

Dose Escalation of *N,N',N''*-Triethylenethiophosphoramidate Combined with Pentoxifylline for Advanced Breast Cancer¹

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ABSTRACT

Pentoxifylline potentiates the cytotoxicity of alkylating agents in preclinical models. In this study we sought to define the maximum tolerated dose (MTD) of *N,N',N''*-triethylenethiophosphoramidate (thioTEPA) with pentoxifylline, and to estimate the antitumor response to this combination in previously treated breast cancer patients. Thirty-five previously treated advanced breast cancer patients received 70 cycles (median, 2 cycles/patient; range, 1-6) of 1600 mg of oral sustained release pentoxifylline every 8 h for 4 doses in combination with escalating doses of i.v. bolus thioTEPA 40-65 mg/m² administered 3 h after the second dose of pentoxifylline. Thrombocytopenia was dose limiting at 65 mg/m² of thioTEPA, and the MTD was defined as 60 mg/m². Among 25 patients treated at the MTD, leukopenia was grade 2 in 9 patients (36%), grade 3 in 4 patients (16%), and grade 4 in 2 patients (8%); thrombocytopenia was grade 2 in 3 patients (12%), grade 3 in 4 patients (16%), and grade 4 in 3 patients (12%). No other thioTEPA-related toxicity was observed. Plasma concentrations of thioTEPA, TEPA, and pentoxifylline were measured in 6 patients. The median (range) area under the plasma concentration *versus* time curve for thioTEPA was 29.4 μM/h (26.2-40.5) and for TEPA was 16.3 μM/h (9.2-21.7 μM-h). The median (range) maximal plasma concentration of pentoxifylline and major metabolites I, IV, and V were 1.2 μg/ml (0.2-7.8), 4.0 μg/ml (0.5-16.4), 0.4 (range 0.1-0.8), and 2.9 (1.1-5.5), respectively. No objective responses were observed among 21 evaluable patients treated at the MTD (95% confidence interval, 0-15%). The combination of pentoxifylline and thioTEPA is well tolerated but not active in previously treated advanced breast cancer patients. Further clinical trials using commercially available oral sustained release pentoxifylline as a modulator of alkylating agents are not warranted.

INTRODUCTION

Alkylating agents are an important class of antineoplastic drugs. Multiple mechanisms of resistance to alkylating agents have been described (1). Mechanisms of drug resistance are potential targets for interventions designed to overcome resistance and improve the therapeutic efficacy of alkylating agents. This strategy has led to the identification of drugs, designated modulators, that experimentally potentiate the cytotoxicity of alkylating agents by interfering with drug resistance through a variety of mechanisms (2).

Methylxanthines are modulators that potentiate the cytotoxicity of alkylating agents in human tumor cell lines and human tumor xenografts in mice (3-9). Two mechanisms for the modulating effects of methylxanthines have been proposed. In cell cultures methylxanthines interfere with DNA repair by accelerating transit through G₂, allowing damaged cells to divide without completing the repair process (3, 10). A second mechanism is possibly related to the effects of the substituted methylxanthine pentoxifylline [1-(5'-oxohexyl)-3,7-dimethylxanthine, Trental; Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ] on tumor oxygenation and blood flow.

Experimental evidence suggests that hypoxia contributes to resistance to radiation therapy and alkylating agents, and the correction of tumor hypoxia may increase the efficacy of these treatments (2, 11-13). Pentoxifylline improves microcapillary blood flow and oxygenation in ischemic muscle, and is approved for the treatment of symptomatic peripheral vascular disease (14, 15). This drug increases RBC and WBC deformability, inhibits platelet aggregation, inhibits fibrinolytic activity, and suppresses production of tumor necrosis factor α and tumor necrosis factor α mRNA expression (15). Like its effect on ischemic muscle, pentoxifylline also improves the oxygenation of tumors and increases tumor blood flow in tumor-bearing mice (16-19). Alkylating agent cytotoxicity is enhanced by pentoxifylline *in vivo* at plasma levels capable of increasing the oxygenation of ischemic muscles but less than those required to accelerate transit through G₂. This suggests that improved tumor oxygenation or blood flow might be a putative mechanism of pentoxifylline modulation (3, 4, 9, 20).

These observations led us to hypothesize that pentoxifylline, a commercially available oral drug with few side effects, could be administered in combination with thioTEPA.⁴ ThioTEPA was utilized because preclinical studies showed pentoxi-

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⁴ The abbreviations used are: thioTEPA, *N,N',N''*-triethylenethiophosphoramidate; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; AUC, area under the plasma concentration *versus* time curve; PR, partial response.

Table 1 Dose escalation of thioTEPA

Dose (mg/m ²)	No. of patients	No. of courses
40	3	10
50	3	7
60	26	46
65	3	7
Total	35	70

fylline enhanced thioTEPA-induced growth delay in a murine EMT6 mouse mammary carcinoma, and because the cytotoxicity of thioTEPA is oxygen dependent (9, 21). In addition, thioTEPA is active in human breast cancer, and its principle toxicity is limited to myelosuppression. In a previous Phase I study, Dezube *et al.* (20) defined the MTD of pentoxifylline as 1600 mg three times daily in combination with a fixed dose of 40 mg/m² of thioTEPA. In the current trial the objectives were to define the MTD of thioTEPA in combination with the 1600 mg dose of pentoxifylline, and to estimate the antitumor response of this combination in previously treated breast cancer patients.

PATIENTS AND METHODS

Patient Characteristics. Patients were 18 years of age or older with histologically confirmed breast cancer, and one or more sites of measurable metastases or evaluable bone metastases. They were required to have an Eastern Cooperative Oncology Group performance status of 0–2 (ambulatory, in bed less than 50% of the day), to have a granulocyte count >1800/ μ l, platelet count >100,000/ μ l, hematocrit >30%, total bilirubin <1.5 mg/dl, aspartate aminotransferase <90 IU/dl, and serum creatinine <1.8 mg/dl, and to be more than 3 weeks since prior chemotherapy, hormone therapy, radiation therapy, or surgery. Patients with a prior history of angina, myocardial infarction, congestive heart failure, atrial or ventricular arrhythmias, or life-threatening visceral metastases such as extensive liver metastases, lymphangitic lung metastases, or carcinomatous meningitis were excluded. Prior treatment could include adjuvant chemotherapy and any number of hormonal therapies for metastases. Prior treatment had to include one prior chemotherapy regimen for metastases, or a documented relapse within 12 months of completing adjuvant chemotherapy.

Eligible patients had either bidimensionally measurable metastatic disease by physical examination, chest X-ray, computed tomography scans, or other imaging procedures, or evaluable bone metastases. Patients with pleural effusions or other nonmeasurable sites were excluded.

Treatment. One thousand six hundred mg of sustained release pentoxifylline (four 400-mg tablets) was administered p.o. every 8 h for a total of 4 doses. The 4 tablets could be taken over 1 h and/or with food. Three h after the second dose of pentoxifylline, thioTEPA was administered by a 10-min i.v. bolus injection according to the dose escalation scheme (Table 1). This schedule was designed to achieve coincident peak levels of thioTEPA, pentoxifylline, and the major active metabolite (Metabolite I) after the second pentoxifylline dose (14).

Treatment cycles were repeated every 21–35 days when the total WBC and platelet counts recovered to 3,000/ μ l and

Table 2 Patient characteristics (n = 35)

Median age (yr)	51 (range, 30–76)
Performance status 0–1	32 (91%)
Prior adjuvant chemotherapy	31 (89%)
Prior chemotherapy for metastases	32 (91%)
Prior exposure to cyclophosphamide	35 (100%)
Prior exposure to doxorubicin	30 (86%)

100,000/ μ l, respectively. Toxicity was graded with the use of the Common Toxicity Criteria. During the dose escalation portion of the study, a minimum of 3 patients were treated at each dose level until DLT was observed in 2 patients after 1 cycle of treatment. DLT was considered grade 3 or higher nonhematological toxicity, or grade 4 hematological toxicity. Once the DLT was reached, the prior dose level was defined as the MTD. Twenty-five patients were to be treated at the MTD to estimate the toxicity and response of the regimen.

Study Parameters. Before treatment, a medical history, physical examination, complete blood count, serum chemistries, chest radiograph, electrocardiogram, and radiological studies imaging sites of metastatic disease were obtained in all patients. Weekly blood counts were performed during treatment, and sites of measurable or evaluable disease were assessed after 2 treatment cycles, or earlier if the patient failed to complete 2 cycles. Response was graded with the use of the Eastern Cooperative Oncology Group criteria (22).

Blood Sampling. Ten-ml blood samples were drawn from two patients treated with 65 and four patients treated with 60 mg/m² of thioTEPA at 0, 15, 30, 45, 60, 90, 120, and 180 min from the beginning of the i.v. bolus infusion. The samples were placed on ice and centrifuged at 4°C for 15 min at 2200 RPM, and the supernate plasma was separated and immediately frozen at –79°C.

Drug and Metabolite Assays. ThioTEPA and TEPA levels were measured with the use of a modification of the method of Cohen *et al.* (23). Pentoxifylline and three of its metabolites (I, IV, and V) were assayed in the laboratory of Dr. Patrick J. Davis (University of Texas, Austin, TX) as described (24). Plasma thioTEPA and TEPA levels were plotted as a function of time after bolus administration of thioTEPA, and the AUC was calculated by the trapezoidal method. Whole body clearance, apparent distribution volume, and steady-state plasma concentrations of thioTEPA and TEPA were calculated by non-compartmental analysis (25). Peak plasma concentrations of pentoxifylline and major metabolites I, IV, and V were measured at 3.25 h after the second dose of pentoxifylline.

RESULTS

Thirty-five patients received a total of 70 cycles (median, 2 per patient; range, 1–6) of pentoxifylline and thioTEPA (Table 1). The median patient age was 51 (range, 30–76) and performance status was 0–1 in 91% (Table 2). Prior treatment included adjuvant chemotherapy (89%) and chemotherapy for metastatic disease (91%). Three patients (9%) who relapsed within 12 months of completing adjuvant chemotherapy were enrolled. Virtually all patients received cyclophosphamide and doxorubicin. Only 2 patients (6%) received more than one prior chemotherapy regimen for metastases.

Table 3 Hematological toxicity in cycle 1 (n = 34)

Dose (mg/m ²)	n	Toxicity Grade			
		0-1	2	3	4
Nadir white blood count					
40	3	3	0	0	0
50	3	3	0	0	0
60	25	10	9	4	2
65	3	2	1	0	0
Nadir platelet count					
40	3	3	0	0	0
50	3	3	0	0	0
60	25	15	3	4	3
65	3	0	1	1	1

Toxicity. Pentoxifylline-related gastrointestinal toxicity was grade 2 (moderate) in 14 patients (40%) and grade 3 (severe) in 3 patients (9%). These symptoms were successfully managed with the use of oral lorazepam and suppositories of nebutal 1 h before the administration of each dose of pentoxifylline. Two patients experienced cardiac palpitations. In one patient, the palpitations occurred 1 h after 1600 mg of pentoxifylline on 2 separate occasions. Electrocardiograms obtained when the patient was no longer symptomatic failed to demonstrate tachycardia or other abnormality. The dose of pentoxifylline was reduced to 800 mg, and no further palpitations occurred. This was the only pentoxifylline dose reduction. The second patient developed paroxysmal supraventricular tachycardia 15 days after receiving pentoxifylline. This patient was converted to normal sinus rhythm with verapamil. This patient was removed from study due to disease progression, and no further pentoxifylline was administered. No other nonhematological toxicity was observed.

Hematological toxicity during cycle 1 of treatment is described in Table 3. Two of 3 patients treated with 65 mg/m² thioTEPA experienced nadir platelet counts of 23,000 and 30,000/ μ l, respectively, and recovery was delayed in each case for more than 5 weeks. Although the strict definition of dose-limiting toxicity was not met, the prolonged duration of platelet recovery was responsible for considering 65 mg/m² of thioTEPA to be dose limiting. This was because it was desirable to treat patients with multiple cycles without undue delay, rather than a single cycle. The MTD thioTEPA dose was then defined as 60 mg/m².

Twenty-five of 26 patients (96%) treated at the MTD thioTEPA were evaluable for hematological toxicity. One patient received spinal irradiation 7 days after receiving cycle 1 and was considered inevaluable. Leukopenia was grade 2 (moderate) in 9 patients (36%), grade 3 (severe) in 4 patients (16%), and grade 4 (life-threatening) in 2 patients (8%), and thrombocytopenia was grade 2 in 3 patients (12%), grade 3 in 4 patients (16%), and grade 4 in 3 patients (12%). Cumulative hematological toxicity was not apparent between cycles 1 and 2 (data not shown). However, only 3 patients received more than 2 treatment cycles, limiting an analysis of cumulative hematological toxicity in subsequent cycles. No other thioTEPA-related non-hematological toxicity was observed.

Pharmacokinetics of ThioTEPA and Pentoxifylline.

The median (range) for the AUC thioTEPA at the 60 mg/m² dose (MTD) was 29.4 μ M/h (26.2–40.5 μ M/h) and for the AUC TEPA was 16.3 μ M/h (9.2–21.7 μ M/h) (Table 4 and Fig. 1). The AUC TEPA/thioTEPA ratio was 0.5. The median (range) maximal plasma concentration of pentoxifylline and major metabolites I, IV, and V were 1.2 (0.2–7.8), 4.0 (0.5–16.4), 0.4 (0.1–0.8), and 2.9 (1.1–5.5) μ g/ml, respectively.

Response. One patient treated at 65 mg/m² of thioTEPA had a PR with interval regression of a supraclavicular node and improvement in multiple sites of bone metastases. After 5 treatment cycles disease, progression was documented. No other responses were observed during the dose escalation portion of the trial.

Twenty-one of 26 patients (81%) treated at the MTD were evaluable for response. Five patients (3 with grade 4 hematological toxicity and prolonged recovery, 1 with newly diagnosed central nervous system metastases, and 1 who underwent surgery for a sigmoid volvulus unrelated to breast cancer) were considered inevaluable because they were removed from study after one treatment cycle and did not have a timely restaging evaluation. Among the 21 evaluable patients, 16 (76%) had measurable metastases and 5 (14%) had evaluable bone metastases. There were no complete or PRs observed (overall response rate, 0%; 95% confidence interval, 0–15%), 3 patients (14%) had stable disease, and 16 patients (86%) had progressive disease.

DISCUSSION

Dose-limiting thrombocytopenia was observed at 65 mg/m² of thioTEPA, and the MTD was defined as 60 mg/m². In Phase I trials of thioTEPA alone, dose-limiting thrombocytopenia occurs at 75 mg/m², and the MTD is 65 mg/m² (26, 27). The slightly lower MTD thioTEPA may be related to an enhancement of hematological toxicity by pentoxifylline, but this seems unlikely. Factors such as the extent of prior treatment the patients received, or the criteria for defining DLT, which included consideration of both the absolute nadir and the duration of thrombocytopenia, were probably responsible for the slightly lower MTD.

Nausea and vomiting was experienced by most patients after pentoxifylline. This is consistent with the results of Phase I trials where gastrointestinal toxicity was dose limiting at 2000–2400 mg of pentoxifylline (20, 30). Although the gastrointestinal symptoms in this trial were successfully managed with an aggressive outpatient antiemetic regimen, further dose escalation of pentoxifylline was precluded. There was no apparent worsening of gastrointestinal toxicity after the thioTEPA infusion perhaps because the patients were receiving an antiemetic regimen before each dose of pentoxifylline.

The other toxicity possibly related to pentoxifylline was cardiac palpitation and arrhythmia, which was observed in 2 of 35 patients (6%). In a prior pentoxifylline study, the frequency of cardiac arrhythmia was also 5% (20). A 0.3% incidence of cardiac palpitation or arrhythmia was observed in patients treated with either placebo or the 400-mg oral sustained release pentoxifylline tablet (14). The 1600-mg dose of pentoxifylline may be associated with a higher incidence of cardiac palpita-

Table 4 Pharmacokinetics of thioTEPA

mg/m ² (n)	AUC ^a (μM/h)	Cl _{ss} ^b (liters/m ² /h)	V _{dss} (liters/m ²)	Ratio AUC TEPA/thioTEPA
thioTEPA				
60 (4)	29.4 (26.2–40.5)	10.8 (7.8–12.1)	12.6 (12.5–16.0)	
65 (2)	29.1 (28.3–30.0)	11.8 (11.4–12.2)	20.6 (20.0–21.3)	
TEPA				
60 (4)	16.3 (9.2–21.7)			0.5 (0.4–0.6)
65 (2)	23.4 (19.2–27.5)			0.8 (0.7–0.9)
Pentoxifylline (1600 mg)				
Parent drug				1.2 (0.2–7.8)
Metabolite I				4.0 (0.5–16.4)
Metabolite IV				0.4 (0.1–0.8)
Metabolite V				2.9 (1.1–5.5)

^a All values are median (range).

^b Cl_{ss}, whole body clearance; V_{dss}, apparent distribution volume; C_{max}, maximal plasma concentration.

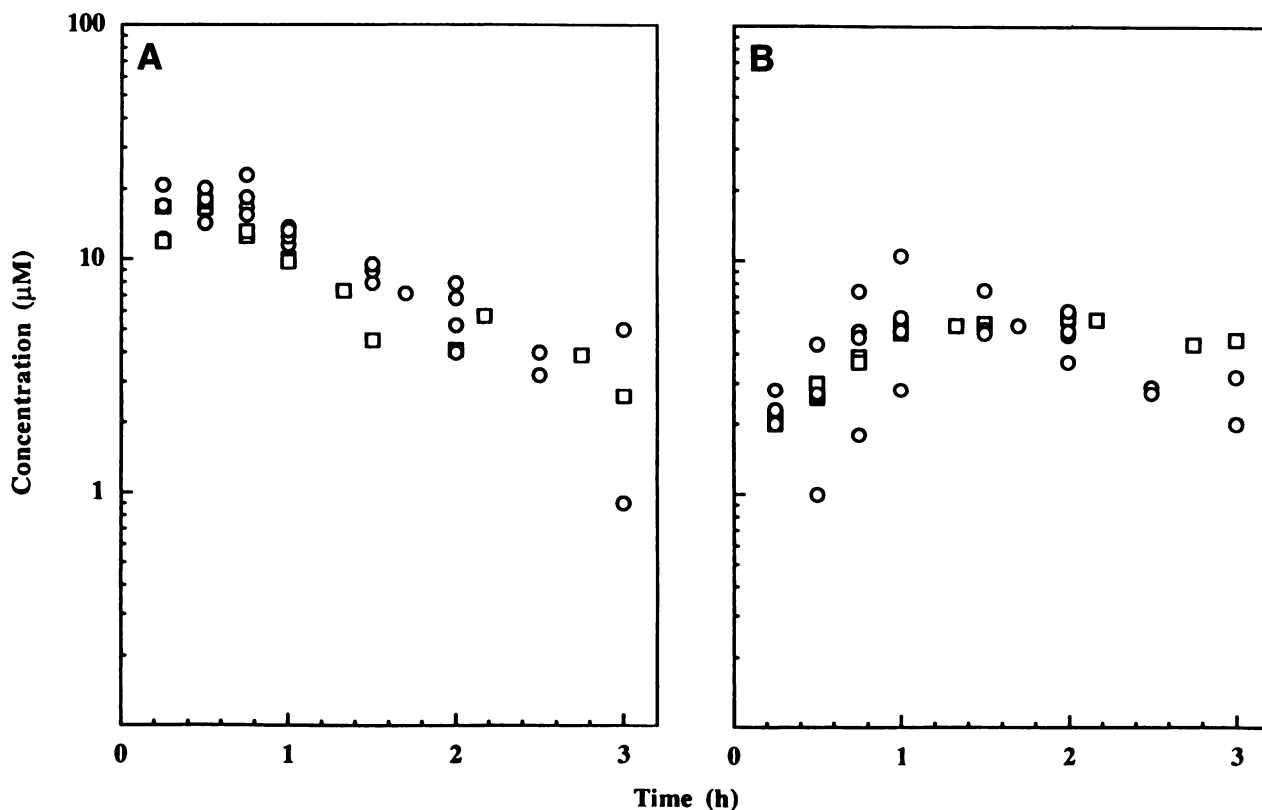


Fig. 1 A, thioTEPA plasma concentrations plotted as a function of time for four women who received 60 mg/m² (○) or two who received 65 mg/m² (□) of thioTEPA in combination with p.o. self-administered pentoxifylline. B, metabolically derived TEPA concentrations in those same plasma samples.

tions or arrhythmia, but the frequency and severity of this toxicity was low and of limited clinical significance.

Although 1 patient had a PR during the dose escalation portion of the study, no responses were observed in 21 evaluable patients treated at the MTD thioTEPA. The lack of activity of the regimen might be attributable to several factors. Plasma

levels of pentoxifylline may have been too low to modulate thioTEPA activity, or in patients previously treated with alkylating agents and anthracyclines, the tumors may have been cross-resistant to thioTEPA by a variety of mechanisms.

Administration of 50 or 100 mg/kg of i.p. pentoxifylline to tumor-bearing animals potentiates the cytotoxicity of thioTEPA,

and doses as low as 5–10 mg/kg i.p. are associated with statistically significant increases in intratumor oxygen tension and tumor perfusion (9, 16–19). The expected pentoxifylline exposure after the 1600-mg oral dose exceeds that observed after i.p. injections of 50 or 100 mg/kg (20, 30). However, the maximum peak pentoxifylline levels after i.p. dosing are at least 10-fold higher than the peak levels observed after oral dosing. It is also possible that a more prolonged duration of pentoxifylline exposure before thioTEPA administration might have enhanced the cytotoxicity of the regimen. A prolonged schedule of pentoxifylline administration was not incorporated into the design of this study due to concerns about gastrointestinal toxicity. The relative importance of maximal peak *versus* prolonged pentoxifylline exposure as they affect the modulation of thioTEPA and other alkylating agents remains to be determined.

The AUC thioTEPA in combination with pentoxifylline was similar to studies of thioTEPA alone (26, 27). In contrast, the values for the AUC TEPA were about 4-fold lower than expected. After an i.v. bolus dose of 65 mg/m² thioTEPA, Heideman *et al.* (26) and O'Dwyer *et al.* (27) reported an AUC TEPA of 90–100 $\mu\text{M}/\text{h}$ as compared to 23 $\mu\text{M}/\text{h}$ in the current trial. (26, 27). Hepatic P-450 cytochromes are responsible for the enzymatic conversion of thioTEPA to TEPA via oxidative desulfuration, and for the extensive first-pass enterohepatic metabolism of pentoxifylline to metabolite I by reduction and metabolites IV and V by oxidation (14, 28, 29). Thus, pentoxifylline might inhibit the activity of the saturable P-450 monooxygenases responsible for TEPA formation. More extensive study is required to precisely define how TEPA formation is affected by pentoxifylline.

The median plasma levels of pentoxifylline and metabolites I, IV, and V were similar to those reported in prior trials (20, 30). Ingestion of food slows the rate of absorption of pentoxifylline but does not affect the AUC (31). The wide range of values for pentoxifylline and metabolites observed in this and other studies may have been due to individual variation in the rate of drug absorption, food ingestion, scheduling, or compliance with self-administration (20).

ThioTEPA is an active drug in breast cancer. The response rate in Phase II trials ranges from 8 to 37% with the use of doses of 12–25 mg/m² (32). To our knowledge, there are no studies of single agent thioTEPA in untreated or previously treated breast cancer patients at doses comparable to the current study. Virtually all patients in this study were treated previously with the alkylating agent cyclophosphamide and the anthracycline doxorubicin. The prospects for obtaining responses in previously treated breast cancer patients is limited due to the development of drug resistance (32). The lack of observed responses in this trial may indicate that pentoxifylline modulation is not sufficient to improve the activity of thioTEPA against tumors already resistant to alkylating agents by a variety of other mechanisms.

The combination of pentoxifylline and thioTEPA is well tolerated but not active in previously treated breast cancer patients. A similar lack of modulating activity of oral pentoxifylline has been noted in another trial (33). Further clinical trials using commercially available oral sustained release pentoxifylline as a modulator of alkylating agents are not warranted.

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