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EFFECT OF TOREMIFENE IN BREAST CANCER PATIENTS. PRELIMINARY COMMUNICATION

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Summary—Toremifene, an antiestrogenic drug administered at three dose levels (60, 120, and 300 mg/day) was investigated in 17 postmenopausal patients with advanced breast cancer previously treated with hormonal and/or cytostatic therapy. The drug proved to be well tolerated at all dose levels without any serious side effects even on prolonged administration. Neither response nor side effects have shown any dose dependency in this small group of patients.

INTRODUCTION

Toremifene has been shown to inhibit at high doses the growth of mouse uterine sarcoma by a mechanism which is not estrogen-receptor mediated [1]. In phase I clinical investigations toremifene was well tolerated up to a daily dose of 460 mg. when administered as a single oral dose during five consecutive days [2]. The aim of this combined phase I–phase II study was to investigate the tolerance, hormonal action and anti-tumor efficacy of toremifene in advanced, ER-rich or ER-undetermined postmenopausal breast cancer using three dose levels, either 60, 120 or 300 mg (high dose) daily.

SUBJECTS AND METHODS

Seventeen postmenopausal women with at least one measurable or evaluable lesion and with histologically or cytologically verified primary inoperable advanced or recurrent breast cancer were included in the study. Previous hormonal therapy or radiotherapy was allowed if it had been stopped at least 2 months before initiation of toremifene treatment. Severe concomitant liver, cardiac or renal insufficiency or marked dementia or other CNS disease were exclusion criteria. WHO index of performance status had to be 3 or better, age less than 75 yr and the life expectancy more than 3 months. Patient characteristics and the site of the lesion are presented in Table 1. At the beginning of the study patients were randomly allocated into 60, 120 or 300 mg treatment groups but the middle dose was soon omitted because 300 mg was well tolerated. The drug was administered as a single oral dose in the morning. Treatment was continued for at least 3 months, until disease progression or serious side effects prevented continuation.

The patients were clinically examined before inclusion in the study and thereafter at 3-month intervals for evaluation of the response. All the symptoms and signs were registered and the status of the lesion was evaluated or its size measured. The following laboratory values were assayed: blood cell count, sedimentation rate, prothrombin III, electrolytes (Na, K, Ca, PO_4), ALP, gamma-GT, s-creatinine, BUN, b-glucose, u-glucose, u-protein, and the following hormones: LH, FSH, SHBG, prolactin, estriol, TSH, T_4 and TRH-released prolactin. The laboratory values were analyzed by standard hospital laboratory methods except hormones which were determined by RIA kits of Farmos Group Ltd, Turku, Finland.

Treatment responses were evaluated at 3-month intervals except during the first 3 months of the treatment when recording was more frequent. Response criteria and duration of response were evaluated according to the UICC accepted criteria. New lesions were looked for only on the basis of symptoms.

RESULTS AND DISCUSSIONS

Of the 17 patients so far entered in the study, 16 were evaluable, i.e. toremifene treatment was 2 months or longer. Treatment responses and the present status of treatment are shown in Table 2. Of the 8 patients in the 60 mg group, two showed partial responses (12+ and 9+ months) and are still under treatment, three minor responses (6.5, 8.5 and 3 months) but have discontinued due to progressive disease or absence to follow-up, and three had progressive disease. In the 120 mg group, one minor response (6 months) and one case of stable disease (5 months) were recorded. In the 6 patients of the 300 mg group, there were two partial responses (2+ months), one case of stable disease (8 months) and

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Table 1. Characteristics of the patients

Age:	Mean 57.5 yr, range 44–72 yr	
Menopausal status:	2–5 yr	3
	6–10 yr	4
	11 + yr	9
Cause of menopause:	Spontaneous	12
	Gynec. op. (before breast cancer)	3
	Radiocastration	1
Predominant lesions:	Soft tissue	2
	Bone	5
	Lung	1
	Multiple	8

three progressions. The observations so far suggest that the efficacy of toremifene in patients with prior hormonal and/or radiotherapy may be comparable with that of other hormonal treatments although the number of patients is insufficient and the duration of the follow-up too short to draw final conclusions.

Toremifene was well tolerated at all doses. No patients were withdrawn from the study because of side effects. Nausea and vomiting, observed at all doses, occurred only at the beginning of the treatment. In one case, a conventional antiemetic drug was administered, otherwise these symptoms disappeared spontaneously. One case of pruritus and dermatitis was observed with 300 mg but this symptom disappeared after local treatment. One patient reported flushes and sweating during the first 10 days but the symptom ceased spontaneously without discontinuation of treatment. The frequency and severity of the side effects were independent of dose.

Table 2. Treatment responses and the present status of toremifene treatment

	Patient	Period of drug administration (months)	Response	Present status
60 mg	P.R.	6.5	MR	Finished (PD)
	K.M.	2	PD	Finished, MFF
	D.A.	8.5	MR	Finished (PD)
	H.J.	3	PD	Finished (PD)
	A.J.	3	MR	Finished, MFF
	L.M.	4	PD	Finished, MFF
	H.G.	12	PR	Under treatment
	S.K.	9	PR	Under treatment
120 mg	H.J.	5	NC	Finished (PD)
	R.Gy.	6	MR	Finished (PD)
300 mg	P.L.	8	NC	Finished (PD)
	Sz.J.	3	PD	Finished (PD)
	A.L.	3	PD	Finished (PD)
	H.J.	12	PD	Under treatment
	M.A.	3	PR	Under treatment
	B.J.	2	PR	Under treatment

PR = partial response, MR = minor response, NC = no change, PD = progressive disease, MFF = missed from follow-up.

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