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TREATMENT OF DISSEMINATED CARCINOMA OF THE BREAST BY METENOLONE ENANTHATE

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Androgenic and oestrogenic hormones have been used in the treatment of disseminated carcinoma of the breast for many years. Prospective analyses have demonstrated that oestrogens are usually more effective than androgens (Council on Drugs 1960, KENNEDY 1965). Both hormones have undesirable side effects, sometimes necessitating discontinuation of treatment. Androgen treatment in high doses for 4 to 6 weeks leads to obvious virilisation, increased libido and hoarseness, side effects unpleasant to most female patients. Sodium and water retention also occurs, increasing the risk of complications such as oedema and thrombo-vascular lesions. Stimulation of the bone marrow may cause polyglobuli, plethora and chest pains simulating angina pectoris.

Metenolone Enanthate has a less virilising effect than testosterone propionate and is in addition not converted to oestrogens. KENNEDY & YARBRO (1968) used this preparation in a hitherto unusually high dosage of 3×400 mg/week in a prospectively randomised trial together with testosterone propionate in the treatment of disseminated carcinoma of the breast. In their series objective remissions were observed in 13 out of 27 patients. In the present material an attempt has been made to reproduce this result in a larger number of cases.

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Table 1

The effect of Metenolone Enanthate on different sites of metastases. Number in brackets indicate static disease

Site of metastases	Incidence of metastases	Therapeutic effect	
		Remission	Failure
Breast	2	2	—
Soft tissue			
cutis, subcutis	22	8	14 (4)
lymph nodes			
Osseous	29	2	27 (11)
Visceral			
liver	4	—	4
lung	7	—	7 (1)
pleura	3	1	2
brain	—	—	—
Total	67	13	54

Objective remission in 8/41 patients.
Static disease in 12/48 patients (evaluated as failures).

Methods and Material

During the period January 1972 to July 1974, 43 patients with microscopically verified inoperable or disseminated carcinoma of the breast have been treated by intramuscular injections of Metenolone Enanthate. Schering AG, Berlin, have supplied a specially manufactured solution with a concentration twice as high as that in the generally available Primobolan Depot, i.e. 200 mg/ml (SH 6.0601 F).

All patients were post-menopausal. Only women with progressive disease have been treated. Previously 11 patients had been treated with other hormones, e.g. oestrogens, gestagens, prednisolone, without evident therapeutic effect. It was ensured that all previous hormone treatment had been withdrawn at least 1 month before the administration of Metenolone Enanthate. Measurable tumours or metastates were controlled regularly once a month. Roentgen examinations of the skeleton were carried out at 3 monthly periods or in the case of progressive symptoms or signs earlier. Blood counts and serum electrolytes and liver function tests were controlled once a month for 3 months and thereafter every second month.

For the evaluation of response the criteria of U.S.A. Cooperative Breast Cancer Group (National Cancer Institute) were applied. Objective remissions were, therefore, only accepted if (a) all demonstrable tumour masses diminished measurably in size, (b) more than 50 per cent of non-osseous lesions decreased in size although all bone lesions remained static, and (c) more than 50 per cent of total lesions improved while the remainder were static.

Only regression of at least 3 months' duration has been evaluated as remission. No simultaneous treatment with other hormones or cytostatic agents has been given during the period.

Initially the dose schedule recommended by KENNEDY & YARBRO of 3×400 mg/week during a period of 3 months was planned. Marked virilisation occurred with this high dose and, as a good clinical effect was observed with 2×200 mg/week, the treatment further commenced on this lower dose.

A total of 43 patients were treated; 2 of these for less than 3 months; they have not been evaluated. In both these cases treatment was discontinued because of progression of the tumour. Thus, 41 patients were treated regularly for at least 3 months with doses of not less than 400 mg/week: 18 patients initially with 3×400 mg/week for 3 months, 2 initially with 3×400 mg/week for 2 months, 1 patient with 2×400 mg/week for 2 months, 2 patients with 2×400 mg/week for 1 month, and 18 patients with 2×200 mg/week for 3 months.

Following the initial treatment the patients received regular maintenance doses of 1×400 mg, 1×200 mg and 1×100 mg/week intra-muscularly, respectively.

Result

The result appears in Table 1. Regressions occurred in 8 of the 41 (8/41) evaluated patients, 33 failed. In the failure group 12 patients were included whose disease remained static, or regression of less than 50 per cent occurred, thus not fulfilling the criteria for remission.

In the group of remissions, total regression of the tumour occurred in 2 patients and more than 50 per cent regression in 6. The mean remission time was 12 months (3–27), the mean treatment time was 15 months (93–810 days) and the mean Primobolan Depot dose was 20.4 g (5.8–37.3).

In the 12 patients of the failure group with static disease or less than 50 per cent regression the mean duration of this relative therapeutic effect was 10 months (4–25). The mean treatment time was 11 months (124–892 days) and the mean dose of Primobolan Depot was 14.6 g (4.4–42.8).

In the 21 patients without any therapeutic effect the mean treatment time was 170 days (90–450) and the mean hormone dose 12 g (5.6–28).

If the 2 patients who were treated less than 3 months are included in the failure group, there remain 8 remissions out of 43 (19 per cent), which is in agreement with the generally observed remission rate for androgenic hormones in the treatment of carcinoma of the breast.

Tumour growth in soft tissue (inoperable primary tumours, local recurrences, skin and lymph node metastases) reacted relatively well to the hormonal treatment, totally in 10/24 cases.

Osseous metastases reacted less well only in 2/29 cases. However, in 11/29 cases the disseminated osseous metastases remained static during the treatment time.

Table 2

The effect of Metenolone Enanthate in 30 patients in relation to the site of metastases and post-menopausal age. Patients treated previously by other agents are not included. Remissions/patients treated. Numbers in brackets indicate static disease

Dominant site of metastases	Menopausal age				Total
	1 year	1–5 years	5–10 years	10 years	
Breast		1/1		1/1	2/2
Soft tissue cutis, subcutis lymph nodes	0/1 (1)		1/1	4/5	5/7 (1)
Osseous	0/3	0/2 (1)	0/1	0/13 (7)	0/19 (8)
Visceral liver			0/1		0/1
lung				0/1	0/1
pleura					
brain					
Total	0/4 (1)	1/3 (1)	1/3	5/20 (7)	7/30 (9)

Visceral metastases regressed in only 1/14 cases. Liver and lung metastases remained unchanged.

If, according to the suggestion of the U.S.A. Cooperative Breast Cancer Group, the pre-menopausal women and those who had received hormonal treatment earlier are excluded, and the material is classified according to the post-menopausal age and localization of the dominant lesion, 7/30 patients (23 per cent) remained as remissions (Table 2).

The number of remissions increased significantly with the duration of the menopause and the age of the patient (Tables 2, 3). The mean age of the patients with remissions was 71 years (51 to 83), of those without remissions 61 (38 to 84) years. No difference could be observed within the group of failures, i.e. between those in whom the disease remained static and those completely without hormonal effect.

The same relationship existed concerning the post-menopausal age and the therapeutic effect. The mean post-menopausal age of the patients with remissions was 24 (3 to 43) years and that of the other patients 11 (1 to 29) years.

In the more than 5 year post-menopausal women the remission rate was higher (7/34) than in the less than 5 year post-menopausal group (1/7). The best therapeutic results were obtained in the more than 5 year post-menopausal women with more than 1 year free interval (Table 3).

Side effects. The most common and unpleasant side effects during the treatment with androgenic hormones are those of virilisation such as hirsutism, hoarseness and

Table 3

The effect of Metenolone Enanthate in relation to post-menopausal age and the free interval. Objective remissions/patients treated. The numbers in brackets indicate static disease

Post-menopausal age	Free interval		Total
	0–1 year	>1 year	
<5 years	0/3 (1)	1/4	1/7 (1)
>5 years	2/11 (2)	5/23 (9)	7/34 (11)
Total	2/14 (3)	6/27 (9)	8/41 (12)

increased libido, developing in almost all patients when Metenolone Enanthate is given in high doses of 400 mg/week for a period of 3 to 5 months.

If higher doses are used, as in 23 of our patients, virilisation developed as early as 2 to 3 months after the beginning of treatment. Cramps in the limbs, particularly in the legs, occurred in 18 patients, and in one even in the facial muscles. The cause of this side effect is uncertain. No electrolyte disturbance was established. The symptoms disappeared rapidly after discontinuation of treatment, or with reduction in dosage to 100–200 mg/week or every other week.

Of the 41 patients, 29, with marked virilisation, developed in addition a facial flush similar to that seen in polycythaemia, probably due to a dilation of skin capillaries and to increased erythrocytes. Most patients increased in weight by a few kilograms, mainly due to sodium and water retention. In elderly patients with latent cardiac decompensation this could easily lead to cardio-vascular failure, and careful control of these patients is essential. Symptoms such as dyspnoea and retrosternal pains simulating angina pectoris occurred in 10/41 patients. All symptoms regressed completely a few weeks after the treatment had been discontinued.

Hypercalcaemia developed in one patient, but this rapidly returned to normal levels after the treatment with Primobolan Depot had been discontinued and phosphate solution administered. No disturbance of liver function was observed during treatment with large doses.

Discussion

The patients in the present material were not randomized with another group of patients treated by other hormones. There was no selection of patients in relation to the grade or type of dissemination of the disease.

In 30/41 patients Primobolan Depot was the first choice of hormonal treatment, in 11 patients it was the second one. One of the 8 objective remissions only, belonged to the second group.

Four patients had liver metastases with slightly increased transaminases but otherwise normal liver function. None of them reacted to the hormonal treatment.

The remission rate of 19 per cent is comparable with the usual response to androgenic hormonal treatment in breast carcinoma, which is inferior to that of oestrogenic hormones. The results were less favourable than those of KENNEDY & YARBRO who reported a remission rate of 48 per cent with Metenolone Enanthate 1 200 mg/week. It is also less than the effect of the nonandrogenic steroid Calusterone (17β-hydroxy-7β, 17α-dimethylandrost-4-en-3-one), obtained by GOLDENBERG et coll. (1973) in a prospective investigation. Objective remission was observed in about 28 per cent of 109 patients with approximately equal effect on local, osseous and visceral metastases. However, it is very difficult to compare results of different therapeutic regimes in tumour patients from various centres because of the differences in regard to assessment of clinical parameters. The virilising effect of Metenolone Enanthate is less than that of testosterone propionate but it is quite obvious after treatment with about 5 to 10 g during 2 to 4 months. The frequently troublesome cardio-vascular side effects and virilisation means an enforced reduction in the hormone dose after a few months of treatment. Experience from this material shows that an initial dose of 2×400 mg weekly is adequate in achieving a full therapeutic effect in 6 to 8 weeks.

Should there be no signs of regression at this time, continuation of treatment is contraindicated with regard to the side effects. In cases with regression, treatment may be continued at a lower dose of 100 to 200 mg/week. This dose is tolerated by most patients for a long period of time.

A surprising feature was the low therapeutic effect on osseous lesions in this series. Objective remission was found in only 2 out of 29 cases, in contrast to the usually observed 20 to 25 per cent. This may depend on the definition of remission and the fact that it is difficult to assess remission with over 50 per cent cases with only osseous metastases, especially if some areas had been irradiated previously. However, 11/29 cases with disseminated osseous metastases classified as failures, remained static during the treatment with Primobolan Depot with a mean time of 10 months, which may be considered as a partial therapeutic effect.

As in all hormone treatment, careful control of patients on treatment with Metenolone Enanthate is necessary, particularly during the initial months of treatment, with regard to possible hypercalcaemia and cardio-vascular failure.

Apart from the anti-tumour effect, the anabolic and bone marrow stimulation activity of Primobolan is very useful in long term treatment of patients with carcinoma with a depressed bone marrow due to metastases, irradiation or earlier cytostatic therapy. Doses of 100 to 200 mg/week seem to delay or prohibit pancytopenia in cases simultaneously treated with cytostatic agents.

SUMMARY

Forty-three patients with disseminated or inoperable carcinoma of the breast were treated with Metenolone Enanthate (Primobolan Depot) with doses of 400 to 1 200 mg/week for at least 3 months. Objective remissions lasting longer than 3 months occurred in 8 out of 41

evaluable patients. Soft tissue metastases responded best. Liver and brain metastases were unaffected. The therapeutic efficiency of Primobolan Depot is comparable to that of testosterone propionate but the agent is less virilising.

ZUSAMMENFASSUNG

Dreiundvierzig Patienten mit disseminierten oder inoperablen Karzinomen der Brust wurden mit Metonolone Enanthate (Primobolan Depot) mit Dosen von 400 bis 1 200 mg/Woche mindestens 3 Monate lang behandelt. Objektive Remissionen, die länger als 3 Monate anhielten, traten in 8 von 41 Patienten, die beurteilt werden konnten, auf. Weichgewebemetastasen reagierten am besten. Leber und Gehirnmetastasen wurden nicht beeinflusst. Die therapeutische Wirksamkeit von Primobolan Depot ist der von Testosteron Propionat vergleichbar, hat jedoch geringeren virilisierenden Effekt.

RÉSUMÉ

Quarante-trois malades atteintes de cancer du sein disséminé ou inopérable ont été traitées par le Méténolone-Enanthate (Primobolan Dépot) à des doses allant de 400 à 1 200 mg par semaine pendant au moins 3 mois. On a observé des rémissions objectives durant plus de 3 mois dans 8 des 41 cas utilisables. Ce sont les métastases dans les tissus mous qui ont le mieux répondu. Les métastases hépatiques et cérébrales n'ont pas été influencées. L'effet thérapeutique du Primobolan Dépot est comparable à celui du propionate de testostérone mais cet agent est moins virilisant.

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