Europ. J. Cancer Vol. 15, pp. 593–601.

0014–2964/79/0401–0593 $02.00/0

Prospective, Randomized Clinical Trial of Two Different High Dosages of Medroxyprogesterone Acetate (MAP) in the Treatment of Metastatic Breast Cancer

F. PANNUTI,* A. MARTONI,* A. R. DI MARCO,* E. PIANA,* F. SACCANI,† G. BECCHI,† G. MATTIOLI,‡ F. BARBANTI,‡ G. A. MARRA,‡ W. PERSIANI,‡ L. CACCIARI,§ F. SPAGNOLO,§ D. PALENZONA¶ and G. ROCCHETTA¶

*Divisione di Oncologia, Ospedale M. Malpighi, Bologna, Italy
†Servizio di Oncologia, Arcispedale S. Maria Nuova, Reggio Emilia, Italy
‡Divisione di Chirurgia generale, Ospedale Morgagni Pierantoni, Forli, Italy
§Sezione di Chemioterapia Oncologica, Ospedale Bellaria- San Camillo, Bologna, Italy
¶Istituto di Genetica, Università degli Studi, Bologna, Italy

Abstract—*We have demonstrated the possibility of administering MAP (i.m.) at much higher doses than was ever previously employed. Daily dosage of* 1500 mg *i.m. of MAP for* 30 *consecutive* days *was an effective* (44% *CR+PR) and well tolerated treatment for advanced breast cancer. The aim of the present prospective and randomized study was to compare the above regimen with a daily dose of* 500 mg *i.m. for* 30 days *in postmenopausal women with metastatic breast cancer. A hundred patients were admitted to the study and* 46 *in each group were evaluable; the groups were similar for age, duration of the disease, time from menopause, performance status, dominant metastatic lesion and previous therapy,* 21/46 (45.7%) *patients in the* 1500 *group and* 20/46 (43.5%) *patients in the* 500 *group showed major objective responses (CR+PR). The incidence of minimal response, no change and progression was* 13, 15.2 *and* 26.1% *respectively in the* 1500 mg *group and* 2.2, 15.2 *and* 39.1% *in the* 500 mg *group. When all kinds of responses as well as the incidence of progression are taken into consideration the activity of the* 1500 mg *regimen was significantly superior. Bone metastasis gave the best response in both groups* (65 *and* 56% *respectively). Mean remission duration for CR+PR was* 6+ *months in both groups.*

Tolerance was good in both groups; a significantly higher incidence of cramps (19%) *and fine tremors* (19%) *was observed in the* 1500 *group but these symptoms disappeared rapidly a few days after the end of treatment. No myelosuppression was observed; on the contrary WBC increased significantly in both groups. A marked improvement of subjective symptoms was seen with both regimens; pain disappeared in* 85% *of patients treated with* 1500 mg *and* 75% *of those treated with* 500 mg.

INTRODUCTION

THE SYNTHETIC progestins employed in the treatment of advanced breast cancer are able to induce median objective remission rates of about 24%. Medroxyprogesterone acetate (MAP) when used at daily low doses (<500 mg/day) induced median objective remission rates of about 13% (Table 1).

In 1973 a few of us [36] showed that, in oncology, it was possible to employ higher daily doses of medroxyprogesterone acetate (MAP) than those that had been previously used (generally less than 500 mg/day i.m.): the maximum tolerable dose (MTD) for MAP given i.m. was found to be 1500 mg/day for 30 days. Subsequently we treated 54 patients suffering from advanced breast cancer with MAP at MTD and obtained a 44% objective remission rate.

Moreover, being in a position to use a more concentrated MAP preparation (F.I. 7401: 200 mg/ml), we were able to treat a further group of 25 patients of the same kind with a daily dose of 200 mg/day i.m. for 30 days and obtained a 45% objective remission rate [37].

The present randomized study, made in cooperation with a number of other Institutes,

Accepted 14 September 1978.

Table 1. Progestin therapy in advanced breast cancer

Drug	No. pts.	Objective response No.	%	References
Progesterone	46	2	5	[1, 2]
Medroxyprogesterone acetate (<500 mg/day)	257	33	13	[3–9]
17-α-Hydroxyprogesterone caproate	62	6	10	[10, 11]
9-α-Bromo-11-β-ketoprogesterone	99	22	19	[12–14]
17-α-Ethynil-19 nortestosterone acetate	451	155	34	[3, 15–23]
Other 19-nortestosterone derivatives	524	118	23	[3, 24–30]
Other progestins	204	55	27	[5, 31–35]
Total	1643	391	24	

has been designed to compare the effects of two different high MAP dosages in the treatment of advanced breast cancer.

MATERIALS AND METHODS

The clinical data referring to the 100 patients treated, who were all in a postmenopausal stage, are shown in Table 2.

Fifty patients at random were put on the A regimen: MAP/1500 (1500 mg of MAP* given i.m.—this dose being split in two halves each given at 12 hr intervals for 30 days) and 50 patients on the B regimen: MAP/500 (500 mg of MAP* i.m.—this dose being split in two halves each given at 12 hr intervals for 30 days).

The duration of the treatment was limited to 1 month:

(1) since after this period the injection area displays intolerance, making it no longer possible to give treatment in the majority of cases and (2) in order to assess possible long-term toxic effects. Patients receiving a total dose of at least 15 g were evaluated for remission.

Evaluation of remission was performed within 6 months from the beginning of the treatment. The evaluation criteria adopted [38] were as follows:

CR—complete disappearance of all lesions for at least 6 months; PR—a reduction superior to 50% in the surface area of all measurable lesions and thickening or no change in osseous lesions for at least 3 months together with remission of pain; MR—a decrease in the surface area of all measurable lesions ranging between 25 and 50% and CR or PR of some lesions with no change in the remainder for at least 1 month; NC—no appreciable change or <25% decrease in measurable lesions, progression (P)—a 25% increase in at least one measurable lesion, occurrence of new lesions or progression of osteolytic metastases; relapse—appearance of new lesions or 25% increase in surface area of all measurable lesions following a period of remission or NC.

The criteria for patient eligibility: histologic diagnosis of advanced breast carcinoma; at least one month free of oncological treatment and no MAP treatment at all; prognosis exceeding two months; age less than 75; normal renal and hepatic function; progressive disease before start of treatment.

Patients with liver metastases or solely pleural effusion were excluded. Before randomizing, patients were stratified according to: (1) time elapsed since menopause: (a) 1–5 yr, (b) over 5 yr; and (2) the site of the dominant lesion: (a) soft tissue (ST), (b) bone (O) and (c) viscera (V). The number of patients falling into the various stratification categories were similar in both regimens (Table 2). Nevertheless, there are some differences between the two groups of patients: 4.5 yr for the median age, 5 months for the free interval. There is also a little difference in previous endocrine therapies (16 vs 22 patients). The comparison index (C.I. = ratio of the number of patients with dominant visceral lesions and total number of patients with dominant soft tissue and bone lesions) was essentially equal being slightly higher in the MAP/1500 group; patients in this group with dominant visceral lesions (which are known to

*Farlutal ® 500, 1000 (Farmitalia); 200 mg/ml vials.

Table 2. Data on treated patients

	MAP/1500		MAP/500	
	Median	Range	Median	Range
Age (yr)	58.5	24–75	63.00	34–75
Free interval (months)	21.00	0–222	16.00	0–144
Interval between first diagnosis and the hormonotherapy (months)	32.00	1–300	25.00	2–152
Time from menopause (months)	124.00	2–360	156.00	9–348
Karnofsky index (%)	60.00	40–100	70.00	40–100
Total dose (g)	45.00	18–65	15.00	6.5–15
Days of treatment	30.00	12–40	30.00	10–35
No. pts randomized	50.00		50.00	
No. pts evaluable	46.00		46.00	
Time from menopause:				
1–5 yr	15.00		12.00	
>5 yr	31.00		34.00	
Dominant metastatic lesion:				
Soft tissue (ST)	10.00		10.00	
Osseous (O)	23.00		25.00	
Visceral (V)	13.00		11.00	
*Comparative index: $CI = \frac{V}{ST+O}$	0.39		0.31	
No. of sites involved				
1	27.00		27.00	
2	12.00		13.00	
3 or more	7.00		6.00	
Previous treatments:				
Mastectomy	44.00		42.00	
Radiotherapy	31.00		28.00	
Oophorectomy	12.00		10.00	
Androgens	4.00		9.00	
Progestagens	0.00		2.00	
Estrogens	0.00		1.00	
Chemotherapy	5.00		13.00	

*See text.

be poorly sensitive to hormone therapy) were 13 against 11 in the MAP/500 group.

All other therapy was omitted during and after MAP treatment to avoid possible anti-tumour effects and/or possible drug interference.

The statistical comparison between the series of all results of both regimens was carried out using the χ^2 test and Student's t-test.

All the radiological data was assessed by a group of four radiologists from non-participating hospitals.

The treatment protocol followed in this randomized and prospective trial was deposited at the Information Office of UICC in Paris (Prot. UICC 75–09) in 1975.

RESULTS

Eight patients were not assessed: 6 due to protocol deviations (3 for MAP/1500 and 3 for MAP/500), 1 did not turn up for monthly control after treatment (MAP/500) and finally 1 due to death after 5 days of treatment with MAP/1500 (acute pulmonary heart: autopsy could not be carried out).

The results are shown in Table 3; 21/46 (45.6%) patients in MAP/1500 group and 20/46 (43.5%) patients in MAP/500 group showed CR + PR. The response rate increases to 58.6% for the MAP/1500 and to 45.7% for the MAP/500 group if MR is also considered. Moreover it reaches 73.8 and 60.9% respectively if patients with NC are also considered. Average duration of CR + PR is 6+ months (range 3+ to 25+) in MAP/150 regimen and 6+ months (range 3+ to 33) in MAP/500 regimen; for CR + PR + MR average duration was 6+ months for both regimens (respective ranges: 3+to25+; 3+to33). The average duration of NC was respectively 5+ months (range 1–11) and 4+ months (range 1–9).

The statistical comparison of the different response kinds shows a significant difference between the two treatments: this difference, which favours MAP/1500 group, is evident

Table 3. Response to therapy

	MAP/1500*			MAP/500*		
CR	0/46 (—)	45.6%	58.6%	1/46 (2.2%)	43.5%	45.7%
PR	21/46 (45.6%)			19/46 (41.3%)		
MR	6/46 (13%)		73.8%	1/46 (2.2%)		60.9%
NC	7/46 (15.2%)			7/46 (15.2%)		
P	12/46 (26.1%)			18/46 (39.1%)		

*Statistical comparison between the two treatments showed significant differences ($\chi^2_{(1)}=4.74$; $P<0.05$) at MR and P level.

when values of MR and P are considered jointly according the the modalities of the χ^2 test.

In Table 4 the results are analyzed in relation to the menopausal status, the dominant metastatic lesion, the number of sites involved, the free interval and the time elapsed from the beginning of disease up to the present treatment. The value of these parameters does not have a statistically significant effect on the comparison between the two regimens.

Also confirmed in this trial is the lower remission rate following hormone therapy in patients with visceral metastases compared to patients with other metastatic sites. The above can be seen in greater detail in Table 5. The MAP/1500 regimen showed higher remission rates in lymph-node, skin, osseous and pleural lesions. However, these differences between the two regimens were not statistically significant.

Figures 1 and 2 show the survival curves of the two groups. In the first general figure, a significant difference is seen only at 3 months after point by point comparison (at 3, 6, 12, 24 and 36 months) according to the χ^2 test.

It should be noted that the curve related to patients treated with MAP/1500 is constantly better than that of the group treated with MAP/500. Figure 2 shows survival curves in more analytic form and for each group in-

Table 4. CR+PR/total pts according to the time from menopause, dominant metastatic lesion, No. of sites involved, free interval and length of disease

	MAP/1500*	MAP/500*
Time from menopause:		
1–5 yr	7/15 (47%)	6/12 (50%)
>5 yr	14/31 (45%)	14/34 (41%)
Dominant metastatic lesion:		
ST	3/9 (33%)	3/10 (30%)
O	15/23 (65%)	14/25 (56%)
V	3/14 (21%)	3/11 (27%)
No. of sites involved:		
1	13/27 (48%)	15/27 (55%)
2	5/12 (42%)	2/13 (23%)
3 or more	3/7 (43%)	3/6 (50%)
Free interval:		
0	2/3 (67%)	2/5 (40%)
0–2 yr	10/21 (48%)	8/24 (33%)
>2 yr	9/22 (41%)	10/17 (59%)
Length of disease:		
0–2 yr	9/19 (47%)	9/19 (47%)
2–5 yr	7/14 (50%)	8/19 (42%)
>5 yr	5/13 (39%)	3/8 (38%)

*No significant difference between the two treatments (χ^2).

Table 5. CR+PR/total pts according to site of lesion

	MAP/1500*	MAP/500*
Primary tumour	—	0/2 (—)
LFG	5/8 (63%)	3/10 (30%)
Skin	10/15 (67%)	3/15 (20%)
Bones	19/29 (66%)	17/29 (59%)
Lung	1/10 (10%)	3/10 (30%)
Pleura	4/7 (57%)	1/5 (20%)

*No significant difference between the two treatments (χ^2).

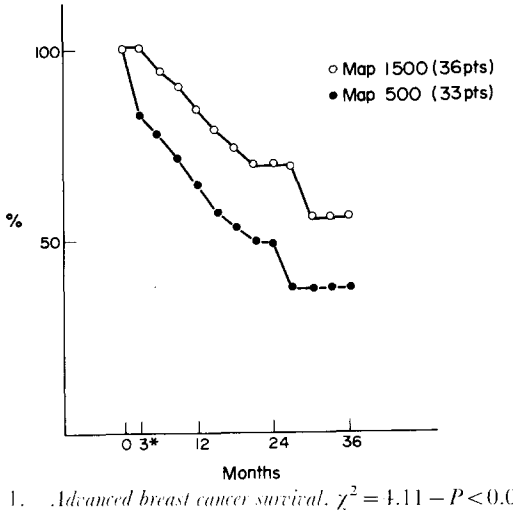

Fig. 1. Advanced breast cancer survival. $\chi^2 = 4.11 - P < 0.05$.

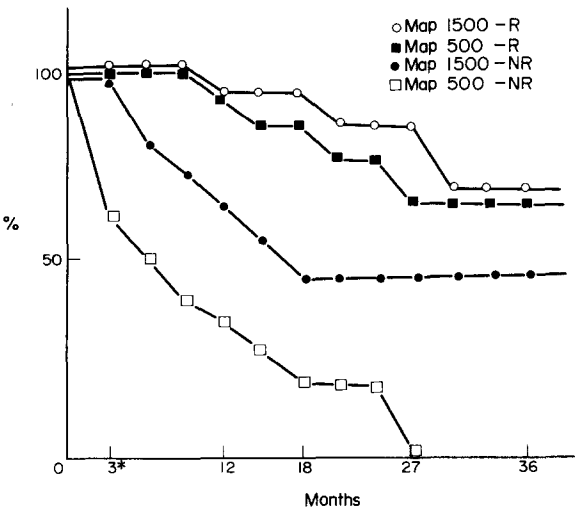

Fig. 2. Advanced breast cancer survival.
MAP 1500 R = MAP 1500 responders (CR+PR→MR) pts 19.
MAP 1500 NR = MAP 1500 non-responders (NC+P) pts 17.
MAP 500 R = MAP 500 responders (CR+PR+MR) pts 21.
MAP 500 NR = MAP 500 non-responders (NC+P) pts 12.
** = Significant difference between the MAP 1500 NR and MAP 500 NR groups* ($\chi^2 = 0.025 - P < 0.05$).

A significant difference does exist ($P < 0.05$) at 3 months between non-responders of the two groups (MAP/1500 regimen has a better survival rate than MAP/500).

In Table 6 the subjective remissions of more important symptoms are given: upon

Table 6. Symptoms of remission (No. of remissions/total pts affected)

	MAP/1500*	MAP/500*
Pain	22/26 (85%)	21/28 (75%)
Dyspnoea	6/9 (67%)	3/6 (50%)
Asthenia	18/25 (72%)	16/24 (67%)
Anorexia	10/10 (100%)	13/16 (81%)
Walking impairment	7/10 (70%)	5/12 (42%)

*No significant difference between the two treatments (χ^2).

dicating the survival of responders (complete response, CR; partial response, PR; minimal response, MR) and of non-responders (no change, NC; progression, P). Statistical point by point comparison (at 3, 12, 18, 27 and 36 months) according to the χ^2 test does not reveal significant differences between responders belonging to the group treated with MAP/1500 and those treated with MAP/500.

In both groups responders (CR, PR, MR) have a better survival rate than non-responders (NC, P). Such difference is statistically significant only at 12, 18 and 27 months. statistical comparison the differences between the two regimens are not significant; it should however be stressed that remission rates are constantly higher for the MAP/1500 regimen. The same considerations apply to the series of pain remission rates during the 4 weeks of treatment (Table 7).

This trial also confirms the finding, which is specific for MAP, that pain from metastatic lesions is promptly relieved in a high number of patients.

Clinical tolerance (Table 8) is qualitatively similar in both groups of patients. There is a

Table 7. Behaviour of pain during the treatment. (No. pts with remission/total pts affected)

	1	2	3	4 (weeks)
MAP/1500*	8/20 (40%)	12/20 (60%)	14/20 (70%)	16/20 (80%)
MAP/500*	6/21 (29%)	8/21 (38%)	10/21 (48%)	15/21 (71%)

*No significant difference between the two treatments (χ^2).

Table 8. Toxicology: side effects

	MAP/1500	MAP/500
Gluteal abscess	7/46 (15%)	1/46 (2%)
Gluteal infiltration	3/46 (6%)	4/46 (9%)
Facies lunaris	5/46 (11%)	2/46 (4%)
Sweating	3/46 (6%)	1/46 (2%)
Fine tremors*	9/46 (19%)	1/46 (2%)
Vaginal spotting	3/46 (6%)	0/46 (—)
Thrombophlebitis	0/46 (—)	0/46 (—)
Cramps*	9/46 (19%)	1/46 (2%)

*Significant difference between the two treatments. ($\chi^2 = 5.66$; $P < 0.025$).

greater incidence of local and systemic clinical side-effects in the MAP/1500 regimen, and this takes on statistical significance for fine tremors and cramps. All the symptoms observed were found to be totally reversible in both groups within 40–50 days following the end of treatment.

The chemical and hematochemical tests that underwent statistically significant changes are given in Table 9 the other tests carried out (RBC, hemoglobin, alkaline phosphatase, SGOT, SGPT, calcium, phosphorus, sodium plasma levels) did not undergo statistically significant changes after treatment. The information given above does not differ from that shown in other groups of patients of the same kind treated with high doses of MAP [36–38].

DISCUSSION

This trial confirms, as previously reported [37, 38], the objective and subjective remission rates and the particular anti-pain effect of MAP administered in high doses to patients with metastatic breast cancer.

Comparison between the two high dose MAP regimens shows a greater statistically significant incidence of MR, a better overall survival rate and a higher remission rate, not statistically significant, for all symptoms considered, in the MAP/1500 regimen.

As for clinical tolerance a higher (statistically significant) occurrence of cramps and fine tremors was found at the higher MAP dosage. The above regimen also induces a

Table 9. Toxicology: blood data

	MAP/1500			MAP/500		
	$\bar{X}$ before	$\bar{X}$ after	P	$\bar{X}$ before	$\bar{X}$ after	P
WBC	6.54	7.95	$P<0.05$	6.50	7.61	$P<0.01$
Platelets	236.00	289.00	$P<0.01$	212.15	264.16	
Bilirubin	0.60	0.47	$P<0.05$	0.61	0.58	
BUN	17.22	18.48		19.82	17.41	$P<0.05$
Creatinine	0.92	0.93		0.83	0.91	$P<0.05$
Uric acid	4.89	4.37	$P<0.05$	4.71	4.72	
Glucose	86.93	75.50	$P<0.01$	94.03	82.87	
Total protein	6.96	6.97		6.83	7.20	$P<0.01$
K*	4.43	4.77	$P<0.05$	4.08	4.30	

*Significant difference ($t = 2.56$; $P<0.05$) between the two treatments.

greater, though not statistically significant, incidence of gluteal abscesses. It should be noted that this treatment regimen had induced, during the first studies some of us carried out [36, 37], an even higher incidence of gluteal abscesses. The availability of a more concentrated drug, and most of all, a better knowledge of the problem will allow us, as has been seen in our most recent experience, to reduce the incidence of this side-effect.

In any case the side-effects observed are reversible in time and do not exclude the possibility of passing on to chemotherapy in the event of progression of the disease. As for the mechanism of action, the results obtained with MAP lead us to believe that the response is not only mediated through hormonal receptors (which probably saturate at lower levels), but also by the drug's own capacity to "interfere" at various levels: directly (externally to the receptors mechanism) at cell-level or indirectly at the level of other endocrinous glands (adrenals, ovaries and hypophysis) and perhaps at an immune level.

In conclusion there are very small differences between the two regimens. Nevertheless taking into account that objectiveness, subjectiveness and survival were superior in MAP/1500 group, today we prefer to treat out patients with the higher dosage. The only disadvantage with this dosage was a higher incidence of side-effects, but as described before [38] all these side-effects are reversible.

Finally, this polycentric study on the one hand confirms our previous results, and on the other bears out the importance that high doses of MAP (daily doses exceeding 500 mg/i.m.) have in the treatment, strategy for this kind of patient. High doses of MAP are an alternative to traditional hormonal manipulation and are perhaps to be preferred as a first choice to polychemotherapy which on the average is capable of inducing 50% remission rates [39].

To this date, local intolerance is the only factor that limits treatment with MAT/1500.

It is our opinion that the difficulties stemming from insufficient local tolerance can be perhaps overcome by taking into account the experience of some of us [40, 41] who found that it was possible to use massive doses of MAP in oncology orally (2000 mg/day for 30 days) without the appearance of notable side-effects. How far oral administration of high doses of MAP may be useful in patients suffering from advanced breast cancer is open to debate and this is a problem we were currently examining.

Acknowledgements—We are grateful to Prof. C. Praga and Dott. F. Tilaro for much helpful advice and criticism in the preparation of the manuscript. We should also like to thank Prof. G. Sanna, Dott. N. Monetti. Dott. P. Morselli and Dott. G. A. Turci for having assessed the radiological data.

REFERENCES

1. D. Gordon, Hormonal therapy in cancer of breast. III. Effect of progesterone on clinical course and hormonal excretion. *Cancer (Philad.)* **5,** 275 (1962).
2. H. Volk, G. C. Escher, R. A. Huseby, F. H. Tyler and T. Cheda, Hormonal therapy in carcinoma of the breast. *Cancer (Philad.)* **13,** 757 (1960).
3. Co-operative Breast Cancer Group, Progress report: results of studies by the Co-operative Breast Cancer Group: 1956–1960. *Cancer Chemother. Rep.* **11,** 109 (1961).
4. Co-operative Breast Cancer Group, Progress report: results of studies of the Co-operative Breast Cancer Group: 1961–1963. *Cancer Chemother. Rep.* **41,** (Suppl. 1) 1 (1964).
5. B. A. Stoll, Progestin therapy of breast cancer: comparison of agents. *Brit. med. J.* **3,** 338 (1967).
6. A. Segaloff, M. Cuningham, B. F. Rice and J. B. Weeth, Hormonal therapy in cancer of the breast. XXIV. Effect of corticosterone and medroxyprogesterone acetate on clinical course and hormonal excretion. *Cancer (Philad.)* **20,** 1673 (1967).
7. M. F. Muggia, P. A. Cassileth, M. Ochoa, Jr., F. A. Flatow, A. Gellhorn and G. A. Hyman, Treatment of breast cancer with medroxyprogesterone acetate. *Ann. intern. Med.* **68,** 328 (1968).
8. I. S. Goldenberg, Clinical trial of Δ^1 testololactone (NSC-23759), medroxyprogesterone acetate (NSC-26386) and oxylone acetate (NSC-47438) in advanced female mammary cancer. A report of the Co-operative Breast Cancer Group. *Cancer (Philad.)* **23,** 109 (1969).

9. D. J. Klaassen, E. F. Rapp and W. E. Hirte, Response to medroxyprogesterone acetate (NSC-26386) as secundary hormone therapy for metastatic breast cancer in postmenopausal women. *Cancer Treat. Rep.* **60,** 251 (1976).
10. L. G. Crowley and I. MacDonald, Clinical trial of delalutin in the treatment of advanced mammary carcinoma in postmenopausal women. *Cancer (Philad.)* **15,** 1218 (1962).
11. V. Jones, M. M. Roberts, C. A. F. Joslin, E. N. Gleave, R. E. Jones, H. Campbell, D. K. L. Davies and A. P. M. Forrest, Progestagens and advanced breast cancer.*Lancet* **i,** 1049 (1971).
12. I. S. Goldenberg, M. A. Hayes, Hormonal therapy of metastatic female breast carcinoma. I. 9-α-bromo- 11-β-ketoprogesterone. *Cancer (Philad.)* **12,** 738 (1959).
13. U. Jonsson, J. Colsky, H. E. Lessner, O. S. Roath, R. G. Alper and R. Jones, Jr., Clinical and pharmacological observations of the effects of 9-α-bromo- 11-β-ketoprogesterone in patients with carcinoma of the breast. *Cancer (Philad.)* **12,** 509 (1959).
14. J. Colsky, B. Shnider, R. Jones, Jr., H. B. Kevinny-Stickel, T. Hall, W. Regelson, O. S. Selawry, A. Owens, Jr., C. O. Brindley, E. Frey III and Y. Uzer, A comparative study of 9-α-bromo- 11-β-ketoprogesterone and prednisolone in the treatment of advanced carcinoma of the female breast. *Cancer (Philad.)* **16,** 502 (1963).
15. S. Curwen, Use of norethisterone acetate (SH 420 Schering A. G. Berlin) in treatment of advanced carcinoma of the breast. *J. Endocr.* **28,** 3 (1964).
16. B. A. Stoll, Therapy by progestational agents in advanced breast cancer. *Med. J. Aust.* **53,** I, 331 (1966).
17. G. Notter and H. Wicklund, Treatment of inoperable and metastasizing carcinoma of the breast with progestogen hormones. *Münch. med. Wschr.* **49,** 2602 (1967).
18. S. Curwen, The value of norethisterone acetate SH/420 in the treatment of advanced carcinoma of the breast. *Acta endocr. (Khb.)* **61,** (suppl. 138), 233 (1969).
19. A. Gorins and A. Netter, L'apport des norsteroides dans le traitement des cancers du sein en phase avancée. *Presse méd.* **77,** 817 (1969).
20. M. T. Guerin and R. A. Guerin, Emploi des progestatifs dans le traitement des stades avancée des carcinomes mammaires et gynécologiques. *Sem. Hôp.* Paris **45,** 3241 (1969).
21. J. C. Petit, Hormone treatment of breast cancer. *Méd et Hyg. (Genève)* **30,** 1183 (1972).
22. G. A. Edelstyn, Norethisterone acetate (SH_{420}) in advanced breast cancer. *Cancer (Philad.)* **32,** 1317 (1973).
23. R. D. Rubens, Norethisterone acetate in treatment of advanced breast cancer. *Europ. J. Cancer* **12,** 563 (1976).
24. A. Segaloff, C. Y. Bowers, E. L. Rongone and P. J. Murison, Hormonal therapy in cancer of the breast. XVI. The effect of 19-nortestosterone propionate therapy on clinical course and hormonal excretion. *Cancer (Philad.)* **12,** 735 (1959).
25. W. Baker and R. Kelley, In *Biological activities of Steroids in Relation to Cancer.* (Edited by G. Pincus and E. P. Vollmer) p. 427. Academic Press, New York (1960).
26. S. di Pietro, Sperimentazione clinica del 4-idrossi- 17-α-metil-19-nortestosterone nel carcinoma mammario diffuso. *Tumori* **50,** 445 (1964).
27. A. Segaloff, J. B. Weeth, M. Cuningham and K. K. Meyer, Hormonal therapy in cancer of the breast. XXIII. Effect of 7-α-methyl-19-nortestosterone acetate and testosterone propionate on clinical course and hormonal excretion. *Cancer (Philad.)* **17,** 1248 (1964).
28. Societa' Italiana di Cancerologia. Gruppo di Studio per la Terapia del Cancro Mammario del Comitato per la Chemioterapia dei Tumori, Confronto tra i risultati ottenuti con terapia androgena e terapia con androgeni e citostatici nel carcinoma mammario avanzato. *Tumori* **54,** 333 (1968).
29. J. H. Soutoul, B. Agabrielle and J. Bertrand, Bilan des resultats cliniques du traitement de 145 cancers génitaux fémins par le diacetate d'éthynodiol (8080CB) à doses élévées et prolongées. *Rev. franç. Gynéc.* **66,** 705 (1971).

30. R. W. Talley, A dose–response evaluation of androgens in the treatment of metastatic breast cancer. *Cancer (Philad.)* **32,** 315 (1973).
31. B. J. Kennedy and J. W. Yarbro, Effect of methenolone enanthate (NSC-64967) in advanced cancer of the breast. *Cancer (Philad.)* **21,** 197 (1968).
32. A. Halden, Antitumor efficiency and toxicity of methyletinolone (NSC-92858) in advanced breast cancer. *Cancer Chemother. Rep.* **54,** 453 (1970).
33. D. L. Ahmann, R. G. Hahn and H. F. Bisel, Disseminated breast: evaluation of hormonal therapy utilizing stilbestrol and medrogestone (AY-62022) single and in combination. *Cancer (Philad.)* **30,** 651 (1972).
34. F. J. Ansfield, H. L. Davis, R. A. Ellerby, G. Ramirez, A clinical trial of megestrol acetate in advanced breast cancer. *Cancer (Philad.)* **33,** 907 (1974).
35. F. J. Ansfield, H. L. Davis, G. Ramirez, T. E. Davis, E. C. Borden, R. O. Johnson and G. T. Bryan, Further clinical studies with megestrol acetate in advanced breast cancer. *Cancer (Philad.)* **38,** 53 (1976).
36. F. Pannuti, A. Martoni, E. Pollutri, P. Camera, F. Losinno and H. Giusti, Massive dose progestational therapy in oncology (medroxyprogesterone). Preliminary results. *Panminerva med.* **18,** 129 (1976).
37. F. Pannuti, A. Martoni, G. R. Lenaz, E. Piana and P. Nanni, Management of advanced breast cancer with medroxyprogesterone acetate (MAP, F.I. 7401, NSC-26 386) in high doses. In *Functional Explorations in Senology.* (Edited by C. Colin, P. Franchimont and W. Gordenne) p. 253. European Press, Ghent (1976).
38. F. Pannuti, A. Martoni, G. R. Lenaz, E. Piana and P. Nanni, A possible new approach to the treatment of metastatic breast cancer: massive doses of medroxyprogesterone acetate (MAP). *Cancer Treat. Rep.* **62,** 499 (1978).
39. S. K. Carter, Integration of chemotherapy into combined modality treatment of solid tumors. IV. Adenocarcinoma of the breast. *Cancer Treat. Rev.* **3,** 141 (1976).
40. F. Pannuti, F. Fruet and A. Cricca, Pilot trial of the use of massive doses of medroxyprogesterone acetate (MAP) orally in oncology. *IRCS med. Sci.* **5,** 433 (1977).
41. F. Pannuti, F. Fruet, E. Piana and E. Strocchi, The anabolic effect induced by high doses of medroxyprogesterone acetate (MAP) orally in oncology. *IRCS med. Sci.* **6,** 118 (1978).