A Phase III Trial of Oral High-Dose Medroxyprogesterone Acetate (MPA) Versus Mepitiostane in Advanced Postmenopausal Breast Cancer

MASARU IZUO, MD,* MINORU YOSHIDA, MD,† TAKESHI TOMINAGA, MD,‡ OSAHIKO ABE, MD,§ KOJI ENOMOTO, MD,§, YASUO NOMURA, MD,‖ KANJI KUBO, MD,¶ AND OSAMU TAKATANI, MD,# FOR THE JAPANESE GROUP FOR MPA TREATMENT OF BREAST CANCER

A randomized controlled trial was performed to compare the therapeutic results of oral high-dose medroxyprogesterone acetate (HD-MPA) *versus* mepitiostane (MS) in the treatment of postmenopausal breast cancer. MPA was given at three doses of 400 mg orally daily to 47 patients and produced objective responses in 19 cases (40.4%). An objective response was seen in 14 of the 40 control patients given MS at two doses of 10 mg orally daily (35.0%). Among patients with bone metastases, 6 of 19 (31.6%) for HD-MPA and 2 of 13 (15.4%) for MS showed objective responses. The other merits of HD-MPA suggested in the study were improvement in performance status, increase in appetite, and myeloprotective effect.

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RECENTLY it has been reported in Europe[1–5] and in Japan[6–8] that high-dose therapy with medroxyprogesterone acetate (HD-MPA), a synthetic progestin preparation, produces good results in the treatment of advanced or recurrent breast cancer. The authors had previously tried oral HD-MPA for Japanese patients with advanced breast cancer and obtained a response rate of 38.2% at a dose of 1200 mg/day.[7,8] The oral HD-MPA treatment at this dosage seemed to be adequate to obtain clinical responses comparable to the previous results by daily intramuscular injection[2,3,5] and did not seem to cause any local adverse effects such as gluteal abscess or induration.

The current study describes the clinical effects of oral HD-MPA on advanced breast cancer in a double-blind controlled study. Mepitiostane (MS),[9] an antiestrogenic androgen that is used orally in Japan to treat breast cancer, was used as the control drug.

Material and Methods

Eligibility criteria were as follows: histologic evidence of advanced breast carcinoma, postmenopausal or ovariectomized status, measurable or assessable tumor lesions in progress, no antineoplastic treatment for at least 4 weeks, no previous endocrine therapy (except adjuvant therapy, and performance status of 0 to 3 by ECOG.

The patients were randomly allocated to two groups by the controllers with the use of a table of random numbers. MPA (17α-hydroxy-6α-methyl-pregn-4-ene-3,20 dione, 17α acetate) was administered to the patients in one group at three doses of 400 mg orally daily, and MS[9] (2α-3α-epithio-5α-androstan-17β-yl 1-methoxy-cyclopentyl ether) was administered to those in the other group at two doses of 10 mg orally daily. MPA was supplied as 200-mg tablets and MS as soft capsules containing 5 mg in sesame oil. Placebos were prepared for both the tablets and the soft capsules. Each patient was given either MPA tablets plus placebo capsules or MS capsules plus placebo

* Chairman, Department of Surgery, Gunma University Hospital, Maebashi, Japan.
† Department of Surgery, Aichi Cancer Center Hospital, Nagoya, Japan.
‡ Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.
§ Department of Surgery, Keio University Hospital, Tokyo, Japan.
‖ Department of Surgery, National Kyushu Cancer Center Hospital, Fukuoka, Japan.
¶ Department of Surgery, National Nagoya Hospital, Nagoya, Japan.
# Department of Internal Medicine, Defense Medical College, Tokorozawa, Japan.
Co-workers in this study are Drs. Yuichi Iino, Takao Yokoe and Hideo Suzuki (Gunma University Hospital); Drs. Shigeto Miura and Hiroshi Murai (Aichi Cancer Center Hospital); Drs. Masatsugu Kitamura and Kazuo Hayashi (Tokyo Metropolitan Komagome Hospital); Dr. Tadashi Ikeda (Keio University Hospital); Dr. Hideya Tashiro (National Kyushu Cancer Center Hospital); Dr. Mitsuo Imura (Defense Medical College).
Address for reprints: Masaru Izuo, MD, Department of Surgery, Gunma University Hospital, 3-39-15, Showa-cho, Maebashi, Japan.
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tablets. The normal procedures for a double-blind trial were strictly followed. Patients were evaluated during the fourth week, and those who showed progressive disease were dropped from the study. The treatment was continued until disease progression or severe complications occurred.

The criteria of the Japan Mammary Cancer Society,[10] which were modified from the criteria of the International Union Against Cancer (UICC),[11] were used to assess response. The patients were examined before the treatment and at 4-week intervals during treatment. On each occasion, physical examination, chest x-ray, skeletal survey, assessment of performance status, and laboratory tests (blood counts, urinalysis, serum protein, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase, alkaline phosphatase, bilirubin, and electrolytes) were carried out. Assessments of the clinical data and laboratory data were done by extramural reviewers several times during the study in each institution.

Results

From September 1981 to December 1983, 112 patients entered into the trial. At the last evaluation of this study (April 1984), 25 patients were excluded. Of those, five patients were premenopausal, four had no evaluable lesion, one had a poorer performance status, and one had a severe complication. The remaining 14 patients were excluded because of previous hormone therapy. Table 1 summarizes the pretreatment characteristics of 87 evaluable patients. Between the two treatment groups, there were no significant differences in all patient characteristics.

Table 2 shows the therapeutic results according to the groups. Nineteen of 47 patients (40.4%) treated with MPA and 14 of 40 patients (35%) treated with MS achieved objective response. The results as to the dominant lesion show that: among patients with soft tissue lesions, 12 of 20 showed a response to MPA and 10 to 20 to MS; among patients with bone lesions, response occurred in 6 of 19 and 2 of 13, respectively; among patients with visceral lesions, 1 of 8 treated with MPA and 2 of 7 treated with MS showed objective response. The response rate in patients with bone lesions was higher with MPA treatment than with MS, although the statistical difference between the two was not significant. Statistical analyses of the response rates according to the postmenopausal age showed no significant difference between the two groups. Regarding the estrogen receptor (ER) status, patients with ER-positive or ER-unknown lesions showed a slightly higher response rate in the MPA group, although there was no significant difference.

The duration of response is shown in Table 3. The average duration of objective regression was 45.17 ± 6.33 and 39.31 ± 5.53 weeks in the MPA and MS groups, respectively.

The improvement of performance status was seen in 11 of 47 treated with MPA and 1 of 40 given MS. The chi-square test revealed a significant difference ($P < 0.05$) between the two groups.

Side effects and their incidences are listed in Table 4. The number of patients with any side effect was 15 of 47,

TABLE 1. Pretreatment Characteristics of Evaluable Patients

Characteristics	MPA (n = 47)	MS (n = 40)	Test (χ^2)
Age (yr)			
<40	0	1	
40–50	9	5	NS
50–60	19	20	
≧60	19	14	
Performance status			
0	15	16	
1	17	15	
2	8	5	NS
3	5	2	
4	2	2	
Menopausal status			
Perimenopause	2	1	
Spontaneous	38	32	NS
Ovariectomy	7	7	
Postmenopausal period (yr)			
<1	6	6	
1–5	16	8	
5–10	6	11	NS
≧10	18	15	
unknown	1	0	
Primary or recurrent			
Primary	9	4	NS
Recurrent	38	36	
Time from recurrence to treatment (mo)			
<2	18	20	
2–7	8	8	
7–13	4	6	NS
13–25	6	0	
≧25	2	2	
Disease-free interval (yr)			
≦2	18	9	NS
>2	20	27	
Dominant lesion			
Soft tissue	20	20	
Osseous	19	13	NS
Visceral	8	7	
No. of lesions			
1	30	29	
2	11	9	NS
≧3	6	2	
Previous therapy			
None	32	27	
Hormone	0	2	
Radiation	2	1	NS
Chemotherapy	11	4	
Hormone + chemotherapy	1	1	
Radiation + chemotherapy	1	5	

MPA: medroxyprogesterone acetate; MS: mepitiostane; NS: not significant ($P \geqq 0.05$).

TABLE 2. Characteristics of Responding Patients

	MPA (n = 47)			MS (n = 40)		
	CR	PR	CR + PR	CR	PR	CR + PR
Total cases	4/47 (8.5)*	15/47 (31.9)	19/47 (40.4)	5/40 (12.5)	9/40 (22.5)	14/40 (35.0)
Dominant lesion						
Soft tissue	4	8	12/20 (60.0)	4	6	10/20 (50.0)
Osseous	0	6	6/19 (31.6)	0	2	2/13 (15.4)
Visceral	0	1	1/8 (12.5)	1	1	2/7 (28.6)
Postmenopausal period (yr)						
<1	0	2	2/6 (33.3)	1	0	1/6 (16.6)
1-5	1	6	7/16 (43.8)	1	3	4/8 (50.0)
5-10	1	1	2/6 (33.3)	1	4	5/11 (45.5)
≧10	2	6	8/18 (44.4)	2	2	4/15 (26.7)
Unknown	0	0	0/1	0	0	0
ER status						
ER(+)	1	4	5/12 (41.7)	2	2	4/11 (36.4)
ER(−)	0	0	0/5	1	1	2/5 (40.0)
unknown	3	11	14/30 (46.7)	2	6	8/24 (33.3)

* Figures in parentheses represent percentage of objective response/number of patients.

MPA: medroxyprogesterone acetate; MS: mepitiostane; CR: complete response; PR: partial response; ER: estrogen receptor.

or 31.9%, for MPA and 18 of 40, or 45%, for MS. The most frequent side effects were moon face for MPA and hoarseness and hirsutism for MS. There were significant differences as to each of the above three items between the two groups. In only three cases of MPA administration was discontinued due to side effects such as moon face, edema, palpitation, or weight gain, but the side effects improved soon after discontinuation of MPA therapy.

No significant abnormality was observed in blood (except leukocytes), bone marrow, liver function, *etc.* MPA induced a significant increase in leukocyte count ($P < 0.05$), whereas MS induced no significant change. MPA also induced a statistically greater increase in body weight ($P < 0.05$).

Discussion

The use of MPA in the treatment of advanced breast cancer was introduced in the early 1960s.[12] However, when MPA was used at low doses of 40 to 300 mg/day, objective regression did not exceed 20% on an average.[12] When higher doses (>500 mg/day intramuscularly) were introduced by Pannuti *et al.*[5] in 1973, the response rate exceeded 40%, but the treatment by daily intramuscular injection sometimes caused gluteal abscess or induration.[2,3,5]

In a preliminary study by our group, MPA given orally was found to be well-absorbed.[6] Various high doses of MPA ranging from 600 to 2400 mg/day by oral route were tried, and the administration of MPA at 1200 mg/day was most useful and resulted in a response rate of 38.2%.[7] In the current double-blind controlled study, the antitumor effect of HD-MPA was compared with that of the control drug, MS. The response rates were 40.4% for HD-MPA and 35% for MS, and the statistical difference between the two was not significant. The response rate by oral HD-MPA in this study was in the same range as that in previous reports for HD-MPA by oral use[13] as well as by intramuscular injection.[2-5] The response rate to MS

TABLE 3. Duration of Response*

	Total no. of patients	<6 mo	6-12 mo	≧12 mo
MPA	47	5 (10.6)‡	6 (12.8)	7 (14.9)
MS	40	5 (12.5)	5 (12.5)	3 (7.5)

* From the date of start of treatment until the date of the first observation of progressive disease.

‡ Figures in parentheses represent percentage.

MPA: medroxyprogesterone acetate; MS: mepitiostane.

TABLE 4. Incidence of Main Side Effects

	MPA (n = 47)	MS (n = 40)
Total no.*	15 (31.9)†	18 (45.0)
Moon face	7 (14.9)‡	1 (2.5)‡
Hoarseness	3 (6.4)§	13 (32.5)§
Hirsutism	0	7 (17.5)§
Acne	1 (2.1)	4 (10.0)
Nausea	2 (4.3)	2 (5.0)
Palpitation	4 (8.5)	0
Edema	2 (4.3)	1 (2.5)
Weight gain	2 (4.3)	1 (2.5)

* Total number of patients who experienced any side effect.

† Figures in parentheses represent percentage to total number of treated patients.

‡ $P < 0.05$ (Fisher's test).

§ $P < 0.01$ (Fisher's test).

MPA: medroxyprogesterone acetate; MS: mepitiostane.

in this study (35%) was similar to that in our previous report,[9] as well. The duration of objective regression seen in patients given MPA was slightly longer than that in patients treated with MS. Statistical analyses of response rates by various stratifications revealed that the rates were not significantly different between the two groups. However, the response rate in bone lesions was higher for MPA than for MS. This finding is similar to results reported in the literature.[13,14]

Both treatments are well-tolerated and have different side effects. Although the discontinuation of MPA due to side effects was necessary in three cases, the side effects disappeared soon after discontinuation of the medication. Laboratory tests revealed no severe change during treatment. Unlike MS, MPA induced leukocytosis, as previously reported by Pannuti *et al.*[5] This phenomenon is considered to be due to the stimulating action of MPA on the bone marrow.[13,15,16] This effect would be useful for asthenic patients with advanced cancer as well as conducive to increases in appetite and weight gain.[4,7,8,12]

This study showed that oral HD-MPA and MS do differ in terms of objective and subjective responses and toxicity.

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