Phase I Trial of Escalating Pentoxifylline Dose with Constant Dose Thiotepa

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ABSTRACT

Pentoxifylline, a methylxanthine, is an effective modulator of alkylating agents in tissue culture and in human tumor explants in mice. In this Phase I trial, escalating dose controlled release pentoxifylline was administered p.o. 3 times daily for 5 days (15 doses) with a constant dose of thiotepa, 40 mg/m² i.v. on day 2. Forty-four courses of escalating doses of pentoxifylline varying from 400 to 2400 mg were administered to 22 patients with refractory malignancies.

Gastrointestinal toxicity, consisting mainly of nausea and vomiting, was dose limiting at 2400 mg pentoxifylline and subsided completely within 24 h of cessation of the drug. Nongastrointestinal toxicity of this thiotepa/pentoxifylline combination was infrequent and included bone marrow depression and supraventricular tachycardia. Increasing the dose of pentoxifylline did not increase the frequency of these rare toxic effects.

Plasma concentrations of pentoxifylline and its major metabolites were determined by gas chromatography. Drug accumulation was noted within a cycle (i.e., by day 5) in only two patients and between cycles in no patient.

The recommended Phase II dose of p.o. pentoxifylline is 1600 mg (four 400-mg tablets) when given 3 times daily for 5 days (15 doses) with 40 mg/m² i.v. thiotepa. Based on an interspecies comparison, this dose exceeds that predicted from mouse models to enhance chemotherapy. This regimen can be safely administered on an outpatient basis, with adequate control of gastrointestinal symptoms achieved by standard antiemetics and intermittent dosing with meals. Phase II trials are required to determine the activity of alkylator/modulator combinations.

INTRODUCTION

Alkylating agents are a heterogeneous class of antineoplastics with broad clinical activity and with an important role in the treatment of selected human cancers (1). The possibility exists for enhancing their specific cytotoxic activity by modulation with nonantineoplastic agents. Greater selective cytotoxicity could be important, for example, in nullifying the resistance tumors often develop against alkylators, since such resistance seldom exceeds 10-fold (2). In contrast, resistance to the antimetabolite methotrexate can exceed 10,000-fold (3). The successful example of modulation of the activity of the antimetabolite 5-fluorouracil by leucovorin has progressed from the laboratory (4) to the patient’s bedside, improving response rates and survival in both metastatic colorectal (5) and head and neck (6) cancers. Investigations into modulation of alkylating agents, therefore, offer potential for improved chemotherapy.

We used a methylxanthine in this study because of the demonstrated ability of methylxanthines to enhance the cytotoxic effects of chemotherapy both in vivo and in vitro. Caffeine, a methylxanthine, substantially enhanced the antitumor effects of bleomycins and phleomycins on rat Walker 256 carcinosarcoma and murine Ehrlich ascites tumor (7). Nitrogen mustard-resistant plasmacytomas implanted in hamsters responded to mechlorethamine when the animals were given caffeine in their drinking water (8). A Phase I/II protocol for pancreatic cancer patients at Memorial Sloan-Kettering using arabinoside-C, cisplatin, and escalating doses of caffeine achieved an impressive 39% response rate (9), although this was not confirmed in a recent abstract (10).

We chose pentoxifylline [1-(5'-oxohexyl)-3,7-dimethylxanthine (Fig. 1), Trental; Hoechst-Roussel Pharmaceuticals, Somerville, NJ] for our Phase I study. It is already approved for the treatment of patients with intermittent claudication from chronic occlusive arterial disease and has a side effect profile more favorable than that of caffeine (11, 12). In a subrenal capsule assay using human bladder or breast cancer xenografts, pentoxifylline potentiated the antitumor effect of thiotepa with no untoward toxicity to normal tissue (13). In a murine in vivo assay by Teicher, pentoxifylline enhanced tumor growth delay when added to thiotepa, cyclophosphamide, cisplatin, or carboplatin. Pentoxifylline’s relative absence of toxicity at clinical doses and its ability to potentiate alkylator treatment served as the rationale for this trial.

The goal of our Phase I study was to establish the dose-limiting toxicity and MTD* of controlled release pentoxifylline in combination with a constant dose of thiotepa. This study’s initial dose level of pentoxifylline was 400 mg p.o. 3 times daily for 5 days (15 doses). At this dose, the incidences of gastrointestinal, neurological, and cardiac (angina) side effects are 2.8%, 1.9%, and 0.3%, respectively (11).

MATERIALS AND METHODS

Patient Characteristics. Twenty-two patients were entered in this study over a 9-month period and were followed for at least 2 months after leaving the study. Patients were required to be 18 years of age or older, to have histologically documented malignancy refractory to standard effective regimens, to be more than 3 weeks from prior chemotherapy, radiation, or surgery, and to have Eastern Cooperative Oncology Group performance status of 0–2 (symptomatic, in bed less than 50% of day) (Table 1). Adequate organ function was required, including bone marrow: WBC, >4,000/mm³; platelets, >100,000/mm³; hepatic: bilirubin, <1.5 times normal; renal: creatinine, <1.5 times normal; creatinine clearance, >50 ml/min; cardiac: no prior myocardial infarction or angina or current arrhythmia (≤3 premature atrial contractions/min were eligible); and neurological: no prior cerebrovascular accidents. A minimum life expectancy as an eligibility criterion was not included. Written and witnessed informed consent was obtained from all patients.

Treatment Plans. Pentoxifylline was administered p.o every 8 h for 5 days (15 doses), with meals or snacks in order to decrease nausea and vomiting. Total pentoxifylline area under the curve was unaffected by concomitant administration of food (14). Thiotepa, 40 mg/m², was administered on day 2, 2 h after the 4th pentoxifylline dose. Patients were discharged after receiving the thiotepa. The remaining 11 doses of pentoxifylline were taken on an outpatient basis. Second and subsequent cycles, given every 28 days, were completely on an outpatient

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2 To whom requests for reprints should be addressed, at Division CG & R, D810a, Dana-Farber Cancer Institute, 44 Binney St., Boston, MA 02115.

3 B. Teicher, Division of Cancer Pharmacology, Dana-Farber Cancer Institute, personal communication of unpublished data.

4 The abbreviation used is: MTD, maximum tolerated dose.
Dose escalation of pentoxifylline followed a modified Fibonacci scheme, beginning at 400 mg p.o. 3 times daily for 5 days (15 doses) and increasing to 2400 mg on the same schedule (Table 2). Three patients were treated at each dose level until significant toxicity was reached. A minimum of 4 weeks elapsed between dose escalations. Escalation continued until 2 of 3 patients treated at a given dose level developed life-threatening (grade 4) organ toxicity or until nausea and vomiting became severe enough that patients had no significant food intake or had 6–10 episodes of vomiting/24 h (grade 3) (see “Appendix”). When dose-limiting toxicity developed in 2 patients, the prior dose was defined as the MTD. An additional 11 patients were accrued at the MTD to ensure that the toxicity of the MTD was acceptable. Dose escalations within patients were not permitted. Antiemetics were administered at the discretion of the treating oncologist.

Study Parameters. Baseline studies in all patients included history, physical examination, complete blood count, serum chemistries, chest radiograph, electrocardiogram, and appropriate baseline scans, radiographs, or serological markers. Complete blood counts, serum chemistries, and electrocardiograms were followed weekly for 3 weeks and then monthly for 2 months. An additional electrocardiogram on day 2 was obtained. Standard toxicity criteria were used for evaluation (see “Appendix”).

Blood Sampling. Serial 10-ml samples for pentoxifylline levels were obtained in sodium heparin-containing Vacutainer tubes (Becton Dickinson no. 6527) as follows: day 2 trough, just prior to 4th dose (inpatient on cycle 1); day 2 peak, 2 h after the 4th dose, just prior to the thiotepa (inpatient on cycle 1); and day 5 peak, 2 h after the 15th dose (outpatient). This latter level was to check for drug accumulation within a cycle. After centrifugation of the specimens, plasma was removed, placed in polystyrene tubes, and stored at −20°C until analysis.

Analysis of Pentoxifylline and Its Metabolites. The extraction and capillary gas chromatography methods described by Burrows (15) were used to measure plasma levels of pentoxifylline and metabolites I, IV, and V (Fig. 1). Pentoxifylline is primarily metabolized by reduction to form the pharmacologically active metabolite I and by oxidation to form the other major metabolites, IV and V (14). Metabolite I enhances in vitro thiotepa-induced lethality to bladder cancer cells to the same degree as pentoxifylline (16). Metabolism is rapid, as evidenced by metabolites appearing within minutes in the plasma. Excretion is via the urine, with the primary excretion products being metabolites IV and V (14). All drug levels are expressed as the sum of pentoxifylline plus metabolites I, IV, and V.

RESULTS

Twenty-two patients received a total of 44 courses of thiotepa/pentoxifylline (Table 2). Two patients died within 28 days of protocol treatment. Each death was attributable to disease. All other patients were followed for a minimum of 28 days after their last protocol treatment. Toxicity data are tabulated in Table 3.

Gastrointestinal Toxicity. Pentoxifylline produced dose-limiting nausea and vomiting. Mild or nonexistent nausea and vomiting (grade 1 or less) occurred in all 6 patients on the first two drug levels. Grade 2 nausea leading to partial decrease in oral intake occurred in 11 of 14 patients at 1600 mg/dose. Grade 3 nausea leading to complete reduction in oral intake was seen in 1 of 14 patients at 1600 mg/dose and in both patients at 2400 mg/dose. No diarrhea occurred. In all patients, gastrointestinal toxicity reversed completely within 24 h of stopping treatment.

Bone Marrow Toxicity. Bone marrow depression was infrequent and not related to the pentoxifylline dose. Grade 3 or greater bone marrow depression occurred in only 2 of 14 patients at 1600 mg/dose (MTD).

Cardiac Toxicity. One possible pentoxifylline-related arrhythmia occurred in a 64-year-old lung cancer patient (800 mg/dose) with a prior history of transient atrial fibrillation as a postoperative complication of a pneumonectomy. Since the operation he had remained in normal sinus rhythm on digoxin. During his third cycle, atrial fibrillation recurred concurrent with disease progression in his mediastinum. Two other patients developed sinus tachycardia.

Other Toxicity. Two patients with breast cancer metastatic to the liver developed rising bilirubin while on the study. Both had evidence of deteriorating liver function from their under-
Table 3 Toxicities of pentoxifylline

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients</th>
<th>Grade 1 or less</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<tr>
<td>800 mg t.i.d.</td>
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<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>1600 mg t.i.d.</td>
<td>14</td>
<td>8</td>
<td>5</td>
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<td>0</td>
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<tr>
<td>2400 mg t.i.d.</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Anemia</td>
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<td>400 mg t.i.d.</td>
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<td>2</td>
<td>1</td>
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<tr>
<td>800 mg t.i.d.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1600 mg t.i.d.</td>
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<td>9</td>
<td>4</td>
<td>1</td>
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<tr>
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<td>1</td>
<td>1</td>
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<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>800 mg t.i.d.</td>
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<td>3</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>1600 mg t.i.d.</td>
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<td>0</td>
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<tr>
<td>Cardiac arrhythmia</td>
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<tr>
<td>800 mg t.i.d.</td>
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<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>1600 mg t.i.d.</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>2</td>
<td>0</td>
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<td>0</td>
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<tr>
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<td>11</td>
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<td>2</td>
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</tbody>
</table>

* See "Appendix."  
* t.i.d., 3 times daily.  
* Nineteen patients had no observed arrhythmia. 2 had sinus tachycardia, and 1 had atrial fibrillation.


defying disease prior to beginning therapy. Lastly, one patient (2400 mg/dose) on phenothiazine antiemetics complained of restlessness with no other neurological symptoms or signs.

Antitumor Effect. Four patients had minor responses or stable disease during this study. One heavily pretreated lung cancer patient (400 mg/dose) had subjective improvement in shortness of breath, bone pain, and fatigue and received 6 cycles of treatment. One breast cancer patient (1600 mg/dose) with bone disease had a considerable improvement in bone pain and fatigue, with stable blastic and lytic disease on roentgenogram.

In two ovarian cancer patients (800 and 2400 mg/dose), both resistant to cyclophosphamide and cisplatin, the tumor marker CA125 decreased by 53% and 43%, respectively.

Pharmacology. During the first cycle, data were obtained for 11 of 14 patients receiving 1600 mg/dose (MTD). The median (range) levels of the day 2 trough, day 2 peak, and day 5 peak, in units of µg/ml, were as follows: 4 (3–9), 8 (4–14), and 6 (1–29), respectively. Although the median drug level on day 5 was lower than that on day 2, 2 of the 11 patients the day 5 level was higher, suggesting drug accumulation within a cycle in a subset of patients (Fig. 2). In 7 patients data were obtained for both first and second cycles and were very similar, suggesting no evidence of drug accumulation between cycles (data not shown).

**DISCUSSION**

The rationale for this Phase I evaluation of pentoxifylline in combination with thiotepa included pentoxifylline's ability to potentiate alkylator therapy to human cancer cells in tissue culture (16) and to human tumor explants in mice (13), its absence of toxicity in the treatment of intermittent claudication (11), and the relatively low levels of alkylator resistance observed experimentally (2). In vitro pentoxifylline enhances by up to 10-fold thiotepa or nitrogen mustard-induced lethality to human bladder cancer cells (16). In vivo pentoxifylline potentiates the antitumor effect of thiotepa on human bladder and breast xenografts in mice (13).

Escalating dose pentoxifylline, ranging from 400 to 2400 mg/dose, was administered p.o. 3 times daily for 5 days (15 doses), with a constant dose of thiotepa of 40 mg/m² i.v. administered 2 h after the 4th dose of pentoxifylline. The administration of 4 doses of pentoxifylline prior to thiotepa allowed for steady state levels of the former; the 11 doses of pentoxifylline after the alkylator permitted chemotherapy-treated cells to proceed through the cell cycle.

Nausea and vomiting were dose limiting at the pentoxifylline dose of 2400 mg. Although nausea and vomiting do not represent the usual life-threatening (grade 4) organ toxicity, they precluded further escalation of p.o. pentoxifylline. The MTD of pentoxifylline at this schedule, when combined with thiotepa, is 1600 mg. At this dose, mostly mild controllable nausea and vomiting occurred.

Nongastrointestinal toxicity was infrequent and not dose related. Grade 3 or greater bone marrow depression occurred.
in 3 of 22 patients. A single episode of atrial fibrillation in a patient with a prior history of that arrhythmia and two episodes of rising bilirubin in the face of enlarging hepatic masses are of uncertain significance. Although it is doubtful that they represent drug-related toxicities, firm conclusions cannot be reached. The single episode of restlessness is confounded by concurrent phenothiazine antiemetics. Drug accumulation was noted within a cycle (i.e., by day 5) in only 2 patients and between cycles in no patient.

In this phase I study, bone marrow depression was infrequent and appeared to be random with regard to pentoxifylline dose. However, insufficient myelosuppression occurred to allow evaluation of whether bone marrow depression is modified by pentoxifylline. In a mouse model, pentoxifylline did not adversely modify the toxic effects of thiotepa. Mice treated with thiotepa/pentoxifylline gained weight at least as rapidly as with thiotepa alone (13). Moreover, in this model, pentoxifylline did not have a negative effect on the lethal dose required to kill 50% or 20% of the mice.

For the MTD to be significant, it should be greater than the dose required for an antitumor effect in mice. Although the whole question of interspecies comparison is difficult, Freireich et al. (17) have worked out one such quantitative interspecies comparison. On a mg/kg basis, the human equitoxic dose can be calculated from the mouse dose by dividing by a factor of 12. A dose of 50 mg/kg i.p., which in a murine in vivo assay by Teicher resulted in enhanced tumor growth delay, would thus be equivalent to a dose of 4 mg/kg in humans. We have far exceeded this equivalent dose at our MTD. In a typical 70-kg patient, our 1600-mg dose corresponds to 23 mg/kg. Almost 100% of p.o. pentoxifylline is recoverable in the urine (14), validating the comparison between the human p.o. and the mouse i.p. routes of administration. Based upon this interspecies comparison (17), the Phase II dose may exceed that required to achieve alkylator modulation by as much as 6-fold. Further important work is needed to explore the relationship between pentoxifylline plasma level and enhancement efficacy in mice versus humans. Such work, however, is outside the scope of this paper which is predominantly a clinical one.

Although our MTD of pentoxifylline exceeds the dose needed to enhance chemotherapy predicted from the aforementioned interspecies comparison, our day 2 peak median level of 8 µg/ml fell 6-short of the 50 µg/ml (200 µM) concentration needed to achieve the same result in tissue culture (13). Therefore, a quantitative discrepancy exists. This brings into question whether the in vivo effect can be accounted for by the previously proposed mechanism in culture. In culture, chemotherapy-treated cancer cells are delayed in G2 to permit DNA repair to be completed prior to mitosis (18). Methylxanthines prevent this G2 arrest, allowing chemotherapy-treated cells to divide without finishing the repair process, thereby leading to nuclear fragmentation and to increased lethality of cancer cells (18). Factors operating only in vivo could be responsible for these concentration differences. Indeed, other biological effects of pentoxifylline are observed at much lower concentrations, in the range of 1 µg/ml. These biological effects have been extensively reviewed and include increasing cyclic AMP levels, increasing RBC deformability, decreasing platelet aggregation by both stimulating prostacyclin synthesis and inhibiting thromboxane synthesis, increasing tissue oxygenation (14), and, as recently described by us, decreasing tumor necrosis factor message accumulation in cancer patients (19). In light of the observation that thiotepa's cytotoxicity is highly oxygen dependent, pentoxifylline's ability to increase tissue oxygenation and, presumably tumor oxygenation, is particularly intriguing (20).

We are encouraged that four heavily pretreated patients had minor responses or stable disease during this study. These included not only subjective improvement in bone pain and energy but also significant objective decreases of the tumor marker CA125 in two ovarian cancer patients whose levels had been increasing on cyclophosphamide and cisplatin therapy. Estey et al. (21) has observed that current effective chemotherapeutic agents had a response rate of only 4.3% on average during their Phase I evaluation. Given the infrequent bone marrow depression seen, we speculate that patient responses may have been even more impressive had we increased the thiotepa dose after we had established the MTD of pentoxifylline. Further clinical studies will determine whether combinations of this type are effective in various tumor types and whether they are more effective than alkylating agents alone.

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APPENDIX: COMMON TOXICITY CRITERIA

Leukopenia: grade 0, WBC >4000/mm³; grade 1, 3000-3900/mm³; grade 2, 2000-2900/mm³; grade 3, 1000-1900/mm³; grade 4, <1000/mm³.

Anemia: grade 0, hemoglobin >14.0 gm/dl (male), 12.0 gm/dl (female); grade 1, 10.0-14.0 gm/dl (male), 10.0-12.0 gm/dl (female); grade 2, 8.0-9.9 gm/dl; grade 3, 6.5-7.9 gm/dl; grade 4, <6.5 gm/dl.

Thrombocytopenia: grade 0, platelets >130.0/mm³; grade 1, 75.0-129.9/mm³; grade 2, 50.0-74.9/mm³; grade 3, 25.0-49.9/mm³; grade 4, <25.0/mm³.

Arrhythmia: grade 0, none; grade 1, asymptomatic, transient (no treatment); grade 2, recurrent, persistent (no treatment); grade 3, requires treatment; grade 4, hypotension, ventricular tachycardia or fibrillation.

Nausea: grade 0, none; grade 1, able to eat reasonable intake; grade 2, intake reduced but can still eat; grade 3, no significant intake.

Vomiting: grade 0, none; grade 1, 1 episode/24 h; grade 2, 2-5 episodes/24 h; grade 3, 6-10 episodes/24 h; grade 4, >10 episodes/24 h or requiring IV support.

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