-hormonotherapy. Details of prior treatment regimens given to the patients who responded are shown in Table 1.

RESULTS

Of the 45 patients entered on study 2 are not evaluable because of inadequate trial. One patient refused treatment after entry on study, and the second patient died 5 days after treatment was started. Forty-three patients are therefore evaluable.

Toxic effects

No life threatening toxicity occurred. Hemopoietic toxicity was the commonest side-effect: 22 patients had leukopenia, in four the white blood cells dropped below 2000/mm^3 in 18 either grade 1 (eg. white blood cells 3.0– < 4.5) or grade 2 (eg. white blood cells 2.0– < 3.0) leukopenia was recorded. Anemia occurred in five patients but thrombocytopenia was not observed. Ten patients developed symptoms of mild to moderate peripheral neuritis necessitating reduction of vindesine dosage, five patients developed alopecia requiring a wig, four patients had edema, mild to moderate nausea and vomiting occurred in only three patients, only one patient had stomatitis; glycosuria and tremor were not encountered in this study.

Table 1. Characteristics of responding patients

Age	PS*	Prior CT†	& response	Dominant disease	Response to MPA & vindesine	TTF‡ in days
74	3	None		Bone and soft tissue	PR	>150
59	1	CMF		Bone and	PR	150
		T	NC	skin		
48	1	CMFVP	Adjuvant	Bone and	PR	420
		DAVTH	NC	pleura		
38	1	CMFPT	Adjuvant	Soft	PR	150
		DAVTH	PD	tissue		
62	1	DAVTH/Mito	CR	Liver	PR	120
52	1	None		Lung	PR	210
55	2	CAF/CMFH	CR	Abdominal	PR	150
37	2	L-PAM	Adjuvant	Lung	PR	90
		DAT	CR			
		Mito-H	CR			
52	1	DAVTH/	PR	Soft	PR	60
		CMFPTH				
		Mito	PD	tissue		
56	2	DAVTH	PD	Bone	IMP	120
		CH	IMP			
51	1	CAF	NC	Bone	IMP	>120
55	2	DAVTH/	CR	Bone	IMP	>150
		CMFPTH				

* = PS - performance status: 0, no symptoms; 1, symptomatic; 2, < 50% of time in bed; 3, > 50% of time in bed.

† = C, cyclophosphamide; M, methotrexate; F, fluorouracil; D, dibromodulcitol; A, adriamycin; V, vincristine; Mito, mitomycin-C; T, tamoxifen; H, fluoxymesterone; P, prednisone.

‡ = TTF, time to treatment failure.

Therapeutic results

Of 43 evaluable patients, nine achieved a partial remission and three patients with bone metastases had significant decrease in analgesic requirement acccompanied by improvement in performance score, radiologically lytic bone lesions showed increased sclerosis and the number of lesions decreased on isotope scans. Table 1 shows discriminants of responding patients as well as the type of prior treatment and response and the duration of response to MPA and vindesine. The median duration of remission was 5 months. Response was therefore recorded in 12 out of 43 (28%), the 95% confidence interval for this response rate is 14–41%.

DISCUSSION

In the treatment of advanced breast cancer combination chemotherapy has proved to be superior to single agent treatment [3]. Some investigators, however, question the rationale of combining chemo- and hormonotherapy, arguing that cellular synchronization in a rest phase by endocrine therapy could interfere negatively with the cell kill potential of chemotherapy [4]. Experimental and clinical data seem to contradict this interpretation and improved response rates were obtained in most of the clinical trials with chemo-hormonotherapy [5–10]. Italian workers reported response rates of 30–38% with oral high dose MPA [11, 12] and we reported response in 35% of elderly women with metastatic breast cancer treated with MPA. We found that patients tolerated high-dose MPA well with minimal side-effects; the absence of serious side-effects suggested that MPA could be a useful hormone to introduce in combination regimens.

In another phase II trial, in which we used vindesine, a newer vinca-alkaloid in 40 patients with metastatic breast cancer, a response rate of 19% occurred in patients who had had prior chemotherapy exposure [2]. Half the patients treated had received previous vincristine therapy; this factor did not appear significant with regard to toxicity or response to vindesine. The two major toxicities encountered were peripheral neuritis and myelosuppression. These results with MPA and vindesine, used singly in previously treated patients with advanced breast cancer, prompted us to undertake the present study in order to investigate the feasibility of combining the two agents and to evaluate the therapeutic efficacy of this combination.

While the combination was well tolerated with no prohibitive side effects, the addition of vindesine to MPA did not appear to result in improved response rates when judged by our results reported with MPA as single agent in elderly women.

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