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Endocrine Treatment with Anti-estrogen, Anti-androgen or Progestagen of Advanced Malignant Melanoma: Three Consecutive Phase II Trials

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Abstract—*Malignant melanoma is generally considered as a hormone-independent tumour. However, epidemiological, clinical and experimental data suggest that steroid hormones can influence the growth of this tumour. The therapeutic efficacy of endocrine treatment was evaluated in three consecutive phase II trials with the anti-estrogen tamoxifen, the anti-androgen cyproterone acetate and the progestagen medroxyprogesterone acetate. The 53 evaluable patients were mainly untreated with other forms of systemic therapy. Using response criteria in accord with WHO, none of the patients in the three trials obtained an objective remission. In summary, the present trials have demonstrated that the clinical course of advanced malignant melanoma is indifferent tocompetitive and additive endocrine treatment.*

INTRODUCTION

THE MODEST effect of cytotoxic therapy in the treatment of malignant melanoma and the suggestions from epidemiological, clinical and experimental data [1] that the growth of malignant melanoma could be influenced by endocrine treatment led us to an assessment of the efficacy of anti-estrogen, anti-androgen or progestagen in the treatment of human malignant melanoma.

MATERIALS AND METHODS

Sixty-three patients with advanced malignant melanoma admitted to the Department of Oncology I, Finsen Institute, were allocated to three consecutive phase II trials from November 1977 to October 1983.

Criteria of eligibility were as follows: patients with (a) advanced progressive malignant melanoma and measurable and/or evaluable lesions according to WHO criteria [2]; (b) performance status $\leqslant 2$ [2]; (c) no previous or concomitant other malignancy; and (d) the patients gave their oral informed consent.

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Patients fulfilling these criteria entered three consecutive trials: trial I with the anti-estrogen, tamoxifen (Nolvadex®), trial II with the anti-androgen, cyproterone acetate (Androcur®) and trial III with the progestagen, medroxyprogesterone acetate (Clinovir®).

The dose of tamoxifen (TAM) was 30 mg daily. The starting dose of cyproterone acetate (CYP) was 50 mg b.i.d., and in the absence of side-effects the dose was escalated to 50 mg q.i.d. after 1 month of treatment. Medroxyprogesterone acetate (MPA) was given at a dose of 300 mg three times daily orally.

Pretreatment examinations included: history, physical examination, chest X-ray, laboratory tests (blood cell counts, se-Ca., liver enzymes, and se-creatinine), and estimation of performance status. All visible and palpable lesions were measured to provide a baseline for subsequent examinations. Patients were assessed 1 month after initiation of therapy and at intervals of 2 months thereafter.

Response to treatment was defined according to the WHO criteria [2] as follows: complete response (CR) = complete disappearance of all measurable lesions; partial response (PR) = 50-99% reduction of measurable lesions and/or recalcification of bone lesions; no change (NC) =

less than 50% reduction of measurable lesions and/or no visible change in bone lesions; progressive disease (PD) = 25% increase of measurable lesions and/or definite decalcification of bone lesions and/or the appearance of new lesions.

In all three trials the treatment was continued until progression of disease, or until any prohibitive side-effect occurred. Time to treatment failure and the duration of response or no change was measured from the onset of therapy until PD was recorded. Survival was estimated as the time from the onset of therapy until death. A Kaplan-Meyer product-limit procedure was used to estimate the median time to treatment failure and the median survival.

RESULTS

A total of 63 patients entered the three trials and the distribution by protocol is shown in Table 1. In trial I four patients were ineligible, three because they had no measurable lesion and one due to previous malignancy. In both trials II and III one patient was ineligible due to lack of a measurable lesion. Four patients were non-evaluable, one in trial I (lost to follow-up) and three in trial II (one lost to follow-up, one never started treatment and one developed colon cancer).

Table 1. Distribution of patients according to trial

	No. of patients		
	TAM	CYP	MPA
Allocated	22	22	19
Ineligible	4	1	1
Non-evaluable	1	3	0
Evaluable	17	18	18

Table 2. Patient characteristics before treatment

	TAM (n = 17)	CYP (n = 18)	MPA (n = 18)
Age (yr)			
Median	58	52	65
Range	33-80	30-78	34-75
Sex			
Female	7	7	4
Male	10	11	14
Disease-free interval (months)			
Median	22	17.5	9.5
Range	0-132	0-150	0-78
Prior therapy			
Cytotoxic therapy	1/17	0/18	1/18
Endocrine therapy	0/17	3/18	3/18
Immunotherapy	0/17	1/18	0/18
Dominant site of disease			
Soft tissue:			
cutaneous	6/17	2/18	6/18
lymph nodes	3/17	5/18	3/18
Lung	7/17	9/18	7/18
Liver	0/17	1/18	2/18
Bone	1/17	0/18	0/18

The pretreatment characteristics of the 53 evaluable patients are shown in Table 2. The age-distribution is similar in all three trials. Although there are fewer females in trial III, the proportions between females and males are not significantly different. For reasons not known to us, the disease-free intervals in the three trials become shorter with time. Most of the patients were previously untreated and the dominant site of disease was in most cases soft tissue or lung.

The overall treatment results are shown in Table 3. None of the evaluable patients obtained a remission and, as can be seen from Table 4, even the duration of no change was in general very short. There is a tendency toward a longer time to treatment failure and prolonged survival in trial I, which probably reflects the fact that these patients were also those with the longest disease-free interval. Side-effects were few and generally mild in character. Only two patients treated with CYP had to stop treatment.

DISCUSSION

The results from the present trials indicate that malignant melanoma is a hormone-independent

Table 3. Response data: best response achieved

	TAM		CYP		MPA	
	No.	%	No.	%	No.	%
Progression	11	(65)	15	(83)	14	(78)
No change	6	(35)	3	(17)	4	(22)
Total	17	(100)	18	(100)	18	(100)

Table 4. Response data

	TAM (weeks)	CYP (weeks)	MPA (weeks)
Duration of no change			
Median	12	8	12
Range	8-52	8-26	8-12
Survival			
Median*	32	12	10
Range	7-168	2-100	2-56+
Time to treatment failure			
Median*	13	8	7
Range	5-56	2-28	2-37

*Derived from life table analysis.

Table 5. Endocrine treatment of malignant melanoma

Hormone/anti-hormone [ref.]	No. of trials	No. of patients	CR + PR	(%)
Estrogens [7]	1	18	2	(11)
Progestins [8, a]	3	62	2	(3)
Pregnenetrione [9, 10]	2	155	11	(7)
Anti-estrogen [5, 11-20, a]	12	192	15	(8)
Anti-androgen [a]	1	18	0	(0)

a, present report.

tumour in terms of response to various endocrine therapies.

Recently, Zava and Goldhirsch [3] reported that the [^{3}H]estradiol-binding proteins in melanoma cells are probably products of the tyrosinase-catalyzed oxidation of [^{3}H]estradiol instead of being specific receptors.

Although binding proteins for progestagens [4, 5] and androgens [4, 6] are found in about 30 and 25% of melanomas respectively, the biochemical characterization of these proteins is not sufficient to permit use of the term 'receptor'. In summary, it seems questionable whether receptors for sex hormones are present in malignant melanomas. This conclusion is in agreement with the overall clinical experiences with endocrine treatment of malignant melanoma. Table 5 summarizes the results from the present and other reports that used comparable criteria of response [5, 7, 20]. Although a response occasionally can be achieved, the overall rate of remission in a total of 442 patients was only 7% (95% C.L.: 5-9%).

This indicates that it is highly unlikely that endocrine therapy will play a role in the future management of malignant melanoma.

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