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Sequential Combination of Tamoxifen and High Dose Medroxyprogesterone Acetate: Therapeutic and Endocrine Effects in Postmenopausal Advanced Breast Cancer Patients

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Abstract—*A sequential combination of tamoxifen and medroxyprogesterone acetate has been evaluated in 42 postmenopausal untreated patients with metastatic breast cancer.*

Patients received tamoxifen 10 mg b.i.d., days 1–14, followed by medroxyprogesterone acetate 500 mg b.i.d., days 15–28, orally in an alternating sequence until progression.

Twenty-two out of 40 evaluable patients showed an objective response to treatment (55%, 95% confidence limits 38–75%). A significantly higher response rate was observed in patients with age ≥ 70 years, with soft tissue dominant lesions and with only one metastatic site. Median time to progression was 41 weeks and the median survival time 88 weeks.

In 4 cases treatment was discontinued because of severe toxicity while in the remaining patients no toxicity (20 patients) or mild side effects (17 patients) have been observed.

After 2 months of therapy, this combination showed a progestogenic effect on the endocrine parameters inducing a significant decrease of SHBG, gonadotropins, testosterone and cortisol. These preliminary clinical results and the moderate toxicity of the sequential combination support the need to further investigate this approach.

INTRODUCTION

THE PALLIATIVE management of metastatic breast cancer has been better defined in recent years. Chemotherapeutic and hormonal modalities produce an objective disease remission in 50–70% [1, 2] and in 25–35% of unselected patients [3–5], respectively. The median response duration, usually not exceeding 10–15 months, and the low complete response rate (less than 20%) with either chemo- or hormonotherapy, explain the small number of long-term survivors.

The apparent plateau in efficacy of cytotoxic chemotherapy, the possibility of recognizing endocrine-dependent tumours according to biochemical, biological and clinical characteristics and the lower morbidity of additive hormonal therapy have increased the interest in endocrine treatments.

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Among the several agents currently used, tamoxifen (TAM) is generally preferred as initial treatment because it is at least as effective as the other procedures with lower side-effects [6–9].

Medroxyprogesterone acetate (MPA) has been demonstrated to be effective against breast cancer. Early experiences with low doses (40–250 mg/day) produced an objective response rate of 25%, which increased to 40% and more with higher dosage (≥ 1000 mg/day) [10–12]. This dose-dependent response rate suggests that MPA may act with several mechanisms.

The superior activity of high dosages seems to be related to the favourable pharmacokinetics and to the complete suppression of the ACTH-dependent adrenal steroid secretion achievable only with high-dose therapy [13, 14].

The use of a sequential TAM–MPA combination therapy in breast cancer is currently under evaluation.

As observed by Iacobelli *et al.* [15] in CG-5 human breast cancer cell line, the sequential combi-

nation showed a stronger inhibition of the cell growth than each agent alone. Also Boccardo *et al.* reported a therapeutic synergism of sequential administration of TAM and MPA in DMBA-induced rat mammary carcinoma [16]. Moreover the *in vitro* and *in vivo* observation of a temporary progesterone receptor synthesis induced by low doses and by a short period of administration of TAM [17–19] suggests the possibility that MPA therapy might be more effective when used after "priming" with TAM [20].

This possibility, together with the equivalent efficacy and the different mechanisms of action are the theoretical rationale for the use of sequential TAM–MPA combination therapy.

To evaluate the antitumour activity, toxicity and the endocrine effects of the rapidly alternating sequential combination with TAM plus MPA, a Phase II trial was carried out in untreated post-menopausal breast cancer patients.

MATERIALS AND METHODS

Patients

Between 1 December 1984 and 31 December 1985, 42 consecutive patients entered the study.

Pretreatment studies included: history and physical examination, chest X-ray, cbc with platelet count, serum chemistry, CEA, liver and bone scan. Skeletal X-ray was required in the case of an abnormal bone scan.

Physical examination and serum chemistry were repeated every month, scan and X-ray were performed every 2 months, if necessary, for tumour evaluation. The performance status was evaluated by standard criteria (Karnofsky).

Eligibility criteria

Eligibility requirements for the study were:

1. Histologic diagnosis of breast carcinoma with recurrent or metastatic or locally advanced (stage IV) disease;
2. measurable and/or evaluable disease;
3. postmenopausal status;
4. absence of previous exposure to any endocrine and/or chemotherapy (with the exception of adjuvant treatments);
5. Karnofsky performance status $\geqslant 50$;
6. normal liver and renal function tests;
7. expected survival $\geqslant 12$ weeks;
8. oral informed consent.

Exclusion criteria were:

1. Concurrent conditions that precluded the use of any drugs employed in the protocol;
2. second neoplasms, excluding *in situ* carcinoma of the cervix or basal cell skin cancer if properly treated;
3. patients affected by brain or liver metastasis or pulmonary lymphangitis;
4. active documented infection;
5. history of congestive heart failure, significant arrhythmia, myocardial infarction or severe hypertension.

Treatment schedule

Endocrine therapy was given as follows: TAM 10 mg b.i.d. for 14 days followed by an oral dose of MPA 500 mg b.i.d. for the subsequent 14 days, in alternating sequence. Courses were repeated at 4 week intervals.

Treatment was continued for at least 2 months for the assessment of response and stopped when evidence of tumour progression arose or in the case of severe toxicity.

Response evaluation

Response to treatment was defined according to the WHO criteria [21] as follows: complete remission (CR) = complete disappearance of all measurable lesions for at least 4 weeks; partial remission (PR) = $\geqslant 50\%$ reduction of measurable lesions; progressive disease (PD) = $> 25\%$ increase of measurable lesions and/or appearance of any new lesions. All other situations not meeting the previous conditions were considered stable disease (SD).

Suitable response criteria were defined for the evaluation of bone metastasis as follows: CR = complete disappearance of all skeletal lesions by X-ray or bone scan for at least 4 weeks; PR = partial reduction $\geqslant 50\%$ or recalcification of lithic lesions or reduction in density of blastic lesions for at least 4 weeks; SD = no visible changes in bone lesions for 8 weeks; PD = increase of measurable lesions, definite decalcification and/or appearance of new lesions.

Duration of response was calculated from the beginning of therapy and until PD.

Steroid receptors and endocrine assays

Whenever possible, biopsies of superficial tumour tissues were performed before treatment for estrogen receptor (ER) and progesterone receptor (PgR) analysis. Details of the determination procedure have been described elsewhere [22].

Samples either with association constant (K_a) higher than $0.56 \times 10^9/M^{-1}$ with more than 10 fmol/mg protein in the case of ER and with K_a values higher than $0.5 \times 10^9/M^{-1}$ and more than 25 fmol/mg in the case of PgR were arbitrarily considered as positive.

In 26 patients blood was collected in the morning (8–10 a.m.) to determine the plasma levels of sex-hormone-binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), cortisol (C), 17-β-estradiol (E) and

testosterone (T) before the beginning of therapy and after 14, 28 and 56 days.

LH, FSH and PRL were determined using the DAB MAIA RIA kit; the values for FSH, LH and PRL are expressed as mIU/ml 2° IRP HGM, mIU/ml 2° IRP HGM and ng/ml NIH-FI, respectively (CV < 8%).

E and T were estimated using direct DAB MAIA RIA and DAB PEG RIA respectively, the values are expressed as pg/ml and ng/ml (CV < 15%).

SHBG levels were estimated using the monoclonal immunoradiometric assay; results are expressed as nmol/l (CV < 5%). C was measured by solid phase AMERLEX RIA and the results are expressed as μg/dl (CV < 5%).

Normal menopausal values obtained in 30 normal menopausal women were: FSH > 25.8 mIU/ml, LH > 25 mIU/ml, PRL 5–25 ng/ml, T 0.2–0.9 ng/ml, SHBG 30–90 nmol/l, E 0–30 pg/ml. Normal values of C measured at 9 a.m. were 8–25 μg/dl.

Statistical methods

A chi-square testing homogeneity of linear relationship was calculated using the Mantel test [23]. The confidence limits for proportion were calculated using the Fisher test [24]. Statistical evaluation of hormonal changes was made according to the Mann–Whitney *U* test. The Kaplan Meier curve for overall survival was plotted.

RESULTS

Out of 42 patients entered 40 were fully evaluable for response and received more than 2 months of therapy. Two patients were not evaluable: the first because of early death due to acute myocardial infarction after 20 days of treatment and the second because treatment was withdrawn due to severe gastric toxicity from MPA. The median age was 70 years (range 42–89); the median performance status (Karnofsky scale) was 80 (range 50–100); and the median disease-free interval was 36 months (range 7–144).

Previous treatment included: radical mastectomy or modified radical mastectomy in 23 patients and adjuvant treatments in 8 patients; 4 of them received CMF chemotherapy for 6 cycles and 3 TAM for 12 months (completed 17, 19 and 60 months in advance, respectively). In the remaining case CMF plus TAM was given for 12 months (completed 78 months before TAM–MPA). Nine patients did not receive any therapy.

The characteristics of the eligible patients are shown in Table 1.

Table 1. Patient characteristics

	No.	(%)
Patients entered	42	
Patients evaluable	40	
Median age in yrs (range)	70	(42–89)
Median Karnofsky performance status (range)	80	(50–100)
Median disease-free interval in mos (range)	36	(7–144)
Predominant metastatic site		
soft tissue	16	(40%)
bone	13	(33%)
viscera	11	(27%)
Sites of disease		
skin	9	
nodes	19	
bone	16	
locally advanced breast cancer	8	
lung	10	
pleura	1	
Metastatic sites		
1	24	(60%)
⩾ 2	16	(40%)
Previous therapy		
surgery	23	(58%)
adjuvant chemo- or hormonotherapy	8	(20%)
none	9	(22%)
Receptor status		
positive	11/14 (78%)	(35%)
negative	3/14 (22%)	
unknown	26/40	(65%)

Antitumour effects and survival

A total of 366 courses of therapy were administered.

The median number of courses was 9.5 (range 3–20) in patients who achieved remission or disease stabilization while it was 3 (range 2–5) in patients with disease progression.

After a median follow-up of 54 weeks (range 3–94), CR was obtained in 8 patients (20%), PR in 14 (35%), SD in 10 (25%) and PD in 8 (20%). The overall objective response rate was 55% (95% confidence limits were 38–75%). In responders the median time to obtain the maximal remission was 12 weeks.

The median duration of response was 64+ weeks (range 28–80+) in CR, 32+ (range 12–68+) in PR and 34 (range 28–88) in SD patients. A detailed analysis of the response related to treatment and predominant metastatic sites is reported in Tables 2 and 3.

A higher response rate was seen in soft tissues (88%; 14 out of 16) and in locally advanced disease (63%; 5 out of 8); lower in bone (38%; 5 out of 13) and in viscera (27%; 3 out of 11).

At the time of this analysis 10 patients are still in remission. Among the 8 patients achieving a CR, 3 relapsed: in soft tissue (1 patient) and bone (2 patients) after 28, 56 and 56 weeks, respectively.

Table 2. Objective responses and their duration in 40 evaluable patients

Type of response	No. of patients (%)	Duration in weeks median (range)
Complete	8 (20)	64+ (28–80+)
Partial	14 (35)	32+ (12–68+)
Stable disease	10 (25)	34 (28–88)
Progressive disease	8 (20)	— —

Table 3. Response according to prognostic factors

Prognostic factor	No. of patients	CR + PR	(%)	SD	(%)	PD	(%)	Significance level (*P*)
Total number	40	22	(55)	10	(25)	8	(20)	—
Age (years)								
≥ 70	21	15	(71)	5	(24)	1	(5)	$\chi^2_2 = 7.33$ ($P = 0.03$)
< 70	19	7	(37)	5	(26)	7	(37)	
Performance status (Karnofsky)								
80–100	28	15	(54)	7	(25)	6	(21)	NS
40–70	12	7	(58)	3	(25)	2	(17)	
Disease-free* interval (months)								
≥ 24	18	11	(61)	3	(17)	4	(22)	NS
< 24	12	5	(41)	3	(26)	4	(33)	
Predominant metastatic sites	16	14	(88)	1	(6)	1	(6)	
soft tissue								
(locally advanced	16	14	(88)	1	(6)	1	(6)	
disease)	(8)	(5)	(63)	(3)	(37)	(0)	(0)	$\chi^2_3 = 12.8$ ($P = 0.02$)
bone	13	5	(38)	4	(31)	4	(31)	
viscera	11	3	(27)	5	(46)	3	(27)	
Number of sites involved								
1	24	17	(71)	4	(17)	3	(12)	$\chi^2_2 = 6.09$ ($P = 0.05$)
≥ 2	16	5	(31)	6	(38)	5	(31)	
Receptor status								
positive	11	8	(73)	1	(9)	2	(18)	NS
negative	3	0	(0)	1	(33)	2	(67)	
unknown	26	14	(54)	8	(31)	4	(15)	

*Ten patients do not appear in this analysis because they presented metastatic disease at the time of the first diagnosis.

PR is still maintained in 5 patients.

Sixteen women died: 12 because of PD and 4 still in PR, 2 because of ictus cerebralis, 1 because of pneumonia and the last because of senectus (89 years).

The median time to progression was 41 weeks and the median overall survival was 88 weeks (Fig. 1).

Prognostic factors

Relative importance of prognostic factors for response were analysed in a logistic model (Table 3). The following variables were identified as the most significant predictors of response: age over 70 years ($P = 0.03$), soft tissue dominant lesions vs. osseus ($P = 0.02$) and vs. viscera ($P = 0.02$), and only 1 site of disease ($P = 0.05$).

Receptor status did not appear as a significant predictor of response in the small number of determinations performed (14 cases).

Endocrine effects

Twenty-six patients were evaluable for assessment of the endocrine parameters before and during the hormonal treatment. The results obtained are summarized in Table 4.

The short period of TAM treatment did not induce any significant modification of the endocrine parameters although a trend to SHBG and C increase and LH and T decrease was observed.

After the following 2 weeks of therapy with MPA the progestogenic activity was prevalent. In fact a

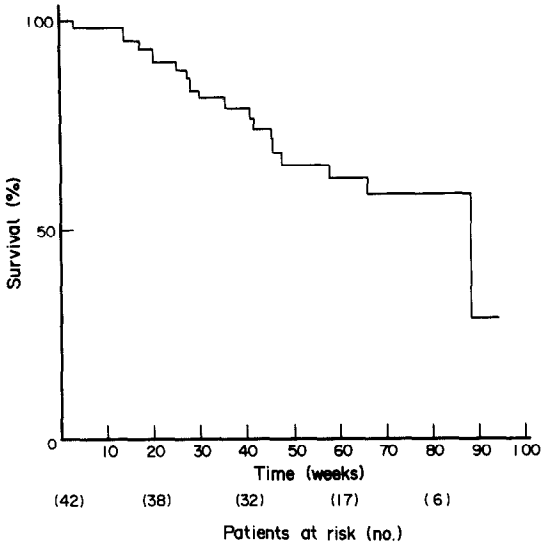

Fig. 1. Overall survival

in 1 patient, metrorrhagia in 2 patients and severe leukorrhoea in one. The most common side effects were: nausea and vomiting, hot flushes and weight gain. Hypercalcaemia and haematological toxicities were not observed.

In 10 patients there was a clear improvement of at least 20 points in performance status. Eighteen (58%) had a marked increase in appetite. In 6 patients (19%) the white blood cell count increased more than 2000/mm^3.

DISCUSSION

Endocrine-dependent breast cancer can be defined according to some clinical characteristics such as advanced age, skeletal and soft tissue metastasis, indolent disease and a long disease-free interval [25]. However, the primary tool used in the therapeutic approach is the tissue receptor assay, because of the strict correlation existing between receptor expression and response to hormonal agents. Response to endocrine therapy in patients with ER-positive cancer is 50–60%, whereas in unselected cases it is 25–30% and in ER-negative patients it decreases to less than 10% [26]. Hormonal treatment is therefore an appropriate first-line therapy in selected postmenopausal breast cancer patients and moreover it does not decrease the chance of response to chemotherapy [27, 28].

Cellular heterogeneity in regard to receptor status [29], cell kinetics with slow and fast proliferating tumours [30] and the development of spontaneous mutations which bear resistant cells [31] explain the difficulty of improving the response rate currently achievable with medical treatments.

Table 4. Effect of administration of tamoxifen and medroxyprogesterone acetate on endocrine parameters in postmenopausal breast cancer patients (results are given as median and range)

Hormones	Days: 0 (n = 26)	14 (n = 21)	28 (n = 23)	56 (n = 20)
SHBG (nmol/ml)	53 (18–61)	61 (27–112)	23+ (7–68)	15† (3–25)
FSH (mIU/ml)	75 (48–164)	67 (32–112)	26† (4–55)	17.5† (2.4–48)
LH (mIU/ml)	63 (15–143)	51 (13–60)	20† (4–53)	16† (2–28)
E (pg/nl)	15 (10–38)	10 (10–29)	10 (10–21)	10 (10–32)
PRL (ng/ml)	10 (5.5–22)	8 (5–16)	13 (6–25)	13 (2–25)
T (ng/ml)	0.4 (0.2–1.6)	0.33 (0.17–2.5)	0.1† (0.1–0.7)	0.1† (0.1–0.5)
C (μg/dl)	14 (11–31.5)	24 (11.5–52.5)	10 (1.2–27)	10* (1–22)

*$P < 0.05$; †$P < 0.01$ vs. basal value (Mann–Whitney U test).

significant decrease of SHBG, FSH, LH, T and C was observed. The same progestogenic effect was maintained after 2 months of therapy. Our study did not show any difference between responder and non-responder patients in the pretreatment prolactin median values (10 μg/ml and 9 μg/ml respectively; P = NS) nor in its behaviour during the treatment.

Toxicity

Forty-one patients were evaluable for toxic-effects (Table 5). The sequential hormonal therapy was generally well tolerated and no side-effects were recorded in 20 cases. Twenty-one patients had one or more side-effects and 4 elderly women stopped the treatment because of severe toxicity consisting of gastric intolerance to MPA after the first month

Table 5. Toxic side-effects in 41 evaluable patients

Pts without side-effects	20	(47.5%)
Pts with one or more side-effects	21	(52.5%)

Toxic effect	Grade mild	moderate	severe
Nausea	7	2	1
Vomiting	3	2	1*
Diarrhoea	2	1	0
Hot flushes	4	2	0
Increased perspiration	2	2	0
Palpitation	1	2	0
Thrombophlebitis	1	1	0
Fatigue	1	2	0
Metrorrhagia	0	1	2*
Leukorrhoea	1	3	1*
Vulvar itch	1	2	0
Moon face	3	1	0
Weight gain	4	2	0
Lethargy	2	1	0
Depression	3	2	0
Nervousness	3	3	0
Irritability	2	0	0
Erhitema	0	1	0

*Patients required suspension of therapy.

Based on these biological considerations and on the observed 20–25% response rate to a second non-cross-resistant endocrine therapy [32], several Phase II studies of polyhormone therapy were conducted [20, 33].

Few randomized controlled clinical trials comparing TAM alone or combined with other hormonal agents have also been reported [34–36]. Although some of these studies produced interesting results, further investigations are needed to establish the superiority of the combinations.

Recently, *in vitro* and *in vivo* experimental studies revealed an increased expression of progesterone receptors after a brief exposure to TAM and a synergistic antineoplastic activity with the sequential administration of TAM and MPA [15, 16]. An increased PgR expression has also been evidenced in humans in about 30–40% of breast tumours, after "priming" with TAM by the "hormonal challenge test" proposed by Baulieau [18] and confirmed, in endometrial carcinoma, by Iacobelli *et al.* [37]. These data suggest that sequential administration of TAM and MPA may produce better results rather than a combination of the two drugs.

The therapeutic activity of this sequential treatment in breast cancer patients has been evaluated in four Phase II studies [38–41] and in two prospective controlled trials [42, 43]. Although the number of treated patients is limited and different schedules have been used, the sequential combination seems highly effective in terms of objective response rate and response duration. Experimental studies seem to suggest the importance of the doses and of the timing of the administration of the two drugs [15, 16]. On these bases, 2 weeks of low doses of TAM and the same period of high doses of MPA were tested in our study. Moreover, not only the efficacy of such treatment, but also its influence on endocrine parameters were evaluated.

The analysis of response according to dominant site of disease shows a high objective remission rate in patients with soft tissue dominant metastasis (88%) and with locally advanced disease (63%).

It is worth noting in our study that the short time required to achieve the maximal response (12 weeks) and its duration.

The side-effects were similar to those previously reported for each drug and this schedule was generally well tolerated by the majority of patients.

No significant modification of the endocrine parameters was observed during the short period of TAM treatment (14 days), while after 2 months of therapy the progestogenic effect of MPA was prevalent, as evidenced by the significant decrease of plasma FSH, LH, testosterone, cortisol and SHBG levels.

A particular behaviour of PRL has been reported in patients with metastatic breast cancer treated with endocrine therapy according to the clinical response [44]. Our study did not show any difference between responder and non-responder patients neither in the pretreatment PRL values nor in its behaviour during the treatment.

Such endocrine effects are in agreement with

those observed by Alexieva-Figusch *et al.* [45] who tested a simultaneous combination of TAM (40 mg daily) plus megestrol acetate (180 mg daily). The only discrepancy concerns the SHBG levels that are increased in their study and decreased in ours. This difference could be due to the time of measurement (after 2 weeks of MPA) and to the type and schedule of the progestative used.

Two major points are still controversial in sequential TAM-MPA hormonotherapy. First, the long pharmacokinetic (4–7 days) half-life of TAM and its metabolites [46], due to the large albumin binding and to the enterohepatic recirculation, can be responsible of a simultaneous presence of the two hormones during the first week of MPA therapy. Therefore a wash-out period of 7–10 days probably avoids this effect. Secondly, even if it appears from the few data available from randomized trials [42, 43, 47] that the response rate between sequential TAM-MPA and MPA as second-line therapy after TAM is superimposable, it is not yet clear if the response duration and survival can be better affected by one of these two strategies. In conclusion the clinical activity and the moderate toxicity of this sequential combination support further investigations focusing on: the optimal doses and timing of the drug's administration, the usefulness of a wash-out period during the sequence and the correlation between PgR induction and clinical response.

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