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SAFETY AND EFFICACY OF TOREMIFENE IN BREAST CANCER PATIENTS. A PHASE II STUDY

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Summary—46 postmenopausal women with estrogen receptor positive breast cancer entered a phase II study with a novel antiestrogen, toremifene. Patients had either recurrent or primarily inoperable advanced disease. No prior or concurrent cytostatic or hormonal treatment was allowed. Eight patients (17%) achieved complete response (CR), 17 (37%) partial response (PR) and 13 (28%) had stabilization of their disease at least for three months. The mean durations of responses were 52+, 53+ and 27+ weeks, respectively, with 5 patients in CR, 6 in PR and 1 with no change (NC) still continuing the treatment. No significant differences could be seen in response rates according to the concentration of estrogen receptors or presence of progesteron receptors in this group of patients. Toxicity was not a problem, in general, the treatment was well tolerated. Two side effects (sweating and vertigo) were classified as severe and one patient after achieving PR interrupted the treatment because of tremor.

INTRODUCTION

Toremifene is a new triphenylethylene antiestrogenic substance developed by Farmos Group Ltd in Finland. Chemically it is 4-chloro-1,2-diphenyl-1-{4[2-(*N*,*N* dimethylamino)ethoxy]-phenyl}-1-butene. It binds to the estrogen receptors of the cytosol, is translocated to the nucleus and blocks estrogen-induced cell proliferation. The antitumor properties are, however, not completely explained by the classical ER-mediated mechanism. In preclinical studies toremifene could be given to animals in higher doses than tamoxifen without any eye or liver toxicity. In phase I studies, the drug was well tolerated even at high dose levels of 460 mg [1].

A phase II study on a multicenter basis was conducted in Finland in order to investigate the efficacy and toxicity of this new drug in breast cancer patients. On the basis of preclinical and phase I data on the antitumor and antiestrogenic properties of the drug the dose level of 60 mg was selected for the first phase II clinical study [2, 3].

PATIENTS AND METHODS

Patients

Between September 1983 and May 1985 49 postmenopausal women with estrogen receptor positive advanced breast cancer, either recurrent or primarily inoperable, were registered for the study. Three of the patients were found to have violated the requirements for entry and were excluded from the analysis. Two of them did not have ER positive tumors and one had severe incompensated heart disease at the time of entry and died three weeks later. The lowest value accepted as ER positive was 8 fmol/mg protein and 20 fmol/mg protein for PgR. Inclusion criteria have been shown in Table 1. 46 patients were eligible for the final analysis in June 1986. The mean age was 65 years (46–80), the mean time after menopause 17 years (1–41), and median Karnofsky index 80 (50–100). There are 3 patients with primarily inoperable tumors, 20 with disease-free interval less than 2 years and 23 with more than 2 years after primary operation. 20 patients had soft tissue disease (local, cutaneous, lymph nodes), 8 visceral (lungs, liver), 6 bones and 12 multiple locations.

Treatment

The treatment consisted of 60 mg toremifene orally as a single daily dose. The treatment was continued for at least six weeks or until progression or significant side effects occurred.

Evaluation was carried out at six week intervals. The response classes, durations of responses and side effects were determined according to the criteria accepted by the UICC [4].

RESULTS

Responses and their durations

The antitumor effect of toremifene in the 46 evaluable patients is presented in Table 2. The mean

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Table 1. Inclusion criteria for the study

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

duration of CR from the time CR was registered was 52+ (5–92+) weeks with 5 patients still in CR. The mean duration of PR from the beginning of the treatment was 53+ (22–84+) weeks with 6 patients continuously in PR. Respectively, the mean duration of NC was 27+ (10–62+) weeks with 1 patient continuing the treatment. Five of the NC patients interrupted the treatment without progressive disease and were changed on other modalities of cancer treatment. Time of progressive disease in the responding patients from the beginning of toremifene treatment is presented in Fig. 1.

Response rates in relation to site of the disease have been shown in Table 3, in relation to ER concentration in Table 4, and PR status in Table 5. The response rate was worst in patients with bone metastases with only one of six patients responding. Several of the multiple site patients had CR in soft tissue disease, but were classified as PR because of worse response in bone metastasis.

Side effects

All side effects were registered very carefully and actively questioned at every visit. 21/46 (46%) patients reported no side effects. 2/46 (4%) had severe side effects: one patient excessive sweating and another vertigo. The severe sweating was transient and the patient with vertigo had the same symptom in a minor degree before the treatment started. An 80 years old lady interrupted the treatment because of tremor which she considered to result from toremifene treatment. Detailed analysis of side effects is presented in Table 6. None of the leukopenias were clinically significant, the two moderate (grade 2) leukopenias had only one value of 2.5 and 2.6 respectively at the first 6 weeks' control. Most of the side effects were transient. No hepatic, renal or pulmonary toxicity or hypercalcemia were observed.

Table 2. Antitumor activity of toremifene in 46 evaluable patients

Response	Number of patients *n*	%
CR	8	17
PR	17	37
NC	13	28
PD	8	17
(CR + PR)	25/46	54%

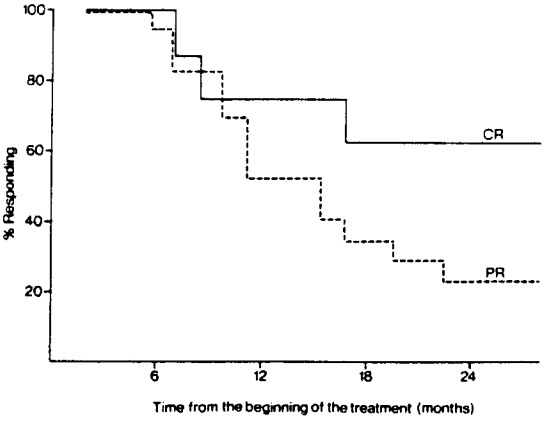

Fig. 1. Duration of objective response to toremifene treatment, 60 mg daily.

CONCLUSION

The results of tamoxifen treatment in ER positive advanced breast cancer are well known; 49% objective response rate with mean duration of 13 months and about 2–3% of patients interrupting the treatment because of intolerance [5]. We have presented the results of a clinical phase II trial with a novel antiestrogenic antitumor substance, toremifene. The overall response rate was 54% and the mean duration of responses (CR + PR) from the beginning of the treatment 15+ months with 11 patients still continuing the treatment. One patient interrupted the treatment because of a side effect. The results indicate that toremifene has good clinical efficacy and is well tolerated in the treatment of ER positive advanced breast cancer of postmenopausal women. Further studies with different dose levels and comparison in a phase III study with tamoxifen are warranted. In

Table 3. Response of breast cancer patients to toremifene treatment in relation to the site of the disease. Several patients with multiple site lesions and PR had complete response in soft tissue but not in bone lesions

(No.)	Soft tissue (20)	Visceral (8)	Bone (6)	Multiple (12)
CR	6	1	—	1
PR	4	3	1	9
NC	5	3	4	1
PD	5	1	1	1
Total response	10/20	4/8	1/6	10/12

Table 4. Response of breast cancer patients to toremifene treatment in relation to ER concentration. Cut-off points of ER level are 30 and 100 fmol/mg protein.

(No.)	<30 (10)	⩾30 (36)	<100 (24)	⩾100 (22)
CR	2	6	4	4
PR	4	13	10	7
NC	2	11	4	9
PD	2	6	6	2
Total response	6/10 60%	19/36 53%	14/24 58%	11/22 50%

Table 5. Response of breast cancer patients to toremifene treatment in relation to ER and PgR status. PgR_x = PgR undetermined.

(No.)	ER+ PgR− (11)	ER+ PgR+ (33)	ER+ PgR_x (2)
CR	3	5	—
PR	4	12	1
NC	1	11	1
PD	3	5	—
Total response	7/11	17/33	1/2

Table 6. Side effects of toremifene treatment as registered using active questioning.

	Mild	Moderate	Severe	Total
Sweat/hot flushes	7	1	1	9
Leukopenia	3	2	—	5
Vertigo	3	—	1	4
Nausea	2	1	—	3
Sleeping disturbances	1	2	—	3
Loss of appetite	1	1	—	2
Upper abdominal pain	1	1	—	2
Muscle stiffness	—	2	—	2
Tremor	—	1*	—	1
Headache	1	—	—	1
Leucorrhea	1	—	—	1
Total	20	11	2	33

*Interrupted due to side effects.

the present study no correlation of response rate with estrogen receptor levels was observed.

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