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HIGH DOSE MEDROXYPROGESTERONE-ACETATE TREATMENT IN ADVANCED MAMMARY CARCINOMA

A phase II investigation

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Since BEATSON (1896) introduced oophorectomy, hormonal treatment has until recently been the main mode of therapy of metastatic mammary carcinoma. In unselected material remissions have been obtained in 20 to 35 per cent of patients treated with ablative hormonal surgery (CARBONE 1977, GRATTAROLA 1976, MECKLENBURG & LIPSETT 1975, NEWSOME et coll. 1977, PUGA et coll. 1976, SEGALOFF 1975, SILVERSTEIN et coll. 1975, YONEMOTO et coll. 1977), as well as with additive hormonal treatment with androgens, oestrogens, progestins and corticosteroids (ANSFIELD et coll. 1974, CARTER et coll. 1977, GOLDENBERG et coll. 1973, KENNEDY 1974, MUGGIA et coll. 1968, NISSEN-MEYER & VOGT 1959, SEGALOFF), and anti-oestrogens (LEGHA & CARTER 1976, LEGHA et coll. 1976, TAGNON 1977, WARD 1973).

The finding of hormonal receptors in mammary carcinoma and their predictive usefulness in hormonal treatment (JENSEN et coll. 1971, LECLERCQ & HEUSON 1977, MCGUIRE 1973, MCGUIRE et coll. 1975) has revived interest in hormonal therapy, particularly with antioestrogen. The antioestrogens Tamoxifen, Nafoxidine and Clomiphene have an objective effect in 50 per cent or more of all cases of oestrogen receptor positive metastatic disease (BARNES et coll. 1977, LECLERCQ & HEUSON, MCGUIRE et coll., MORGAN et coll. 1976, MOURIDSEN et coll. 1977) like other forms of hormonal treatment (LEGHA & CARTER).

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Progestin may act as antioestrogen both directly on tumor cells by inhibiting binding of oestradiol to receptors (GURPIDE 1976) and indirectly by reducing the amount of oestrogen available to the tumor cells by increasing the catabolism of oestrogen, decreasing the conversion of androgen to oestrogen and by medical suppression of hypophyseal release of LH and FSH (GURPIDE, HELLMAN et coll. 1976, MASCIA et coll. 1977). Furthermore, progesterone receptors may perhaps be inhibited by progestin.

Previously progestin in metastatic breast carcinoma has been reported to give a response rate of 10 to 35 per cent after small and intermediate doses (50 to 400 mg) of medroxyprogesterone (MAP) (ANSFIELD et coll., GOLDENBERG 1969, MUGGIA et coll., SEGALOFF et coll. 1967, SEGALOFF, STOLL 1967). Higher rates of remission have been found in patients treated with a high dosage of MAP, $\leq 1\,000$ mg/day (PANNUTI et coll. 1975, 1976, AMADORI et coll., 1976). These clinical results and biologic actions of progestin motivated the use in this department of high dosage MAP in very advanced breast carcinoma. The main purpose was to assess the clinical effect and the tolerance of patients who had previously been treated with different kinds of hormones or combination chemotherapy.

Material and Methods

The criteria for inclusion in the material consisting of 25 patients were measurable lesions, Karnofsky's performance index >30 points (KARNOFSKY & BURCHENAL 1949), relapses after other endocrine treatment or resistance to combination chemotherapy. All patients were postmenopausal, either naturally or artificially, and all were evaluable. The median age was 69 years (range 34 to 94 years). Seventeen patients were 60 to 79 years old. In 22 patients the primary therapy had been modified radical mastectomy followed by postoperative irradiation of the regional lymph nodes and operation fields. Two patients had received irradiation of their primary inoperable tumors. One patient had not been treated by any local therapy. The first median relapse-free interval was 18 months (0 to 110 months). The median time between the diagnosis of a relapse or a metastasis and MAP therapy was 20 months (range 0 to 64 months).

Previous treatment of metastases. In 23 patients several modalities of treatment for metastases had been tried (Table 1). The median number of previous courses was 3 (range 0 to 5). Only 2 patients received MAP as the primary treatment of metastases, as they were scored 40 points according to Karnofsky's index, indicating poor tolerance to combination chemotherapy, which otherwise should have been the treatment modality.

The previous hormonal treatment had consisted of oophorectomy (9 patients), andogrens (10 patients), oestrogens (3 patients), and corticosteroids (2 patients). These therapeutic measures had resulted in 5 partial remissions and no changes in 4.

Table 1

Previous therapy of metastases

Hormonal treatment	
Oophorectomy	9
Androgen	10
Oestrogen	3
Corticosteroid	2
Tamoxifen	20
Cytotoxic chemotherapy	
CMFP (Canellos et coll.)	6
VACM (Mattsson et coll.)	12
Radiation therapy	11
Surgery	
Osteosynthesis	4
Tracheostomy	1
Extended cutaneous excision	1
No previous treatment	2

In 5 of 20 patients previously treated with Tamoxifen 30 mg a day a partial remission with a median duration of 6 months (range 3 to 11 months) was obtained. Before MAP-treatment 15 of 18 patients had had a remission (median duration 12 months) in association with combination chemotherapy with either Vincristine, Adriamycin, Cyclophosphamide and Methotrexate with citrovorum factor rescue (MATTSSON et coll. 1977 a, b) or Cyclophosphamide, Methotrexate, 5-Fluorouracil and Prednisone (CANELLOS et coll. 1974).

Eleven patients had been subjected to local palliative irradiation of the skeleton (24 Gy).

Examinations before the MAP-therapy was started: the extent of the disease was assessed by clinical and gynecologic examination, chest and skeletal radiography, isotope scanning of the liver and fine needle aspiration biopsy of accessible metastases in the skin, lymph nodes, lungs, and liver. When clinically indicated, these examinations were supplemented by mammary radiography, urography, ultrasonic examination of the abdominal and pelvic cavity and isotope scanning of the brain and of the skeleton. Laboratory examinations included determination of haemoglobin, erythrocytes, leukocytes, differential counts, platelets, serum-iron, total iron-binding capacity, electrolytic status, creatinine and liver function. Electrophoresis, ECG, microscopy of the urinary sediment and CEA were also performed. The patients' symptoms were recorded according to Karnofsky's performance scale.

Spread of metastases and performance state. The median number of organs with metastases was 3 (range 1 to 6). The dominant site was in soft tissues in one patient,

Table 2

Results of MAP-therapy

	No. of patients	Duration of remission		Alive in remission	Alive with a relapse
		Median	Range		
Partial remission	7	5+	(2+–13+)	5	1
No change	7	4	(3–6)	3	1
Progressive disease	11				

in the skeleton in 3 and in the viscera in 21. The most common tissue involved was bone (21 patients). The other metastatic sites were the lungs in 12, pleurae, liver and lymph nodes in each of 9, the skin in 6 and the breast in 3 patients. Other less common sites were the brain, peritoneum, mediastinum, bowel, ovaries and uterus. The median Karnofsky's performance index was 60 points (range 40 to 80).

Treatment and follow up. The patients were treated with medroxyprogesterone-acetate (MAP, Farlutal, Farmitalia) intramuscularly in the buttocks in a dose of 1 000 mg a day for 30 days. The patients, who had then obtained a remission ($\geqslant$no change) by this induction regimen of MAP (30 g), continued to take a maintenance dose of 1 000 mg a week until progressive disease was detected.

The effect was estimated every other week for 12 weeks by means of physical examination, assessment of Karnofsky's performance index and determination of the haemoglobin, leukocytes, differential count, liver function, creatinine, electrolytic status. Chest and skeletal radiography and isotope scans of the liver were obtained at least once every 4 weeks. Other examinations performed to document the remission were ultrasonic examination of the abdominal and pelvic cavity, isotope scanning of the brain, and mammary radiography.

After the first 12 weeks of treatment the follow-up was individualized, but at intervals of at most three months, remissions were evaluated and the Karnofsky's performance index of the patients was assessed. After 6 and 12 months' treatment the pretreatment examinations were repeated in all survivors. Of the 12 patients who died, 11 were examined post mortem.

Assessment of response. The criteria used for remissions were those recommended by HAYWARD et coll. (1977). Complete remission is a disappearance of all known disease. In cases with lytic bone metastases, radiography must have shown that the lesions have calcified. Partial remission is a decrease of 50 per cent or more in measurable lesions and objective improvement of evaluable but non-measurable lesions and no new lesions. No change is recorded when the size of measurable lesions decreases less than 50 per cent or increases less than 25 per cent. Progressive disease is recorded when some lesions regress, while others progress or new lesions appear, or when some or all lesions progress or new lesions appear.

Table 3

Results of MAP-therapy in relation to dominant metastatic organ

Organ	Partial remission	No change	Progressive disease
Soft tissue	—	1	—
Bone	2	—	1
Visceral	5	6	10
Total	7	7	11

Results

The overall response rate was 28 per cent (partial remission in 7/25, Table 2). To date (1 February 1978), the median duration of these partial responders is 5+ months (range 2+ to 13+ months). Five of these patients are alive in remission and one with a relapse, now responding to combination chemotherapy. The one responder who had died had a remission for 5 months. Seven patients had no change for a median duration of 4 months (range 3 to 6 months). Three of them are still alive without signs of tumor progression and one with a relapse, which has become stationary during combination chemotherapy. The other 3 patients with no change died after 3, 6 and 8 months, respectively. Combination chemotherapy was tried, but no response was obtained. The 11 non-responders had a median survival of 4 months (range 0.5 to 9 months). Two of them are still alive and responding to combination chemotherapy. Three of the patients with progressive disease did not respond to subsequent combination chemotherapy. Five non-responders did not receive any treatment when the disease progressed because of lesions which were too extensive.

In 2 out of 3 patients with dominant bone metastases and in 5 out of 21 with visceral metastases a remission occurred (Table 3). The response did not vary significantly with the number of metastatic organs involved, although 2 out of 5 with one organ with metastases responded, compared with 3 out of 10 patients with metastases in 4 or more organs (Table 4).

Previously 5 out of 21 patients had a remission in association with hormonal treatment other than Tamoxifen (Table 5). Three of these responders and one non-responder had a remission by MAP therapy. Before treatment with MAP, 20 patients had also received Tamoxifen, which resulted in partial remission in 5 patients. When one of these responders relapsed, she responded to MAP-treatment. Furthermore, among the 15 Tamoxifen-resistant patients, MAP-therapy resulted in 4 partial remissions and in no changes in 4 (Table 5).

Fifteen of 18 patients had previously had a remission during combination chemotherapy. When they were later treated with MAP, 4 of these 15 had a partial

Table 4

Results of MAP-therapy in relation to number of metastatic organs

No. of metastatic organs	Partial remission	No change	Progressive disease
1	2	1	2
2	1	2	—
3	1	3	3
⩾4	3	1	6
Total	7	7	11

$0.5 < p < 0.7$ Kruskal-Wallis log rank test

remission and 3 evidenced no change. None of the 3 non-responders to combination chemotherapy responded to MAP-therapy (Table 5).

The subjective improvement of the partial responders as measured by Karnofsky's performance index was 10 to 40 points (median 20). The seven patients with no change had a median improvement of 20 points (range 0 to 30). In no patient was MAP-therapy followed by a decrease of performance. On the contrary, 4 of the 11 patients with a progressive disease improved subjectively with relief of pain, increased appetite and better feeling of well-being.

The therapy was well tolerated. Only 5 patients complained of some distention in the buttocks following the injections. All but one patient had local infiltration at the site of injection. In one patient a severe bleeding occurred, probably due to a puncture of a muscle artery. A necrotic ulcer developed, which healed after plastic surgery. No patient had any objective or subjective retention of water. No renal, gastrointestinal, haematologic or gynecologic adverse effects occurred. Three patients had transient, moderate elevation of liver function. Slight moon-face, as in Cushing's disease, occurred in 4 patients, but no other adverse effects of adrenocorticoid could be detected.

Discussion

The overall rate of objective response (28 %) by high dosage MAP in these patients with advanced disease who previously had been heavily treated with other means is encouraging. The results compare favourably with the rate of remission obtained by other primary hormonal therapy in unselected metastatic breast carcinoma (CARTER et coll., GOLDENBERG et coll., KENNEDY, LEGHA & CARTER, MECKLENBURG & LIPSETT, NOTTER 1975, PUGA et coll., SEGALOFF, SILVERSTEIN et coll., TAGNON, YONEMOTO et coll., WARD, WESTERBERG et coll. 1976).

The response rate in the present material was lower than that reported by PANNUTI et coll. (1975, 1976) and AMADORI et coll. This could be explained by the

Table 5

Results in relation to outcome of previous treatments of metastases

Results of previous therapy of metastases		Results of MAP		
		Partial remission	No change	Progressive disease
Hormonal therapy other than Tamoxifen				
Objective response	5	3	1	1
No change + progressive disease	16	1	3	12
Tamoxifen				
Objective response	5	1	1	3
No change + progressive disease	15	4	4	7
Combination chemotherapy				
Objective response	15	4	3	8
No change + progressive disease	3		1	2

disease being more advanced (median number of metastatic sites 3, dominant visceral metastases 21/25) and by the previous more extensive treatment (median number of previous treatments 3). KENNEDY has shown that the rate of remission following hormonal therapy is related to the extent of the tumor. An established fact is that the chance of a new remission in patients not responding to other types of hormone therapy is less (HASKEL 1977). At any rate, the response rate in these previously heavily treated patients is about the same as that followed by small and moderately large doses of MAP as the primary treatment of metastases (ANSFIELD et coll., GOLDENBERG 1969, MUGGIA et coll., SEGALOFF et coll., STOLL).

The duration of remission seemed to be short in most of these advanced cases. A possible explanation is that most tumors consist of both hormone-dependent and hormone-independent cells (TAGNON 1976, WITTLIFF et coll. 1976). Furthermore, TAGNON (1977) has produced some evidence that hormone therapy might eradicate tumor cells with oestrogen receptors and together with KENNEDY's observation of the importance of the tumor burden, there may be a better possibility of increasing hormone-independence with increasing tumor volume and previous hormonal treatment, as in the present material.

Long and uniform experience has shown that the chance of a remission following hormonal therapy in patients with visceral metastases, particularly in the liver, is poor. The literature contains no conclusive data about the content of hormone receptors at different metastatic sites. Available data on the rate of response in

various organs indicate that the hormone-dependent tumor cells occur in the different organs in the following order: soft tissue, bone, lung, pleurae, and then the other viscera. Also other factors may be important, such as the available therapeutic concentration of the drugs and the complex importance of different hormones to promote or suppress tumor growth (GURPIDE). At any rate, in the present series MAP had an objectively demonstrated effect in 5 of 21 patients with dominant visceral metastases. In addition, in 6 patients the disease became stationary.

Interesting both from theoretical and clinical points of view is the fact that there were 4 partial responders and 4 unchanged of 15 patients who had not responded to antioestrogen treatment. Progesterone is considered to act both by inhibiting oestradiol-binding to receptor protein in the cytoplasm of the tumor cells (HSVEH et coll. 1975) and by the inhibition of the hypophyseal release of FSH, LH and ACTH (GURPIDE, GORDON et coll. 1971). Furthermore progesterone depresses the level of oestradiol by enzymatically accelerated catabolism of oestrogen, and secondary to increased catabolism of androgen reduces the conversion of androgen to oestrogen (GORDON et coll.). With special regard to MAP, TERENIUS (1974) has shown that MAP has a very high affinity for progesterone receptors in experimental animals. MAP has also a direct anti-proliferative effect, as demonstrated by its inhibition of DNA and RNA-synthesis (NORDQUIST 1970) and its reduction of mitotic index in adenocarcinoma of the endometrium (BINARD 1970). WILLIS et coll. (1977) have shown that Tamoxifen invariably depresses the serum LH and FSH. However, in the non-responders also oestradiol was increased. The results of MAP in these non-responders may be due to the progesterone-mediated increased catabolism of oestradiol, by which the oestradiol available to tumor cells was depressed. Furthermore, a competitive inhibition at receptor levels might have occurred.

Although the number of patients is relatively small, the results suggest no cross-resistance between Tamoxifen and MAP. Thus, high dosage MAP can induce remission in Tamoxifen-resistant patients since partial remission was obtained in 4 patients and no progression of the disease in 4. High dosage MAP could therefore be recommended to postmenopausal patients with metastases from breast carcinoma at least as a second line hormonal therapy, particularly in elderly patients or in those in such poor condition that they do not tolerate combination chemotherapy.

Previously 15 out of 18 patients in the present material had responded to combination chemotherapy. All these patients had relapsed and were subsequently treated with MAP, which resulted in partial remission in 4 and no change in 3. No adverse effect of previous cytotoxic chemotherapy was observed. On the basis of the hypothesis that mammary carcinoma consists of both hormone-dependent and hormone-independent tumor cells, an interesting approach is to combine high dosage MAP with cytotoxic drugs. Promising results have already been obtained in two randomized investigations (MASCIA et coll., STOTT et coll. 1973) and in one non-randomized controlled investigation (HUYS et coll. 1976). Recently BRUNNER et coll. (1977) in another randomized investigation did not find any advantage of adding

MAP to combination chemotherapy. These 4 materials differed from each other in the dose of MAP and cytotoxic drugs used; in the three with increased response rate the dose of MAP was 800 mg, 1 000 mg, and 4 200 mg a week, respectively. The dosage of MAP is of crucial importance. PANNUTI et coll. (1975) and AMADORI et coll. have shown a dose-response relationship. ROBUSTELLI DELLA CUNA et coll. (1978) found the same response rate to 500 mg MAP a day and 1 000 mg a day (44 versus 41 %). Therefore, the most appropriate dose seems to be $\geqslant$ 500 mg a day as a dose of 50 to 400 mg gave a response rate of 9 to 30 per cent (ANSFIELD et coll., GOLDENBERG, MUGGIA et coll., PANNUTI et coll. 1975, STOLL).

In the material of MASCIA et coll. the determinations of serum FSH, LH and prolactine were made prospectively. Patients treated with combined chemotherapy and MAP (600 mg a day) had significantly lower FSH and LH than the group that received chemotherapy only. These findings might help to explain the better effect of the combined therapy and lend support to the suggested dosage ($\geqslant$ 500 mg a day) necessary to inhibit the hypophyseal release of FSH and LH.

The present results did not vary significantly with the number of metastatic organs involved, a finding contrasting with what was stated in a previous report of combination chemotherapy in breast carcinoma metastases (MATTSSON et coll. 1977 a). This may be explained by the different actions of cytotoxic drugs. The effect of chemotherapy depends primarily on the growth fraction, which varies approximately inversely with the tumor burden. Some preliminary data suggest a larger content of glucolytic enzymes in tumors responding to cytotoxics (SAVLOV et coll. 1977). On the other hand, a low level of glucolytic enzymes was associated with the presence of oestrogen receptors (HILF et coll. 1973). Another observation indicates that a primary tumor with a large growth fraction, as measured by a high thymidine-labelling index, tends to recur early and probably contains a low incidence of oestrogen receptor (MEYER et coll. 1977).

High dosage MAP was well tolerated. Only one severe complication occurred; it was probably related to accidental puncture of a muscle artery. In no other case was aseptic necrotic ulceration observed. This is in contrast with the results reported by PANNUTI et coll. (1976). Aseptic necrotic ulcerating has been attributed to the use of MAP in soluble form. However, as the present patients received a median dose of 30 g (range 30 to 108 g) without that type of adverse effect, it seems probable that previously described aseptic ulcerations were not due to the solution of MAP in se, but to needle punctures of arteries or too high pressure in the muscle tissue at the site of injection. A necrotic aseptic ulcer might occur secondary to bleeding and muscular injury.

Measured by Karnofsky's performance index the median improvement was 20 points (range 0 to 40 points). Furthermore, in 4 cases of progressive disease the quality of life improved. The most important subjective benefits were increased appetite, better feeling of well-being and reduction of pain. MARTINO & VENTAFRIDDA (1976) have analysed MAP for its analgesic efficacy in women with advanced breast

carcinoma and severe chronic pain, not controllable with conventional analgetics. They found high dosage MAP to give substantial relief, which was in part due to the euphoric effect of the steroid.

In conclusion, high dosage MAP has produced promising results without any noteworthy adverse effects in very advanced and heavily pretreated patients with breast carcinoma metastases, although the duration of the remissions was short. Particularly interesting is the effect on Tamoxifen-resistant metastatic disease, which suggests another mode of action besides the direct effect on tumor cells. Previous combination chemotherapy and hormonal treatment did not have any adverse effect on the rate of remissions. Randomized investigations comparing high dosage MAP with Tamoxifen in receptor positive metastatic disease and relapses after combination chemotherapy have been activated. Thus, it appears that MAP implies a new possibility of treating advanced mammary carcinoma.

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SUMMARY

In a phase II investigation of high dose medroxyprogesterone treatment of advanced and previously with other methods heavily treated patients with mammary carcinoma, 7 of 25 patients had a partial remission with a median duration of 5+ months. In a further 7 patients the disease became stationary. As measured by Karnofsky's scale, a median improvement of 20 points was obtained in these 14 patients. In 4 of 15 patients who had not responded to Tamoxifen treatment, a partial remission occurred following MAP therapy. The patients tolerated MAP well.

ZUSAMMENFASSUNG

In einer Phase II Untersuchung über die Medroxyprogesterone-Behandlung in hoher Dosierung bei vorgeschrittenen und zuvor mit anderen Methoden hochbehandelten Patienten mit Mamma-Karzinom hatten 7 von 25 Patienten eine partielle Remission mit einer mittleren Dauer von 5+ Monaten. Bei weiteren 7 Patienten wurde die Erkrankung stationär. Gemessen mit der Karnofskyschen Skala, wurde eine mediane Verbesserung von 20 Punkten bei diesen 14 Patienten erreicht. Bei 4 von 15 Patienten, die nicht nach Tamoxifen-Behandlung verbessert wurden, wurde eine partielle Remission nach MAP-Therapie erzielt. Die Patienten vertrugen MAP gut.

RÉSUMÉ

Dans une phase II d'une recherche sur le traitement par de hautes doses de médroxyprogestérone de malades atteintes de cancer du sein et ayant subi auparavant de lourds

traitements par d'autres méthodes, 7 malades sur 25 ont eu une rémission partielle d'une durée médiane de 5 + mois. Chez 7 autres malades la maladie est devenue stationnaire. En utilisant l'échelle de Karnofsky, une amélioration médiane de 20 points a été obtenue chez ces 14 malades. Chez 4 des 15 malades qui n'avaient pas répondu au traitement par Tamoxifen, une rémission partielle a suivi le traitement par MAP. Les malades ont bien toléré le MAP.

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