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Toremifene, a New Antiestrogenic Compound, for Treatment of Advanced Breast Cancer. Phase II Study

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Abstract—*Forty-six postmenopausal women with estrogen receptor positive advanced breast cancer were treated with the novel antiestrogen toremifene in this phase II study. The patients had no prior or concurrent hormonal or cytostatic treatment. Sixty milligrams of toremifene was given as a single daily dose for a minimum treatment period of* 6 *weeks. Eight patients* (17%) *achieved complete response,* 17 (37%) *partial response and* 12 (26%) *showed no change. The median durations of responses were* 93, 66 *and* 24 *weeks, respectively. Three patients still continue the treatment in complete response, four patients in partial response. No significant differences in response rates could be seen when related to different estrogen receptor concentrations. The treatment was well tolerated, only two patients had remarkable side-effects; one of the patients interrupted the treatment mainly because of tremor. Our conclusion is that toremifene is an effective, safe and in clinical practice easily applied choice of treatment in estrogen receptor positive advanced breast cancer.*

INTRODUCTION

THE FIRST synthetic non-steroidal antiestrogen for pharmaceutical use, ethamoxytriphetol, was introduced in 1958 by Lerner *et al.* [1]. It was, however, too toxic and ineffective. Clomiphene, nafoxidine and tamoxifen, which are triphenylethylene compounds, have since then been introduced as antiestrogenic agents. In the treatment of unselected breast cancer patients all of these drugs give a response in about one third of the patients. Clomiphene and nafoxidine are no longer used for breast cancer because of their side-effects. Tamoxifen has a better therapeutic index and has become a first-line treatment of advanced hormone dependent breast cancer.

Tamoxifen is not only antiestrogenic but has also partial agonist activity. Whether the agonistic activity is harmful or not is an open question [2, 3]. Several novel antiestrogens have been developed with higher estrogen receptor affinity, better antiestrogenic properties and less agonistic activity than tamoxifen [4–11]. A higher receptor affinity or a better antagonist/agonist ratio does not, however, seem to result in enhanced antitumor efficacy [2, 3]. These characteristics are also species and organ specific [12], which poses special problems for all research efforts in this field.

Trioxiphene mesylate is one of the new antiestrogens with low intrinsic estrogenic properties and a four-fold higher affinity for estrogen receptors of induced murine mammary carcinoma than tamoxifen [11]. In 1986 two reports of trioxyiphene mesylate on the treatment of advanced breast cancer were published. It was concluded that this new drug was not more effective and had the same [13] or a higher [14] toxicity when compared with tamoxifen.

Toremifene is a new triphenylethylene antiestrogenic substance developed by Farmos Research Laboratory in Finland (Farmos' compound Fc1157a). Chemically it is 4-chloro-1,2-diphenyl-1,1,4,2-(*N*,*N*-dimethylamino)ethoxy phenyl-1-butene. It binds to estrogen receptors, is translocated into the nucleus and blocks estrogen-induced cell proliferation. In rats, toremifene is almost a pure antiestrogen, in mice also partially agonistic [15]. According to Zaccheo *et al.* the antiestrogenic/estrogenic ratio of toremifene was more favorable than that of tamoxifen [16]. The antitumor proper-

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Table 1. Inclusion criteria

Postmenopausal
Advanced breast cancer
Estrogen receptor positive tumor
Measurable or evaluable (= bones only) disease
No prior hormonal or cytostatic treatment
Karnofsky index ≥50
No severe heart, liver or renal disease nor uncontrolled diabetes
Life expectancy >3 months
Informed consent

Table 2. Patient characteristics

Mean age 64.5 years (45.8–80.3)
Mean postmenopausal time 17.3 years (1–41)
Relapse-free interval
≤2 years 20 patients
>2 years 23 patients
primary disease 3 patients
Mean Karnofsky index 80 (50–100)

ties are not, however, completely explained by the classical estrogen receptor mediated mechanism, since at high doses toremifene, in contrast to tamoxifen, has an antitumor effect on the mouse uterine sarcoma which is an ER negative tumor [17]. In a phase I study on healthy volunteers the drug was well tolerated at doses of up to 460 mg/day administered as a single peroral dose or on 5 consecutive days [18].

This paper presents the first phase II multicenter study of toremifene. The study was carried out to investigate the efficacy and toxicity of toremifene in postmenopausal patients with estrogen receptor positive breast cancer.

PATIENTS AND TREATMENT

Patients

The study protocol was accepted by the ethical committees of all the participating hospitals and informed consent was received from all the patients. From September 1983 to May 1985 49 postmenopausal women with either recurrent or primarily inoperable, advanced estrogen receptor positive breast cancer were registered for the study. Three of the originally registered patients did not fulfil the entry criteria (Table 1) and were excluded from the final analysis. Two of them did not have ER positive tumors. One patient had severe cardiac failure at the time of entry and died 3 weeks later. ER was considered positive when the ER content exceeded 7 fmol/mg cytosol protein. The patient characteristics are presented in Table 2. Twenty patients had only soft tissue disease, eight only visceral, six skeletal metastases and 12 had metastatic disease in two or more different tissues.

Table 3. Response rates with toremifene

	N		%	
CR	8		17	
		25/46		54%
PR	17		37	
NC	12		26	
PD	9		20	

Treatment

Based on preclinical and phase I data on toremifene a daily dose of 60 mg was selected and given orally as a single dose in the mornings. Treatment continued for at least 6 weeks or until progression or until significant side-effects were encountered.

Evaluation

The patients were examined clinically before the treatment and at 6 week intervals after this for evaluation of the response. At each visit symptoms and signs were registered, and any palpable lesions were measured. The following laboratory tests were made: blood count, erythrocyte sedimentation rate, serum potassium, sodium, chloride, calcium, ALP, ASAT, gamma glutamyl transferase, creatinine, FSH, LH and urinanalysis. Chest X-rays, abdominal ultrasonograms, bone scintigrams and bone X-rays were obtained at the beginning of the treatment and at 6 week intervals to evaluate the measurable lesions, when present. If there were no measurable lesions, these examinations were made at 3–6 month intervals or if any symptoms appeared. The response criteria and duration of responses were recorded according to the criteria accepted by UICC [19]. The duration of the complete responses was measured from the time CR was recorded, and the duration of the partial responses from the beginning of the treatment.

RESULTS

The antitumor effect of toremifene in the 46 evaluable patients is presented in Table 3. The median duration of complete response was 93 (range 18–147+) weeks and three patients are still in complete remission. The median duration of partial response was 66 (range 24–141+) weeks. Four patients have still PR and are continuing treatment. In six patients there was only partial response due to bone metastases, although there was CR in the metastases of other sites. The median duration of stabilization of the disease was 24 weeks, range 12–72 weeks. Four patients in this group discontinued the treatment at a time when the disease showed no signs of progression. In these cases the

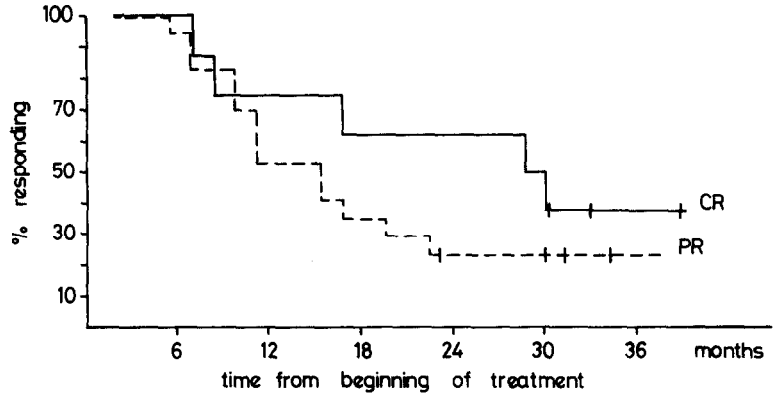

Fig. 1. Time to progressive disease for the responding patients.

Table 4. Response in relation to site of disease

	Soft tissue	Visceral	Bone	Multiple
No.	20	8	6	12
CR	6	1	—	1
PR	4	3	1	9
NC	4	3	4	1
PD	6	1	1	1

treatment was changed to other modalities of cancer therapy, because the unchanged situation was unbearable for the patients. The time to progression of the disease from the beginning of treatment is presented in Fig. 1 for the patients who responded.

The response rates in relation to the site of the disease are presented in Table 4. The objective response rate was poorest in the patients who had bone metastases: only one out of six patients had PR and the bone disease of four patients was stabilized. However, there were seven women in the group of patients with metastases in multiple sites who also had bone metastases and who got relief of pain and whose S-ALP values normalized and the lytic metastases became sclerotic. Four of eight patients with only visceral metastases responded. Two patients had only liver metastases and six lung/pleural metastases. Of the patients with liver metastases one had PR and the other stabilized disease. In addition there were two complete and three partial responses in patients with lung metastases among the 12 patients with multiple metastatic sites.

The efficacy of the treatment was not related to estrogen receptor concentration (Tables 5 and 6). Neither was there any measurable difference when efficacy was related to the presence or absence of progesterone receptors (Table 7), although the number of PR-negative patients (PR < 20 fmol/mg protein) was only 11. The response rate was not related to the disease-free interval. The response rate may be slightly better among patients with a longer time between menopause and diagnosis of mammary cancer (Table 8).

Table 5. Response according to ER concentration (cut-off point 30 fmol/mg protein)

	<30	≥30
No.	10	36
CR	2	6
PR	4	13
NC	1	11
PD	3	6

Table 6. Response according to ER concentration (cut-off point 100 fmol/mg protein)

	<100	≥100
No.	24	22
CR	4	4
PR	10	7
NC	3	9
PD	7	2

Table 7. Response in relation to ER and PR status

	ER+ PR+	ER+ PR−	ER+ PR*x*
No.	33	11	2
CR	5	3	—
PR	12	4	1
NC	11	—	1
PD	5	4	—

Table 8. Response in relation to the time after menopause

	<10 years	10–20 years	>20 years
No.	16	13	17
CR	1	3	4
PR	7	4	6
NC	3	4	5
PD	5	2	2

Table 9. Side-effects

	Mild	Moderate	Severe	Total
Sweating/hot flushes	8	1	1	10
Leucopenia	3	2	—	5
Vertigo	2	—	1	3
Nausea	2	2	—	4
Sleeping disturbance	1	1	—	2
Loss of appetite	1	1	—	2
Epigastric pain	1	1	—	2
Muscle stiffness	—	2	—	2
Tremor	—	1*	—	1
Headache	1	—	—	1
Leucorrhea	1	—	—	1

*Interrupted due to side-effects.

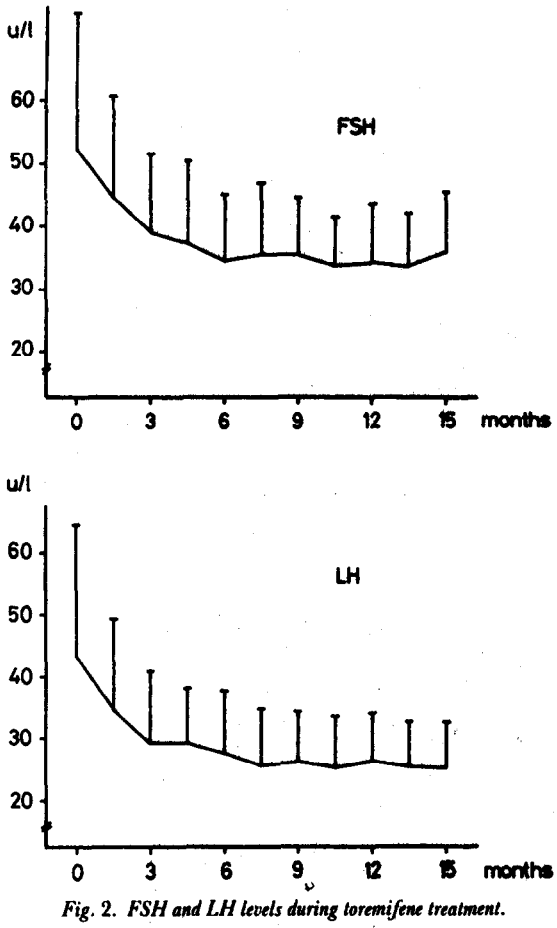

Fig. 2. FSH and LH levels during toremifene treatment.

Almost every patient had a distinct decrease of the erythrocyte sedimentation rate already after the first 6 weeks of treatment. The FSH and LH values decreased during treatment (Fig. 2), while the other laboratory variables showed no consistent changes.

During the treatment one patient developed a non-Hodgkin's lymphoma and one a superficial T_1N_0 transitiocellular bladder carcinoma. The treatment of the former patient was changed to cytostatics and she achieved complete response but died later of uncontrolled breast cancer. The latter patient continued toremifene treatment for 19.5 months when the breast cancer began to progress and the therapy was changed. The bladder cancer is under control.

SIDE-EFFECTS

Side-effects were specifically asked for and all, even suspected, side-effects were registered. Side-effects were generally mild and transient. Sweating/hot flushes was the most common symptom reported (Table 9), but only two patients found them disturbing. Severe sweating was transient in one patient. One patient had severe vertigo, but she had had vertigo already before treatment, though milder. One patient aged 80 years discontinued treatment because of tremor while the disease was in complete response. The lowest WBC counts were 2.5 and 2.6. These values were recorded only once at the first evaluation after 6 weeks of treatment and were transient. No hepatic, renal or pulmonary toxicity or hypercalcemia was observed. One 74-year old patient who was in complete response got a transient cerebral ischemic attack after 72 weeks of treatment, and although she recovered in a few hours treatment was stopped since she was in CR. These symptoms were evidently not associated with toremifene. No venous thromboses were diagnosed.

DISCUSSION

This study evaluated the efficacy and toxicity of a novel triphenylethylene antiestrogen, toremifene, in the treatment of postmenopausal women with estrogen receptor positive breast cancer. The overall response rate was 54% and is well comparable with other hormonal treatments [20, 21]. Soft tissue and visceral metastases responded equally. Bone metastases seemed to respond less favorably, but if all patients with bone metastases are included (even those with disease in multiple sites), eight of 16 patients with bone involvement had partial response.

The estrogen and progesterone receptor levels were measured either from the primary or some metastatic lesion. The receptor levels were not associated with the rate of response, but the small number of patients gives reason to interpret this finding with caution. It will be of interest to study the efficacy of the drug in ER negative tumors.

The median duration of CR was 21.6 months and the median duration of partial response 15.5 months. In several studies the mean or median duration of response of tamoxifen therapy is between 9 and 18 months [20, 21]. Thus, toremifene appears to be well comparable with tamoxifen.

The side-effects were carefully screened and registered, but only two patients complained of disturbing side-effects and no serious side-effects occurred. Toremifene seems to be at least as well tolerated as tamoxifen at the doses used in this study (60 mg daily). Because this new drug was well tolerated even at high doses in phase I studies, there are studies going on where higher doses (100–240 mg daily) are used for treatment of breast cancer. A randomized study where tamoxifen and toremifene are being compared has also been started.

Toremifene is an effective drug with long lasting responses for the treatment of estrogen receptor positive advanced breast cancer. The drug has no serious side-effects and is thus well tolerated. Further studies will situate its role in the treatment of breast cancer.

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