Pergamon

European Journal of Cancer Vol. 30A, No. 7, pp. 959–964, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00+0.00

0959-8049(94)E0083-G

Comparison of Chemotherapy With or Without Medroxyprogesterone Acetate for Advanced or Recurrent Breast Cancer

T. Tominaga, O. Abe, A. Ohshima, H. Hayasaka, J. Uchino, R. Abe, K. Enomoto, M. Izuo, H. Watanabe, O. Takatani, M. Yoshida, K. Sakai, H. Koyama, T. Hattori, T. Senoo, Y. Monden and Y. Nomura

The usefulness of CAF [cyclophosphamide (CPA)/doxorubicin (ADR)/5-fluorouracil (5-FU)]+ medroxyprogesterone acetate (MPA) therapy for advanced/recurrent breast cancer was studied in a randomised trial at 56 institutions. Patients received CAF therapy [CPA: 100 mg, orally, days 1–14; ADR: 30 mg/m^2, intravenously (i.v.), days 1 and 8; 5-FU: 500 mg/m^2, i.v., days 1 and 8) in arm I, or CAF+MPA therapy (CAF+MPA 1200 mg, daily) in arm II. The response rate was significantly higher ($P = 0.041$) in arm II (53.5%, 46/86) than arm I (36.6%, 30/82). The response rate by tumour site was significantly higher for lymph node and bone lesions in arm II. Partial response duration and overall response duration were significantly longer in arm II. Incidences of anorexia and nausea/vomiting were significantly higher in arm I but in arm II, moon face, oedema and vaginal bleeding were significantly higher. Many patients in arm II demonstrated improvement in performance status and weight loss, suggesting a beneficial effect of MPA. The chemoendocrine therapy with CAF+MPA appears to be more beneficial than CAF alone in the treatment of advanced/recurrent breast cancer.

Key words: breast cancer, medroxyprogestone acetate (MPA), CAF therapy
Eur J Cancer, Vol. 30A, No. 7, pp. 959–964, 1994

INTRODUCTION

MEDROXYPROGESTERONE ACETATE (MPA) is a progesterone agent which was first synthesised in 1958. It has been reported to have antioestrogenic, antiandrogenic and antigonadotropic activities [1], and to show antitumour effects against carcinomas of the breast, endometrium and other hormone-dependent tumours [2, 3].

Attention has been paid to the clinical efficacy of MPA against breast cancer since the effect of its high dose administration was first reported by Pannuti and colleagues [4] in the early 1970s. Besides a high response rate, beneficial effects of MPA including moderation of anorexia and other gastrointestinal disorders and improvement in performance status (PS), have been reported [5–7].

As has been reported [8], chemoendocrine therapy with MPA and chemotherapy was more effective than each therapy alone in DMBA-induced mammary tumour in rats; the combined therapy is expected to be clinically useful.

In the present study, we compared the efficacy of the combination of MPA and cyclophosphamide, doxorubicin, 5-fluorouracil (CAF) therapy [9, 10] with CAF therapy alone in advanced or recurrent breast cancer patients.

PATIENTS AND METHODS

Patients

The subjects of the study were 226 patients with advanced or recurrent breast cancer who had not received previous treatment or had failed to respond to previous treatment. They were selected from the patients who visited the 56 participating hospitals across Japan (Appendix) between June 1987 and May 1989.

Correspondence to T. Tominaga at the Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo.
O. Abe is at the St Luke's International Hospital, Tokyo; A. Ohshima is at the Department of Cancer Prevention, The Osaka Cancer Prevention and Detection Center, Osaka; H. Hayasaka is at the 1st Department of Surgery, Sapporo Medical College, Sapporo; J. Uchino is at the 1st Department of Surgery, Hokkaido University School of Medicine, Sapporo; R. Abe is at the 2nd Department of Surgery, Fukushima Medical College, Fukushima; K. Enomoto is at the Department of Surgery, School of Medicine, Keio University, Tokyo; M. Izuo is at the Tokyo Woman's Medical College, Tokyo; H. Watanabe is at the 1st Department of Surgery, St Marianna University School of Medicine, Kawasaki; O. Takatani is at the Sakitama Hospital, Omiya; M. Yoshida is at the Department of Surgery, Aichi Cancer Center, Nagoya; K. Sakai is at the 2nd Department of Surgery, Osaka City University, Medical School, Osaka; H. Koyama is at the Department of Surgery, The Center for Adult Diseases, Osaka; T. Hattori is at the Department of Surgery, Research Institute for Nuclear Medicine and Biology, Hiroshima University, Hiroshima; T. Senoo is at the Center for Adult Diseases, Kurashiki; Y. Monden is at the 2nd Department of Surgery, School of Medicine, The University of Tokushima, Tokushima; and Y. Nomura is at the Department of Breast Surgery, National Kyushu Cancer Center Hospital, Fukuoka, Japan.
Received 22 Oct. 1993; accepted 24 Dec. 1993.

Methods

Treatment schedules. The induction regimens employed were the combination of cyclophosphamide (CPA) plus doxorubicin (ADR) plus 5-fluorouracil (5-FU) (CAF therapy) in arm I, and the same CAF therapy combined with MPA (CAF + MPA therapy) in arm II.

Patients who achieved complete response (CR) or partial response (PR) with either of the induction regimens and stable patients received oral 5-FU in arm I or 5-FU combined with MPA in arm II as a maintenance regimen. The doses and administration schedules for the induction and maintenance regimens are shown in Table 1. The induction regimens were given, in principle, in three cycles of 4 weeks each, and the maintenance regimens were continued as long as possible.

Allocation of patients. The envelope method was employed, and patients were randomly assigned to arm I or arm II.

Assessment of effect. The effect of each therapy was assessed in accordance with the "Standards for Assessment of the Therapeutic Effects in Advanced and Recurrent Breast Cancer Patients" (Japan Breast Cancer Society, 1987) and "Criteria for the Evaluation of the Clinical Effects of Solid Cancer Chemotherapy" (Japan Society for Cancer Therapy, 1986). The durations of response and survival were assessed by a follow-up examination in August 1991. The median follow-up duration was 172.9 weeks (arm I: 176.3 weeks, arm II: 170.1 weeks).

The background factors of the patients, effects and side-effects were statistically compared between therapy groups by the χ^2-test, *t*-test and Mann–Whitney U test, respectively. The generalised Wilcoxon test and log–rank test were employed for comparison of the durations of response and survival, respectively.

RESULTS

Eligibility

Of the 226 patients registered in this study, 27 were ineligible because of insufficient withdrawal duration from previous treatment (18 patients), no assessible lesion (7 patients) or cancers other than breast cancer (2 patients) leaving 199 eligible cases. For 31 of these treatment did not comply with the treatment schedule due to early termination of treatment (16 patients), inappropriate observation of the lesion (8 patients), misallocation to arms (5 patients) or treatment by other therapies (2 patients) and these were defined as incomplete cases. Complete cases in this study, therefore, totalled 168. Evaluation of response rate, durations of response, PS and body weight change was made for complete cases. 27 incomplete cases (but not the 5 patients for misallocation and 2 for other therapies) were added to complete cases in evaluation of response rate and side effects, yielding 192 accessible cases.

Patients' characteristics

Data on the background factors of eligible cases are shown in Table 2. There was no significant difference between arms in relation to age, menopausal status, advanced/recurrent carcinoma, disease-free interval, with/without previous treatment, histology, site of tumour, or the cycle of induction treatment.

Clinical effects

A comparison of response rates for the 168 complete cases is shown in Table 3. The response rate was significantly higher ($P = 0.041$) in arm II (53.5%, 46/86; CR:11, PR:35) than in arm I (36.6%, 30/82; CR:10, PR:20). Response rate for the 192 assessible cases was 47.5% (48/101; CR:11, PR:37) in arm II compared to 33.0% (30/92; CR:10, PR:20) in arm I ($P = 0.057$).

Response rate as a function of the site of tumour was significantly higher in arm II for lymph node (75.0 versus 38.5%, $P = 0.021$) and bone (36.6 versus 10.7%, $P = 0.034$) (Table 4).

Data on the duration of response are shown in Table 5. PR duration (median value) was 33.7 weeks in arm II versus 14.1 weeks in arm I, with a significant prolongation ($P = 0.001$) in arm II. Overall response duration was 44.6 weeks in arm II versus 26.1 weeks in arm I, showing a significant prolongation ($P = 0.023$) in arm II. Duration of CRs were not significantly different ($P = 0.64$).

The duration of 50% survival was 94.8 weeks in arm II and 82.4 weeks in arm I with slight prolongation in arm II, but there was no significant difference between arms ($P = 0.210$) (Figure 1).

Side-effects observed in both arms included alopecia, anorexia, nausea and vomiting, which were thought to be attributable to the CAF therapy. The incidence, however, of anorexia, nausea and vomiting was significantly lower in arm II. Moon-face, oedema and vaginal bleeding, in contrast, occurred at a higher incidence in arm II (Table 6).

Changes in WBC and platelet counts are shown in Figures 2 and 3. WBC count was significantly higher in arm II at 5 weeks and 9 weeks after the treatment started, whereas platelet count was significantly higher in arm II at 3 weeks and 7 weeks after the treatment started.

The effects of the treatments on PS were evaluated by the change in grade before and after treatment, and categorised as improved, unchanged, or deteriorated. Improved cases

Table 1. Treatment schedule

	Induction regimen (one cycle/4 weeks)				Maintenance regimen		
	Drug	Route	Dose	Schedule	Route	Dose	Schedule
Arm I	CPA	p.o.	100 mg	days 1–14			
(CAF)	ADR	i.v.	30 mg/m^2	days 1, 8			
	5-FU	i.v.	500 mg/m^2	days 1, 8	p.o.	200 mg	Daily
Arm II	CPA	p.o.	100 mg	days 1–14			
(CAF+MPA)	ADR	i.v.	30 mg/m^2	days 1, 8			
	5-FU	i.v.	500 mg/m^2	days 1, 8	p.o.	200 mg	Daily
	MPA	p.o.	1200 mg	daily	p.o.	1200 mg	Daily

p.o., oral; i.v., intravenous. CPA, cyclosphosphamide; ADR, doxorubicin; 5-FU, 5-fluorouracil; MPA, medroxyprogesterone acetate; CAF, CPA + ADR + 5FU.

Table 2. Patients' characteristics (eligible cases)

	Arm I	Arm II	Total
Number of patients	96	103	199
Mean age (years)	52.6	53.2	
Menopausal status			
Pre	35	33	68
Peri	11	10	21
Post	43	52	95
Castrated	7	8	15
Advanced/	19	20	39
Recurrent	77	83	160
Disease-free interval (years)			
0	19	20	39
<1	15	22	37
1–2	18	14	32
2–3	12	17	29
3<	32	30	62
Previous treatment			
Yes	54	55	109
No	42	48	90
Histology			
Papillary tubular	15	13	28
Scirrhous	33	32	65
Solid tubular	31	40	71
Others	5	6	11
Unknown	12	12	24
Site			
Breast	10	16	26
Skin and subcutaneous	21	20	41
Lymph node	28	31	59
Lung	24	31	55
Pleura	14	9	23
Liver	14	22	36
Bone	31	44	75
Other	4	1	5
Induction treatment (cycles)			
<1	6	5	11
<2	15	12	27
<3	24	18	42
3≤	51	68	119

accounted for 7.9% of the patients in arm I and 15.6% in arm II, while deteriorated cases accounted for 32.6% in the former and 20.8% in the latter. The data indicate that arm II had a significantly higher percentage of improved cases with fewer deteriorated cases ($P = 0.029$) (Table 7). The incidence of loss of body weight after the treatment was 36.3% in arm II versus 66.7% in arm I, which was a significant difference ($P < 0.001$) (Table 8).

DISCUSSION

Endocrine therapy combined with chemotherapy for advanced or recurrent breast cancer is expected to be more beneficial than either of the therapies alone. There have been reports [11] of an increase in response rate in comparative studies of chemotherapy and chemoendocrine therapy. Our previous study [12] comparing CAF with CAF plus tamoxifen demonstrated a good result for the chemoendocrine regimen in terms of response rate, but it failed to show prolongation of the durations of response and survival.

A synergetic effect has been reported with the combination of 5-FU and MPA in human cell lines and mice, and, in addition, effects to relieve the lethal toxicity, weight loss and myelosuppression induced by 5-FU have been reported [13, 14].

In our present study, the results obtained in the group treated with the MPA plus chemotherapy combination (arm II) were significantly better than the results for the group treated with CAF alone with a response rate of 53.5% in arm II and 36.6% in arm I. The results as a function of the tumour site were significantly better for lymph node and bone lesions in arm II. Particularly noteworthy is that the effect on bone lesions, which had been thought to respond poorly to chemotherapy, was favorably enhanced.

With regard to the duration of response, significantly greater prolongation was obtained in arm II for duration of PR and overall response duration. There has been another report [15] showing the same benefits of MPA with significant increase in response rate and significant prolongation of the duration of response by combination of MPA plus chemotherapy compared with chemotherapy alone.

The duration of survival was longer in arm II, though the difference between arms was not statistically significant. However, it has been reported that the survival in responding patients was significantly prolonged in the group treated with MPA combined with chemotherapy [16]. The result of our study suggests that MPA might play an important role in prolonging the duration of survival, but this should be confirmed by further studies.

Nausea, vomiting and anorexia occurred at a significantly lower incidence and moon face, vaginal bleeding and oedema at a significantly higher incidence in arm II. Both WBC (recovered level) and platelet count (lowest level during the cycle) were significantly higher in arm II, indicating a protective effect of MPA on myelosuppression.

There have been other reports [17, 18] on the effects of the combination of MPA with chemotherapy in alleviating gastrointestinal disorders, such as nausea and vomiting, associ-

Table 3. Response rate for complete cases (n = 168)

	n	CR	PR	NC	PD	CR+PR	(%, 95% CI)	χ^2-test
Arm I	82	10	20	25	27	30	(36.6, 26.2–48.0)	$P = 0.041$*
Arm II	86	11	35	22	18	46	(53.5, 42.1–64.3)	
Total	168	21	55	47	45	76	(45.2, 37.7–52.7)	

*P<0.05. 95% CI: 95% confidence interval; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table 4. Response rate as a function of tumour site

	CR	PR	NC	PD	CR+PR	(% 95% CI)	χ^2-test
Breast							
Arm I	3	3	2	1	6/9	(66.7, 29.9–92.5)	$P=1.000$
Arm II	4	3	2	1	7/10	(70.0, 34.8–93.3)	
Skin and subcutaneous							
Arm I	5	2	5	8	7/20	(35.0, 15.4–59.2)	$P=0.545$
Arm II	4	5	4	5	9/18	(50.0, 26.0–74.0)	
Lymph node							
Arm I	3	7	13	3	10/26	(38.5, 20.2–59.4)	$P=0.021$*
Arm II	12	6	2	4	18/24	(75.0, 53.3–90.2)	
Lung							
Arm I	4	4	6	6	8/20	(40.0, 19.1–64.0)	$P=1.000$
Arm II	5	7	9	7	12/28	(42.9, 24.5–62.8)	
Pleura							
Arm I	0	3	7	3	3/13	(23.1, 5.0–53.8)	$P=0.554$
Arm II	0	4	2	3	4/9	(44.4, 13.7–78.8)	
Liver							
Arm I	1	2	7	4	3/14	(21.4, 4.7–50.8)	$P=0.569$
Arm II	0	7	6	6	7/19	(36.8, 16.3–61.6)	
Bone							
Arm I	0	3	16	9	3/28	(10.7, 2.3–28.2)	$P=0.034$*
Arm II	0	15	21	5	15.41	(36.6, 22.1–53.1)	
Other							
Arm I	1	2	0	1	3/4	(75.0, 19.4–99.4)	$P=0.820$
Arm II	0	0	1	0	0/1	(0.0, 0.0–97.5)	

*$P<0.05$. See Table 3 for abbreviations.

ated with chemotherapy, and in moderating chemotherapy-induced bone marrow suppression, presenting as a decrease in WBC count. Others have reported that MPA combined with chemotherapy allowed the scheduled doses of chemotherapy to be accomplished [19], and the time required for one cycle of chemotherapy to be shortened [20], suggesting that MPA has unique properties which are not available with other hormone agents.

Thrombosis, which had attracted much attention in Japan because of reports of some cases developing this condition, was observed in only 1 patient in our study.

The effect of MPA in improving PS has been compared with that of mepitiostane in a double-blind study by Yoshida and colleages [21] who reported that the PS improvement rate was significantly higher in patients treated with MPA than in those treated with mepitiostane. Increase in body weight reflecting the recovery of appetite has also been reported with MPA [22, 23]. Chemotherapy is sometimes accompanied by the deterioration of PS or loss of body weight, which negatively affects the quality of life of the patient. Addition of MPA to chemotherapy is expected to play an important role in improving the quality of life due to its effects improving the PS and inhibiting loss of body weight.

Our present study on the MPA plus chemotherapy regime demonstrated the following effects of the therapy: (1) an increase

Table 5. Duration of response

	Median (weeks)	Max (weeks)	Min (weeks)	*g*-Wilcoxon test
CR duration				
Arm I	46.1	139	10	$P=0.640$
Arm II	42.0	185	8	
PR duration				
Arm I	14.1	96	4	$P=0.001$†
Arm II	33.7	175	4	
Overall duration				
Arm I	26.1	143	6	$P=0.023$*
Arm II	44.6	199	9	

*$P<0.05$; †$P<0.01$. CR, complete response; PR, partial response.

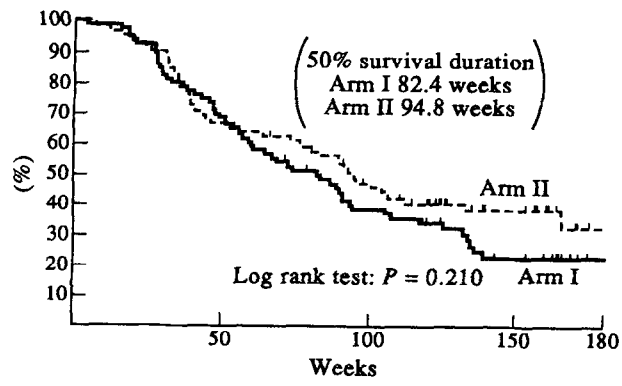

Figure 1. Survival curves (Kaplan–Meier method).

Table 6. Side-effects

	Arm I (%) (n = 91)	Arm II (%) (n = 101)	χ^2-test
Alopecia	66 (72.5)	80 (79.2)	P=0.835
Anorexia	55 (60.4)	45 (44.6)	P=0.040*
Nausea and vomiting	55 (60.4)	40 (39.6)	P=0.006†
Malaise	35 (38.5)	34 (33.7)	P=0.588
Stomatitis	23 (25.3)	21 (20.8)	P=0.571
Fever	21 (23.1)	19 (18.8)	P=0.583
Moon face	3 (3.3)	32 (31.7)	P<0.001†
Oedema	4 (4.4)	15 (14.9)	P=0.029*
Vaginal bleeding	2 (2.2)	14 (13.9)	P=0.008†
Diarrhoea	5 (5.5)	8 (7.9)	P=0.704
Other	10 (11.0)	18 (17.8)	P=0.257

*P<0.05; †P<0.01.

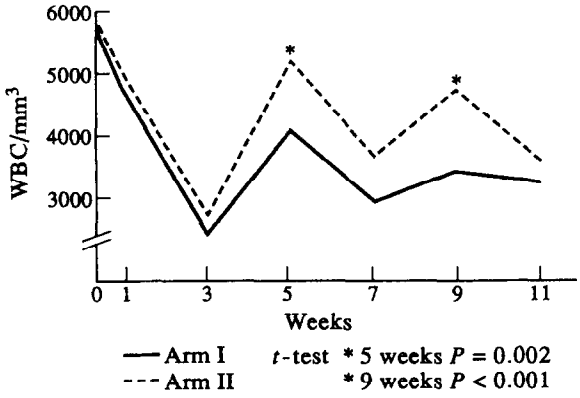

Figure 2. Changes in white blood cell count.

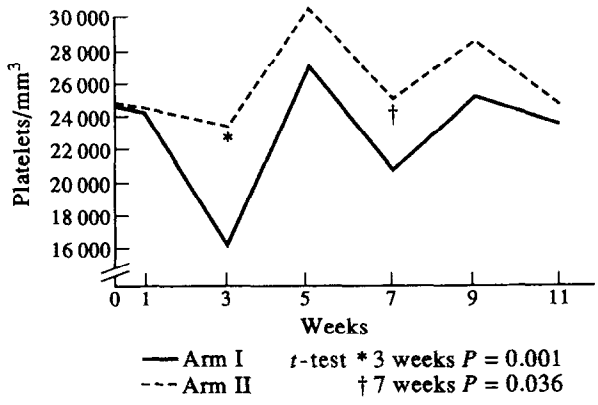

Figure 3. Changes in platelet count.

in response rate (for lymph node and bone lesions, in particular); (2) prolongation of the duration of response (PR duration and overall response duration); (3) moderation of the digestive symptoms and bone marrow suppression induced by CAF therapy; and (4) improvement in the PS and inhibition of loss of body weight.

Based on the above results, MPA combined with CAF therapy is more beneficial than CAF therapy alone in the treatment of advanced or recurrent breast cancer.

Table 7. Changes in performance status

	Arm I (%) (n = 91)	Arm II (%) (n = 101)
Improved	7 (7.9)	15 (15.6)
Unchanged	53 (59.5)	61 (63.5)
Deteriorated	29 (32.6)	20 (20.8)
Not measured	2	5

U-test; P=0.029.

Table 8. Changes in body weight

	Arm I (%) (n = 91)	Arm II (%) (n = 101)
Gain	27 (33.3)	58 (63.7)
Loss	54 (66.7)	33 (36.3)
Not measured	10	10

χ^2-test; P<0.001.

1. Di Marco A. *The Antitumor Activity of 6α-Methyl-17α-acetoxy Progesterone (MPA) in Experimental Mammary Cancer: Role of Medroxyprogesterone in Endocrine-related Tumors*. New York, Raven Press, 1980, 1–20.
2. Nomura Y, Tashiro H, Takaeko F. Effects of antiestrogens and medroxyprogesterone acetate on the clonogenic growth of tamoxifen-sensitive and resistant human breast cancer cells. *Jpn J Cancer Chemother* 1985, **12**, 844–850.
3. Tominaga T, Yoshida Y, Kitamura M. Inhibitory effects of oral administration of medroxyprogesterone acetate and mepitiostane on 7,12-dimethylbenz (a) anthracene-induced rat mammary cancer. *Jpn Pharmacol Ther* 1984, **12**, 3933–3939.
4. Pannuti F, Martoni A, Pollutri E, Camera P, Lenaz GR. Medroxyprogesterone acetate (MPA): effects of massive doses in advanced breast cancer. *IRCS Med Sci* 1974, **2**, 1605.
5. Ganzina F. High-dose medroxyprogesterone acetate (MPA) treatment in advanced breast cancer. A review. *Tumori* 1979, **65**, 563–585.
6. Pannuti F, Fruet F, Cricca A. Pilot trial of the use of massive doses of medroxyprogesterone acetate (MPA) orally in oncology. *IRCS Med Sci* 1977, **5**, 433.
7. Pannuti F, Fruet F, Piana E, Strocchi E, Cricca A. The anabolic effect induced by high doses of medroxyprogesterone acetate (MPA) orally in cancer patients. *IRCS Med Sci* 1978, **6**, 118.
8. Ishikawa H, Iino Y, Izuo M, Takigawa H. Effects of chemoendocrine therapy with medroxyprogesterone acetate (MPA) on growth of DMBA-induced rat mammary tumor. *Jpn J Cancer Clin* 1986, **32**, 151–155.
9. Abe O, Izuo M, Enomoto K, *et al.* Clinical study group of adriamycin for breast cancer in Japan. Combination chemotherapy of cyclophosphamide, adriamycin and 5-fluorouracil (CAF) in advanced and recurrent breast cancer. *Jpn J Cancer Chemother* 1982, **9**, 866–873.
10. Kubo K, Abe O, Izuo M, *et al.* Clinical study group of adriamycin for breast cancer in Japan. Clinical evaluation of adriamycin for advanced breast cancer (No. 3)—A joint study by 26 institutes on the "CAF" and "CMcF" regimens. *Jpn J Cancer Chemother* 1983, **10**, 2523–2531.
11. Nomura Y. Chemo-endocrine therapy for advanced breast cancer. *Jpn J Cancer Chemother* 1988, **15**, 3214–3220.
12. Nomura Y, Abe O, Izuo M, *et al.* Clinical study group of adriamycin for breast cancer in Japan. Clinical evaluation of adriamycin for advanced and recurrent breast cancer (No. 4)—Joint study by 30 institutes on duration of remission using various maintenance therapies in patients treated with CAF. *Jpn J Cancer Chemother* 1988, **15**, 1863–1871.
13. Ishida H, Okabe M, Gomi K, Horiuchi R. Effect of medroxyprogesterone acetate on the anticancer activity of 5-fluorouracil against

human breast and stomach cancer cells. *Jpn J Cancer Chemother* 1993, **20**, 625–630.
14. Ashizawa T, Ishida H, Okabe M, Gomi K. Effect of medroxyprogesterone acetate on antitumor efficacies and side effect of 5-fluorouracil. *Jpn J Cancer Chemother* 1993, **20**, 941–947.
15. Robustelli Della Cuna G, Cuzzoni Q, Preti P, Bernardo G. *Concurrent Hormonal and Cytotoxic Treatment for Advanced Breast Cancer: Role of Medroxyprogesterone in Endocrine-related Tumors*, vol. 2. New York, Raven Press, 1983, 131–140.
16. Robustelli Della Cuna G, Pellegrini A. *Medroxyprogesterone Acetate in Combination with Chemotherapy for Advanced Breast Cancer: Updated Results and Criticisms: Role of Medroxyprogesterone in Endocrine-related Tumors*, vol. 3. New York, Raven Press, 1984, 91–104.
17. Bonsignori M, Rossi G, Sturba F, *et al.* MPA Hematology Italian Cooperative Group. Protective effect of high-dose medroxyprogesterone acetate (HD-MPA) on hematological toxicity induced by chemotherapy for advanced solid tumors: a multicentric controlled clinical trial. *Chemioterapia* 1986, **5**, 134–139.
18. Wils JA. Myeloprotective effect of high dose medroxy-progesterone acetate (MPA). *Chemioterapia* 1988, **7**, 60–62.
19. Focan C, Baudoux A, Beauduin M, *et al.* Adjuvant breast cancer project, Belgium. Improvement of hematological and general tolerance to CMF by high dose Medroxyprogesterone acetate (HD-MPA) adjuvant treatment for primary node positive breast cancer (analysis of 100 patients). *Anticancer Res* 1986, **6**, 1095–1099.
20. Yanagawa Y, Okazaki T, Okamura S, Ueki M, Sugimoto O. Effect of medroxyprogesterone acetate on side effects of CAP therapy for gynecological malignant tumors. *Jpn J Cancer Chemother* 1989, **16**, 2393–2398.
21. Yoshida M, Miura S, Murai H, *et al.* Japanese group for MPA treatment of breast cancer. Clinical evaluation of medroxyprogesterone acetate in advanced breast cancer—a double-blind controlled trial with mepitiostane. *Clin Eval* 1985, **13**, 381–418.
22. Tominaga T, Izuo M, Nomura Y, *et al.* Research group for the MPA treatment of breast cancer (Japan). Oral high-dose medroxyprogesterone acetate (MPA) in the treatment of advanced and recurrent breast cancer: a dose response evaluation. *Jpn J Cancer Chemother* 1982, **9**, 1994–2004.
23. Yoshida M, Murai H, Miura S. Therapeutic effects of medroxyprogesterone acetate in recurrent or advanced breast cancer. *Jpn J Cancer Chemother* 1985, **12**, 516–523.

APPENDIX
56 participating hospitals across Japan:

(1) The First Department of Surgery, Hokkaido University, School of Medicine.
(2) The Second Department of Surgery, Hokkaido University, School of Medicine.
(3) The First Department of Surgery, Sapporo Medical College.
(4) Department of Surgery, Sapporo National Hospital.
(5) The Second Department of Surgery, Tohoku University, School of Medicine.
(6) The Second Department of Surgery, Fukushima Medical College.
(7) The First Department of Surgery, Hirosaki University, School of Medicine.
(8) Department of Surgery, Centre for Adult Diseases, Miyagi.
(9) Department of Surgery, Sendai National Hospital.
(10) Department of Surgery, School of Medicine, Keio University.
(11) The Second Department of Surgery, Jikei University School of Medicine.
(12) The Second Department of Surgery, Tokyo Woman's Medical College.
(13) Department of Surgery, Tokyo Woman's Medical College Daini Hospital.
(14) Department of Surgery, Tokyo Metropolitan Komagome Hospital.
(15) Department of Internal Medicine, National Cancer Centre.
(16) The First Department of Surgery, St Marianna University School of Medicine.
(17) The Third Department of Internal Medicine, National Defense Medical College.
(18) Department of Surgery, Kanagawa Cancer Centre.
(19) Surgery Clinic, Breast Endocrinology Clinic, Saitama Cancer Centre.
(20) The Second Department of Surgery, School of Medicine, Gunma University.
(21) Department of Surgery, Niigata Cancer Centre.
(22) Department of Surgery, Mito Kyodo General Hospital.
(23) Department of Surgery, Gunma Cancer Centre.
(24) Department of Surgery, Takasaki National Hospital.
(25) Department of Surgery, Maebashi Red Cross Hospital.
(26) Department of Surgery, Tochigi Cancer Centre.
(27) The Second Department of Surgery, School of Medicine, Gifu University.
(28) The Second Department of Surgery, Medical School, Nagoya City University.
(29) Department of Surgery, Aichi Cancer Centre.
(30) Department of Surgery, Nagoya National Hospital.
(31) Department of Surgery, Marumo Hospital.
(32) Department of Surgery, Research Institute for Microbial Diseases, Osaka University.
(33) The Second Department of Surgery, Osaka City University, Medical School.
(34) The First Department of Surgery, Kinki University School of Medicine.
(35) Department of Surgery, Osaka Teishin Hospital.
(36) Department of Surgery, Osaka National Hospital.
(37) Department of Surgery, The Center for Adult Diseases, Osaka.
(38) Department of Surgery, Osaka Prefectural General Hospital.
(39) The Second Department of Surgery, Kyoto Prefectural University of Medicine.
(40)) The First Department of Surgery, Nara Medical University.
(41) The First Department of Surgery, School of Medicine, Kanazawa University.
(42) The Second Department of Surgery, Wakayama Red Cross Hospital.
(43) The Second Department of Surgery, School of Medicine, The University of Tokushima.
(44) Department of Surgery, Kagawa Prefectural Central Hospital.
(45) Department of Surgery, Shikoku Cancer Centre.
(46) Department of Surgery, Kochi Municipal Hospital.
(47) Department of Surgery, Research Institute for Nuclear Medicine and Biology, Hiroshima University.
(48) Department of Endocrine Surgery, Kawasaki Medical School.
(49) Department of Surgery, Omoto Hospital.
(50) The Second Department of Surgery, Faculty of Medicine, Kyushu University.
(51) The Second Department of Surgery, Kumamoto University, Medical School.
(52) The First Department of Surgery, Kurume University, School of Medicine.
(53) Department of Breast Surgery, National Kyushu Cancer Centre Hospital.
(54) Department of Surgery, Kitakyushu City Kokura Hospital.
(55) Department of Surgery, Oita Prefectural Oita Hospital.
(56) The First Department of Surgery, Nagasaki University, School of Medicine.