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Phase I clinical and pharmacokinetics study of high-dose toremifene in postmenopausal patients with advanced breast cancer*

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Summary. Toremifene is an antiestrogen that binds strongly to estrogen receptors (ER). A total of 19 previously treated postmenopausal women with metastatic breast cancer whose performance status was good and whose ER status was positive or unknown were studied to determine the maximum tolerated dose of toremifene. Cohorts of patients received 200, 300, or 400 mg/m^2 p.o. daily until relapse or unacceptable toxicity had occurred. Nausea, vomiting, and dizziness were dose-related. Three of five patients receiving 400 mg/m^2 experienced moderate or severe vomiting and another developed reversible disorientation and hallucinations. Mild sweating, peripheral edema, vaginal discharge, and hot flushes were encountered at all doses. Reversible corneal pigmentation was identified in seven cases but was not of clinical importance. The pharmacokinetics of toremifene was studied weekly and in detail on day 42 using a high-performance liquid chromatographic (HPLC) assay that identified the parent compound and three active metabolites, *N*-desmethyltoremifene, (deaminohydroxy)toremifene, and didemethyltoremifene. Steady state was achieved at 1–3 weeks. The toremifene area under the curve and the maximal concentration were dose-dependent at high doses. The recommended phase II dose is 300 mg/m^2 p.o. daily.

Introduction

Toremifene is a triphenylethylene antiestrogen (4-chloro-1,2-diphenyl-1-{4-[2- (*N,N*- dimethylamino)-ethoxy]-phenyl}-1-butene) that was synthesized in 1981; it binds to estrogen receptors (ER) with an affinity that amounts to about 5% of that of estradiol and is similar to that of tamoxifen [7]. Structurally, toremifene differs from tamoxifen only by the substitution of one atom of chlorine in place of a hydrogen. Toremifene has shown activity against both the ER-positive human breast-cancer cell line MCF-7 and the dimethylbenzanthracene (DMBA)-induced mammary carcinoma in rats [9, 15, 16]; the growth of an ER-negative, tamoxifen-resistant murine uterine sarcoma was significantly inhibited by high doses of toremifene. This unexpected activity and the occasional responses obtained in some patients with tamoxifen-resistant breast cancer suggest that toremifene and tamoxifen may differ in their mechanism of action [3]. These findings provided a rationale for the investigation of high-dose toremifene to define its maximum tolerated dose (MTD).

Clinical phase I trials of oral toremifene have been performed using single or 5-day dosing to 460 mg or daily dosing to 400 mg/day [11, 12, 21]. Mild nausea and vomiting was seen but was severe in only one patient at 40 mg/day and one subject at 200 mg/day. Adverse central nervous system effects were noted but were not dose-related. These studies did not establish an MTD.

Phase II trials of toremifene in patients with breast cancer have shown its activity to be dependent on the prior treatment [4, 22, 23]. In these studies, the complete plus partial objective response rate varied from 21% in patients receiving 20 mg/day to 68% at 240 mg/day. Only a few patients who had progressed on tamoxifen responded to toremifene. A number of factors such as patient selection and the number of subjects studied may have contributed to the observed variation in response rate. However, given these data, further investigation of the dose-limiting toxicity of high-dose toremifene appeared relevant.

This report describes a clinical and pharmacokinetics study of high-dose toremifene. The aims of this study were to establish the MTD of continuous-dose oral toremifene using standard World Health Organization (WHO) toxicity criteria [13], to develop an assay for and investigate the pharmacokinetics of toremifene and its metabolites at high-dose steady state, and to document any clinical responses.

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Patients and methods

Patients' eligibility. Eligible patients were required to have histologically proven metastatic or locally advanced breast cancer, an unknown or positive ER status (>10 fmol/mg protein), an Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2, evaluable or measurable breast cancer, a life expectancy of at least 8 weeks, and normal renal and hepatic function (serum creatinine values of <0.15 mmol/l and bilirubin levels of <3 times the normal value); in addition, an interval of 4 weeks must have elapsed since any prior endocrine therapy or chemotherapy and an interval of 6 weeks since previous radiotherapy or mitomycin C treatment. All subjects were required to be postmenopausal and to be capable of giving written informed consent to participate in the study.

Patient assessment and follow-up. Using WHO toxicity criteria, toxicity was monitored weekly for the first 6 weeks of treatment and monthly thereafter. Systemic disease workup was performed on study entry and then at 12-week intervals or until the removal of patients from the study. The workup consisted of a liver scan; a bone scan; skeletal X-rays; liver-function tests; biochemistry, including serum calcium; and a full blood examination. Biochemistry was performed monthly throughout the treatment period. An ophthalmological examination was carried out pretreatment, every 4–6 weeks during the treatment period, and then intermittently after cessation of the treatment.

Treatment plan. Cohorts of six evaluable patients were entered in the study at a starting dose of 200 mg/m^2, which was escalated by 100 mg/m^2 until the MTD had been reached. Toremifene (Farmitalia Carlo Erba, Australia) was given daily as one morning dose, with doses being rounded to the nearest 20 mg because 20 mg was the smallest tablet size. If three of six patients at any dose level developed severe WHO grade 3 or 4 toxicity, the study was stopped at that dose level.

Response criteria. For response assessment, we used the WHO criteria for reporting results of cancer treatment [13].

Blood sampling and drug assay. From all patients, predose blood samples (10 ml) were taken on days 0, 7, 14, 21, 28, and 35. On day 42, patients were admitted for a 24-h pharmacokinetics study. Subjects were not instructed to fast or to alter their diets otherwise. Blood was collected at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h via an indwelling catheter kept patent with heparinized saline. All blood samples were collected into heparinized tubes and centrifuged immediately, and the plasma was frozen at –70° C until analysis. Urine was collected prior to dosing, and total urinary volumes at 4, 8, 12, and 24 h were recorded and aliquots were frozen for later assay.

Toremifene and three metabolites (supplied by Farmos Group, Oulu, Finland) were quantified in plasma and urine using a high-performance liquid chromatographic (HPLC) method [25]. Briefly, plasma proteins were precipitated with acetonitrile (1 : 2, v/v) containing the internal standard (Fc-1226a, Farmos Group) and the samples were centrifuged. Supernatant (100 µl) was injected onto a C-18 Novapak column and eluted with a mobile phase of acetonitrile, 100 mM ammonium acetate, and triethylamine (65 : 35 : 0.05, by vol.) at pH 6.4. Ultraviolet detection was carried out at 277 nm. The limit of quantitation for toremifene, *N*-desmethyltoremifene, and (deaminohydroxy)toremifene was 200 ng/ml plasma. Didemethyltoremifene was identified late in the trial and was therefore quantitated in nine patients only.

Pharmacokinetics. The concentrations of toremifene and metabolites in the five weekly samples from each patient were tabulated along with the exact interval between the last dose and the sample. Also included in these "steady-state" calculations were the predose and 24-h samples from the pharmacokinetics study performed at 6 weeks. For the 24-h pharmacokinetics studies, the area under the curve of plasma concentration versus time (AUC) for 0–24 h was calculated using the linear trapezoidal method. It was not possible to determine the terminal elimination half-life since it is much longer than 24 h [12]. The maximal concentration (c_{max}) and the time required to reach this concentration (t_{max}) were tabulated from the actual data. Mean values and standard deviations for these parameters were calculated for the 200- and 300-mg/m^2 dose levels.

Ethical considerations. The protocol was written to comply with the Ethics Guidelines of the National Health and Medical Research Council of Australia and the Ethics Committee of the Peter MacCallum Cancer Institute. Patients gave separate written informed consent for both the clinical and the pharmacological studies. The protocol and documentation required compliance with the guidelines for good medical practice.

Table 1. Toxicity documented during the present study

Toxicity	Dose (mg/m^2)	Patients (*n*)	Worst WHO toxicity grade				
			0	1	2	3	4
Nausea and vomiting	200	8	3	4	1	0	0
	300	6	0	2	4	0	0
	400	5	0	2	2	0	1
Dizziness	200	8	6	2	0	0	0
	300	6	2	3	1	0	0
	400	5	1	2	1	1	0
Sweating	200	8	6	1	1	0	0
	300	6	3	3	0	0	0
	400	5	2	3	0	0	0
Peripheral edema	200	8	6	2	0	0	0
	300	6	2	3	1	0	0
	400	5	2	3	0	0	0
Vaginal discharge	200	8	6	2	0	0	0
	300	6	3	3	0	0	0
	400	5	5	0	0	0	0
Hot flushes	200	8	7	1	0	0	0
	300	6	2	4	0	0	0
	400	5	3	0	2	0	0

Results

Of the 19 women entered in this trial, 7 had an ECOG performance status of 0, 7 had a status of 1, and 5 had a status of 2. The median age was 60 years (range, 38–79 years). In general, patients had been heavily pretreated (median, 2 prior treatments; maximum, 7), and only three subjects had received no prior endocrine therapy. In all, 15 had undergone prior tamoxifen therapy and 17 had received prior radiotherapy. Eight patients received 200 mg/m^2 toremifene (actual dose, 240–400 mg/day), 6 were given 300 mg/m^2 (actual dose, 430–580 mg/day), and 5 received 400 mg/m^2 (actual dose, 540–790 mg/day). One patient scheduled to receive 400 mg/m^2 was given 380 mg/m^2 (actual dose, 680 mg) in error.

The major toxicity was nausea and vomiting, which appeared to be dose-related (Table 1). At the 200- and 300-mg/m^2 dose levels, nausea and vomiting was easily controlled by the administration of toremifene at night or by occasional low oral doses of metoclopramide. However, nausea and vomiting was moderate or severe in three of five patients at 400 mg/m^2 and was responsible for the cessation of treatment in one subject at that level. Dizziness was also dose-related, with four of five patients experiencing this toxicity at 400 mg/m^2. In addition to the

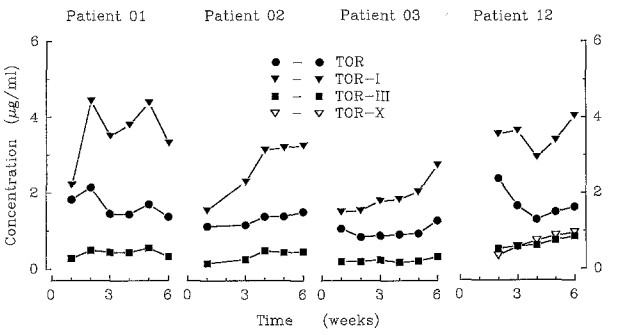

Fig. 1. Toremifene and metabolite plasma concentrations measured in weekly predose blood samples obtained from representative women (*Patients 1–3*) receiving 200 mg/m^2 toremifene and from one woman (*Patient 12*) receiving 300 mg/m^2

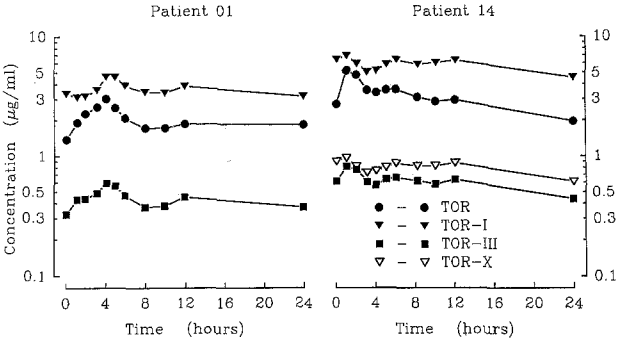

Fig. 2. Plasma concentration-time profiles resulting from the 24-h pharmacokinetics study performed on day 42 in representative women receiving 200 (*Patient 1*) or 300 mg/m^2 toremifene (*Patient 14*)

toxicities detailed in Table 1, two patients receiving 400 mg/m^2 experienced reversible disorientation and hallucinations that required cessation of the drug after only 1 week. A further patient at this dose level developed reversible ataxia.

Sweating, peripheral edema, vaginal discharge, and hot flushes were occasionally seen at all doses but were mild and not of clinical importance. Hypercalcemia was seen in three patients and was a manifestation of proven progressive metastatic bone disease in all cases. One subject had mild hypercalcemia on the day of study entry, in violation of the protocol.

The median duration of toremifene treatment was 18 weeks at the 200- and 300-mg/m^2 dose levels and only 1 week at the 400-mg/m^2 dose level. Among the patients receiving 400 mg/m^2, treatment was discontinued early in two cases because of toxicity and in two others due to disease progression. One patient continued to receive 400 mg/m^2 at 22 weeks.

Routine slit-lamp ophthalmological examinations were performed on study entry and at 4- to 6-week intervals thereafter. Corneal pigmentation was seen in 7 of 19 patients (at 200 mg/m^2 in 3 cases and at 300 mg/m^2 in 4 cases). The patient who received 400 mg/m^2 for 22 weeks did not develop this complication. This abnormality was a brown discoloration appearing in the lower third of the corneal epithelium in a vortex pattern. It was not associated with any symptom or visual abnormality as determined on ophthalmological assessment. The median time required to develop the discoloration was 12 weeks (range, 4–23 weeks). It did not require cessation of the drug. The abnormality was reversible in all five patients thus far retested following the discontinuation of toremifene. The median time to a normal corneal examination after cessation of the drug was 12 (range, 10–22) weeks.

In all, 10 of 19 patients had stable disease for at least 8 weeks, 7 developed disease progression, and 2 were not evaluable for response. Two of the stable patients achieved an objective partial response [13] involving symptomatic control at one of their metastatic sites, with other sites remaining unchanged. The median duration of stable disease was 24 weeks.

Steady-state concentrations of toremifene were generally achieved in most patients within 1 week (Fig. 1). Since the samples were taken just prior to dosing, these values represent minimal concentrations. Mean predose concentrations of toremifene and metabolites calculated for individual patients using a minimum of three samples are presented in Table 2. The mean interval between the last dose and the blood sample was 26±2 h. Some samples were not included because they were taken at 12 h following the administration of a dose in the evening. One patient receiving 300 mg/m^2 was excluded from these calculations because this interval was <12 h. The overall mean steady-state trough concentration of toremifene was 1.53 and 2.17 μg/ml at 200 and 300 mg/m^2, respectively. The concentrations of *N*-desmethyltoremifene were more than double those of toremifene, whereas (deaminohydroxy)toremifene and didemethyltoremifene levels were much lower.

Table 2. Mean weekly predose toremifene and metabolite concentrations for individual patients

	Mean predose concentration (μg/ml)			
Patient number	TOR	TOR-I	TOR-III	TOR-X
200 mg/m^2:				
1	1.68	3.76	0.43	NA
2	1.23	2.74	0.38	NA
3	0.97	1.90	0.22	NA
6	1.88	3.39	0.46	NA
7	1.83	3.86	0.64	NA
8	1.56	2.58	0.52	NA
Mean	1.53	3.04	0.44	
SD	0.36	0.76	0.14	
300 mg/m^2:				
9	2.06	3.74	0.75	NA
10	1.79	3.22	0.51	NA
11	2.92	6.66	0.85	1.01
12	1.63	3.39	0.65	0.68
14	2.44	4.43	0.37	0.63
Mean	2.17	4.29	0.63	0.77
SD	0.52	1.40	0.19	0.21

NA, Not assayed; TOR, toremifene; TOR-I, *N*-desmethyltoremifene; TOR-III, (deaminohydroxy)toremifene; TOR-X, didemethyltoremifene

The full pharmacokinetics study was performed in six patients each at 200 and 300 mg/m^2 and in one subject at 400 mg/m^2. Representative concentration versus time profiles are shown in Fig. 2. Toremifene was rapidly absorbed, reaching a peak within 1–6 h (mean, 3 h), but

Table 3. Summary of 24-h toremifene and metabolite pharmacokinetics

	200 mg/m²			300 mg/m²		
	t_{max} (h)	c_{max} (μg/ml)	AUC (μg ml⁻¹ h)	t_{max} (h)	c_{max} (μg/ml)	AUC (μg ml⁻¹ h)
TOR	2.5±1.0	2.79±0.69	41.4±11.2	3.2±1.9	4.00±0.95	55.3±12.4
TOR-I	7 (3–26)	3.95±0.92	74.0±22.1	6 (1–26)	5.42±1.11	102.4±25.7
TOR-III	2.5 (1–6)	0.66±0.19	11.3± 3.7	3 (1–6)	0.99±0.20	16.4± 3.1

All data represent mean values ± SD except for the metabolite t_{max} data, which indicate median values and ranges (n = 6 patients). TOR, Toremifene; TOR-I, *N*-desmethyltoremifene; TOR-III, (deaminohydroxy)toremifene

concentrations tended to decline somewhat erratically thereafter, with frequent rises being observed in plasma toremifene concentrations. At 200 and 300 mg/m², the c_{max} and AUC values for toremifene, *N*-desmethyltoremifene, and (deaminohydroxy)toremifene were all proportional to the dose. The pharmacokinetics are summarized in Table 3.

For didemethyltoremifene, the c_{max} was 1.04±0.18 μg/ml and the AUC was 19.4±2.6 μg ml⁻¹ h in four patients receiving 300 mg/m². Few toremifene or metabolite peaks were detected in the patients' urine, suggesting that renal excretion plays a minor role in toremifene elimination.

Patient 17 was the only subject receiving 400 mg/m² who completed 6 weeks of therapy and underwent a 24-h pharmacokinetics study. In this subject, the steady-state trough concentrations of toremifene and *N*-desmethyltoremifene were 1.6 and 3.1 μg/ml, and the c_{max} and AUC of toremifene were 2.7 and 34.2 μg ml⁻¹ h. These values are comparable with those found in patients receiving 200 mg/m², suggesting that this subject did not completely absorb the drug. Alternatively, extensive metabolism may have occurred, although increased metabolite levels were not detected.

Discussion

The MTD of toremifene was explored in this study because other hormonal agents such as medroxyprogesterone acetate may exhibit a dose-response relationship [17, 19]. This phase I study was developed to investigate high-dose therapy for future phase II studies. An international randomized phase III trial is currently comparing toremifene at total doses of 60 and 200 mg in previously untreated breast-cancer patients with the intent of further examining the dose-response relationships of toremifene in breast cancer.

This study established an MTD for daily oral toremifene of 400 mg/m², or a total dose of 540–790 mg. At that level, the dose-limiting toxicities were nausea and vomiting and dizziness. These toxicities were dose-related and intolerable. Reversible disorientation, hallucinations, and ataxia were also seen at this dose. Sweating, peripheral edema, vaginal discharge, and hot flushes were observed at all dose levels and were not clearly dose-related. The recommended phase II dose for high-dose toremifene is 300 mg/m²/day.

Approximately 2% of ER-positive women on tamoxifen and 15% of those on estrogens eventually develop hypercalcemia as a flare response accompanied by worsening bone pain [10, 14, 18, 24]. This study was designed to identify any important changes in serum calcium levels. Hypercalcemia was seen in three patients on study. All three of these subjects showed clear radiographic and biochemical evidence of progression of bone metastases at the time at which hypercalcemia developed. It appears unlikely that the hypercalcemia seen in these cases represented a flare reaction.

Retinopathy with macular edema has been described in patients receiving long-term high-dose tamoxifen [6]. Thus, all patients in the present study were subjected to ophthalmological assessments pretreatment and at intervals of 4–6 weeks thereafter. Corneal pigmentation (cornea certiculata) was seen in 37% of patients; it was reversible in all five patients who were retested following cessation of the drug and was of no clinical importance. Retinopathy with macular edema was not seen. Although some corneal changes have been described in subjects treated with tamoxifen [6], this pigmentation has not previously been reported in patients receiving toremifene. It resembles the reversible corneal verticulata seen observed during treatment with the antiarrhythmic drug amiodarone [2, 5].

Toremifene is extensively (99.7%) bound to serum proteins [20], therefore, only the total toremifene concentration was measured in our patients' samples. Daily oral dosing of 200 and 300 mg/m² toremifene produced steady-state concentrations of the parent drug within 1 week. This contrasts with the apparent elimination half-life of 4.5–7.3 days [1, 26], which would imply that a period of at least 13 days (three half-lives) would be required to reach 88% of steady state. The toremifene steady-state trough concentration at 200 mg/m² is in agreement with that reported by Wiebe and co-workers [26].

During the 24-h study, plasma levels of toremifene often increased after 6–8 h (in 12 of 13 patients). At least two possible explanations related to enterohepatic recycling might account for this observation. First, biliary excretion of the parent compound and subsequent reabsorption may have occurred. Second, this increase might have involved biliary excretion of a metabolite, reabsorption of the metabolite, and its conversion back to toremifene. Enterohepatic recirculation of toremifene has been reported by other investigators [1, 26]. Toremifene is extensively metabolized, and up to ten metabolites have been identified in human feces [1].

Toremifene metabolites have biological activity [8]. Results of in vitro and animal studies indicate that the metabolites do not significantly contribute to the antitumor effect of toremifene in DMBA-induced rat mammary cancer. However, *N*-desmethyltoremifene and didemethyltoremifene are as effective as the parent compound in inhibiting the growth of MCF-7 cells in culture. In addition, many of the metabolites produce hormonal effects that are similar to those caused by toremifene and may therefore play a role in the drug's antitumor activity. *N*-Desmethyltoremifene, the main metabolite in humans, is equivalent to toremifene in its ability to bind to estrogen receptors and in its estrogenic and anti-estrogenic activities.

In conclusion, toremifene given continuously at oral doses of 300 mg/m^2/day was well tolerated. Any mild nausea that develops at that dose can be overcome by nocturnal dosing. It may be appropriate to perform an ophthalmological examination at 12 weeks to identify corneal verticulata. Our study on the steady-state pharmacokinetics of toremifene and its metabolites indicates that at least some of the antitumor activity of the drug may be attributable to these metabolites.

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