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A Phase I Clinical and Pharmacological Study of Weekly Intravenous Infusions of Piritrexim (BW301U)

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Abstract—*Thirty-eight patients with advanced resistant cancers were enrolled on this study of piritrexim (PTX; BW 301U) administered intravenously weekly for 4 weeks. Of 50 courses of treatment begun, 39 evaluable 4-week courses of the drug were completed by this group of patients. Dosages ranged from 44 to 530 mg/m²/week. One patient at each dosage level received an initial weekly dose of PTX in oral form accompanied by pharmacokinetic blood sampling after the oral dose and also after a subsequent intravenous dose.*

Toxicities included mild nausea and vomiting, and moderate to severe peripheral vein phlebitis. Anemia and thrombocytopenia were the dominant hematological toxicities. One patient with pulmonary metastases from malignant fibrous histiocytoma experienced a 12-week partial response to PTX treatment at a dosage of 400 mg/m²/week.

Pharmacokinetic analysis of plasma for PTX concentrations was accomplished utilizing a competitive protein binding assay. The estimated total body clearance ranged from 136 to 173 ml/min/1.73 m². Mean terminal half-life after intravenous administration was 5.61 ± 2.38 h (S.D.), and after oral administration was 5.72 ± 2.04 h. Mean systemic bioavailability after oral administration was 75 ± 56%.

INTRODUCTION

THE prompt development of anticancer drug resistance in tumors has stimulated a major investigational effort to characterize the etiology and mechanism of this tumor adaptation. Among the recognized mechanisms of resistance are the reduction of carrier-mediated active transport of anticancer agents into the tumor cell and reduction of tumor cell membrane permeability to the agent, mechanisms which may be particularly germane to antifolate resistance. Methotrexate is an antifolate whose potential effectiveness may be limited by its water solubility, poor membrane permeability, and a requirement for active transport into the tumor cell. Metoprine, a 2,4-diaminopyrimidine, is a potent dihydrofolate reductase (DHFR) inhibitor with antitumor activity and lipid solubility, characteristics which suggest a potential for overcoming drug transport-related resistance by permitting passive diffusion of the drug through the tumor cell membrane [1]. However, some undesirable features of metoprine, viz, its long half-life, troublesome CNS toxicities, modest antitumor activity at clinically tolerable dosages, and inhibition of histamine metabolism, have limited its development as a useful anticancer agent [2].

Piritrexim [PTX; BW301U; 2,4-diamino-6-(2,5,-dimethoxybenzyl)-5-methylpyrido [2,3-D] pyrimidine] (Fig. 1) was synthesized and found to possess the favorable features of metoprine and few of the undesirable attributes. PTX is a potent inhibitor of DHFR, is a modest inhibitor of histamine N-methyltransferase, and is lipid soluble [3]. PTX exhibits good antitumor activity against *in vivo* Walker 256 carcinosarcoma, L1210 and P388 leukemias, sarcoma 180 and Ehrlich ascites tumor

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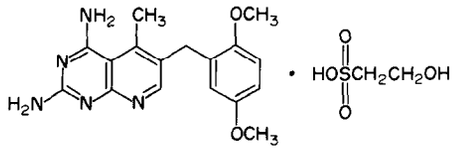

Fig. 1. Structure of piritrexim.

[4, 5]. PTX appears to be a relatively selective inhibitor of DHFR, although its cytotoxic effects are only partly reversed by calcium leucovorin. Complete reversal of PTX cytotoxicity in some cell lines is accomplished by exposure of treated cells to calcium leucovorin and thymidine. However, complete reversal of piritrexim antifolate toxicity in animals is easily accomplished with calcium leucovorin alone [6]. The pharmacokinetic profile for PTX administered to animals shows elimination of the drug by rapid and extensive metabolism. The entry of PTX into cells is rapid and directly proportional to its extracellular concentration. Rapid inhibition of uridine incorporation into DNA is observed with increasing intracellular concentrations of PTX [6]. Because of its lipid solubility and consequent rapid entry into cells, PTX may be effective in treating MTX-resistant tumors that exhibit defective MTX uptake or elevated levels of DFHR [7].

Animal toxicology studies have produced evidence of bone marrow suppression, gastrointestinal ulceration, and reticuloendothelial atrophy in treated rats and dogs [6]. Renal toxicity was infrequently observed.

PTX was selected as the most active of the 2,4-diaminopyrimidines with the most favorable toxicity profile, particularly with respect to avoidance of inhibition of histamine metabolism.

MATERIALS AND METHODS

Patients

Between March 1984 and June 1986, 38 patients were enrolled on this study. Patients were eligible for this study if they had a histological diagnosis of cancer for which effective therapy no longer existed. Patients had to have evidence of adequate hepatic, renal and bone marrow function consistent with adequate metabolism of PTX. Patients had to have a life expectancy of at least 12 weeks and a Karnofsky performance status of at least 60% or better. Patients must not have received chemotherapy for at least 2 weeks or radiotherapy for at least 4 weeks prior to entry on the study. Patients provided written informed consent according to institutional and Federal guidelines for participation in this study.

Prior to treatment, patients were required to undergo a complete history and physical examination including measurement of all clinically detectable malignant lesions. In addition, a complete blood count, reticulocyte count, 20-channel blood chemistry profile, prothrombin time, partial thromboplastin time, EKG, and urinalysis were performed.

Treatment program

PTX isethionate was provided by the Burroughs Wellcome Company in sterile ampoules containing 80 mg of the free base in 10 ml of vehicle (propylene glycol:water, 1:1 v/v). The drug was diluted in sterile 5% dextrose in water to provide a final infusion concentration not exceeding 0.36 mg/ml free base. With increasing PTX dosage, lower concentrations were formulated in an effort to reduce observed toxicity (*vide infra*). For selected patients receiving oral PTX isethionate, capsules were provided containing either 25 or 100 mg as the free base at a dose rounded down to the nearest 25 mg.

Eligible patients were admitted to the General Clinical Research Center of the Audie L. Murphy Memorial Veterans Administration Hospital. Patients received PTX by intravenous infusion at a rate of 3.6 mg/min for dosages of 222 mg/m^2 or less, and at a rate of 2.5 mg/min for dosages equal to or exceeding 311 mg/m^2. A complete course of therapy was defined as PTX given weekly for 4 consecutive weeks followed by a 2-week rest period. Additional courses of treatment were repeated at the conclusion of the 2-week rest. Three patients were treated at each dosage level; a fourth patient was accrued to each dosage level for whom the first weekly dose was administered orally and all subsequent weekly doses intravenously. Treated patients were followed with weekly physical examination, toxicity query, tumor measurements, urinalysis, and complete blood count. Biweekly chemistry profile, haptoglobin, prothrombin time, and partial thromboplastin time were also obtained.

Clinical trials of PTX administered on a daily schedule for 5 days permitted estimation of a safe starting dosage for the present trial of 44 mg/m^2 weekly for 4 weeks [8]. Subsequent dosage escalations for this trial were 89, 148, 222, 311, 400 and 530 mg/m^2.

The first three patients of each cohort treated at a given dosage level had blood samples for pharmacokinetic determinations obtained preinfusion, at end of infusion and at 2.0 and 6.0 h after the first and fourth weekly infusion. This abbreviated sampling schedule provided assurance that PTX pharmacokinetic behavior approximated its known disposition observed in other clinical studies. A fourth patient treated at each dosage level had blood samples drawn at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, 12.0, 18.0, 24.0 h, and, if feasible, at 36 and 48 h following the first weekly oral dose and the fourth weekly intravenous

dose. A serum sample was obtained at 2 h postinfusion for haptoglobin determination to seek evidence of drug-induced hemolysis.

Patients were monitored for response to treatment using standard response criteria and physical or radiological measurements for evaluable or measurable lesions. Patients were taken off study if disease progression was observed, if intolerable toxicity was induced or if the patient refused further therapy.

With higher doses of PTX, phlebitis of the peripheral vein into which the drug was infused was observed with increasing frequency. In an effort to ameliorate this troublesome toxicity, all doses of PTX above 222 mg/m^2/week were diluted to assure that the concentration of the drug did not exceed 0.25 mg/ml. In addition, the infusion rate of the drug did not exceed 2.5 mg/min. Four patients were premedicated intravenously with hydrocortisone succinate, 100 mg, for two of four weekly doses in an effort to determine whether toxicity might be reduced by this maneuver.

Pharmacokinetic determination

Blood samples for pharmacokinetic analysis were collected in EDTA and centrifuged at 1500 ***g*** for 10 min. Plasma was decanted into polypropylene tubes and frozen at −20°C until analysis.

A competitive protein-binding assay for PTX that makes use of a commercially available radioassay kit for methotrexate has been developed [9]. After it is selectively extracted from plasma, PTX competes with [^{125}I]methotrexate for binding to dihydrofolate reductase isolated from *L. casei*. Free drug is separated from bound drug by absorption to dextran-coated charcoal. PTX is measurable over a range of 0.01–10.0 μg/ml in plasma with a coefficient of variation <15%. The limit of sensitivity of the assay is about 2 ng/ml. An excellent correlation between this assay and a previously published HPLC method was found.

The area under the plasma concentration–time curve, AUC, was determined by the trapezoidal rule. The apparent half-life, $t_{1/2}$, was determined by a log–linear least-squares fit of the terminal phase of the plasma concentration–time curve. The oral bioavailability, F, of PTX was determined by the following equation:

$$F(\%) = \frac{\text{AUC (p.o.)} \times \text{dose (i.v.)}}{\text{AUC (i.v.)} \times \text{dose (p.o.)}} \times 100.$$

RESULTS

Clinical results

The characteristics of the 38 patients eligible for treatment are shown in Table 1. Thirty-nine 4-week courses of PTX were administered to these patients. Four patients had received no prior therapy, five patients had received radiation therapy, seven had received chemotherapy, and the remaining 22 patients had received both radiation therapy and chemotherapy. A predominance of patients with non-small cell lung cancers and with head and neck cancers was observed in this study.

Table 1. Patient characteristics

Category	No.
Eligible patients	38
Median age, years (range)	61 (23–72)
Median performance status, Karnofsky (range)	70 (50–90)
Patients with prior therapy	
Radiation alone	5
Chemotherapy alone	7
Radiation and chemotherapy	22
None	4
Patient tumor types	
Non-small cell lung	13
Head and neck	8
Colorectal	3
Adenocarcinoma, unknown primary	3
Breast	2
Malignant melanoma	2
Soft tissue sarcoma	3
Bladder	1
Skin, squamous	1
Small cell lung	1
Ovary	1

An evaluable course of treatment is defined as four weekly doses administered to an eligible patient. Less than 4 weeks treatment was regarded as an inevaluable course and is not reported in the toxicity tables. Significant hematological and non-hematological toxicities were observed among the treated patients. As shown in Table 2, mild to moderate anemia was induced at all dosage levels and did not appear to be a clearly dose-related phenomenon. No clinical or laboratory evidence of hemolysis was detected in any treated patient. Thrombocytopenia was sporadically noted yet again was not definitely dose-related. In three courses of treatment, thrombocytopenia was severe; one patient experienced thrombocytopenia which appeared consistent with idiopathic thrombocytopenic purpura. Only two courses of PTX were accompanied by leukopenia or granulocytopenia. In no case did hematological toxicity represent a well-characterized dose-limiting toxicity.

A variety of non-hematological toxicities occurred without a clear relationship to increasing drug dosage. Dominant among these were nausea, vomiting and peripheral vein phlebitis at the site of drug infusion. Table 3 demonstrates that these toxicities

Table 2. Hematological toxicity

Dosage of piritrexim (mg/m²)	44	89	148	222	311	400	530
	Courses with toxicity						
WBC nadir (/μl)							
>4000	4	5	4	6	2	14	1
3000–3999	0	0	0	0	2	0	0
2000–2999	0	0	1	0	0	0	0
1000–1999	0	0	0	0	0	0	0
0–999	0	0	0	0	0	0	1*
PMN nadir (/μl)							
>1500	4	5	5	6	4	14	1
1000–1499	0	0	0	0	0	0	0
500–999	0	0	0	0	0	0	0
250–499	0	0	0	0	0	0	0
0–249	0	0	0	0	0	0	1*
Hemoglobin (g/dl)							
>10.0	3	2	1	5	2	8	0
9.0–9.9	1	1	1	1	1	4	1
8.0–8.9	0	2	3	0	0	2	0
7.0–7.9	0	0	0	0	1	0	0
0–6.9	0	0	0	0	0	0	1*
Platelets (/μl)							
>150,000	4	5	2	5	4	13	1
100,000–149,999	0	0	1	1	0	1	0
50,000–99,999	0	0	1	0	0	0	0
25,000–49,999	0	0	0	0	0	0	0
0–24,999	0	0	1	0	0	0	1*
Total courses	4	5	5	6	4	14	2
Total patients	4	4	5	4	3	10	2

*Death on study after a single week's dose of 530 mg/m².

tended to be mild, were inconsistently produced at all dosage levels, and did not represent dose-limiting toxicities. However, because increasingly severe phlebitis was observed at the 311 and 400 mg/m² dosage levels, attempts were made to extend infusion times of more dilute solutions of PTX (not exceeding 0.25 mg/ml and as low as 0.144 mg/ml at infusion rates not exceeding 2.5 mg/min for dosages equal to or exceeding 311 mg/m²) in an effort to ameliorate the severity of this toxicity. Peripheral vein phlebitis occurred at the intravenous drug infusion site. Its onset generally preceded conclusion of the drug infusion, the reaction progressed for several hours after the infusion was completed and persisted for days. Skin erythema was observed overlying a firm and tender venous cord which usually migrated proximally for several centimeters along the infused limb. Skin changes and tenderness improved over the following week but at times persisted until the next weekly infusion date. The preadministration of hydrocortisone in two of four weekly treatments among four patients receiving five courses of treatment at 400 mg/m² failed to ameliorate the phlebitits when compared to those weekly treatments without hydrocortisone.

It was elected to discontinue the study after two patients had been treated at 530 mg/m² (one evaluable 4-week course) because drug infusion times were approaching 24 h in duration, an unacceptable prolongation of treatment for an inpatient weekly administration schedule.

PTX induced several other toxicities that occurred without any discernible dose-related trend. Nine courses of treatment were accompanied by a distortion of taste, usually described by patients as a metallic taste. During seven courses of treatment, patients described the onset of fatigue at the conclusion of and briefly after drug infusion. Additional toxicities included (in order of declining frequency) mild peripheral edema, self-limited fever and chills, eructation, rash, diarrhea, somnolence, mild oral mucositis, vertigo, headache, facial flushing, mild dyspnea, and tingling in the extremities. Transient liver transaminase elevations, elevated prothrombin time, hypotension, atrial fibrillation, and serum creatinine elevation were isolated toxic events that required no specific therapeutic intervention. It is speculative whether some of these toxicities may represent inhibition of histamine metabolism by PTX.

Anticancer activity was observed in one patient with malignant fibrous histiocytoma metastatic to the lungs. A prompt and marked partial response occurred in this patient treated at 400 mg/m², persisting until progression of the lung metastases after the third four-dose course of therapy. This patient had not received prior treatment with methotrexate but had been heavily treated with other antineoplastic agents and radiation therapy. Neither of two other patients with metastatic breast cancer and a patient with recurrent squamous carcinoma of the epiglottis who had previously received methotrexate responded to PTX at dosages of 148, 222, and 89 mg/m², respectively.

Table 3. Non-Hematological toxicity

Dosage of piritrexim (mg/m²)	44	89	148	222	311	400	530
	Courses with toxicity						
*Nausea/vomiting**							
Grade 1	0	1	1	2	2	8	1
Grade 2	0	0	0	0	0	1	0
Phlebitis							
Mild	1	2	1	1	1	2	0
Moderate	0	0	0	2	0	4	0
Severe	0	0	0	0	0	0	1
Total courses	4	5	5	6	4	14	2
Total patients	4	4	5	4	3	10	2

*Southwest Oncology Group Toxicity Criteria: Grade 1: nausea, no vomiting; Grade 2: vomiting which can be prevented by treatment; less than six episodes per day.

Table 4. *Mean* (± *S.D.*) *piritrexim plasma concentrations* (mcg/l)

Dosage (mg/m^2)	Duration (h) of infusion	Rate (mg/m^2/min)	Time post-infusion (h) 0.0	2.0	6.0
44	0.38 ±0.07	1.97 ±0.36	5.50 ±1.14	1.60 ±0.79	0.56 ±0.28
89	0.99 ±0.24	1.40 ±0.27	10.2 ±3.49	4.11 ±4.88	2.10 ±2.92
148	1.38 ±0.32	1.93 ±0.44	8.40 ±2.73	4.77 ±2.26	1.51 ±0.82
222	2.17 ±0.40	1.75 ±0.29	8.76 ±3.86	4.99 ±1.04	2.20 ±1.10
311	8.30 ±0.15	0.63 ±0.01	8.01 ±3.12	3.51 ±1.17	1.25 ±1.10
400	8.16 ±0.35	0.82 ±0.04	8.18 ±0.42	3.87 ±1.00	2.40 ±0.73

Table 5. *Piritrexim systemic bioavailability after oral dosing*

Patient No.		Dosage level (mg/m^2)	Total dose (mg)	AUC (mcg.h/ml)	$t_{\frac{1}{2}}$ (h)	F(%)	Cl_{tot} (ml/min)
4	i.v.	44	69	13.64	3.48	—	84
	oral		50	16.58	2.72	168	—
8	i.v.	89	150	126.00	10.79	—	20
	oral		150	49.77	9.24	40	—
11	i.v.	148	250	52.80	5.21	—	79
	oral		250	75.25	6.79	143	—
13	i.v.	148	250	44.88	5.17	—	93
	oral		250	19.23	4.56	43	—
20	i.v.	222	375	67.60	4.88	—	92
	oral		375	42.33	4.71	63	—
26	i.v.	311	513	64.03	4.39	—	134
	oral		525	14.84	5.92	23	—
29	i.v.	400	744	84.58	5.33	—	147
	oral		725	38.75	6.08	47	—
				Mean i.v.	5.61	—	93
				± S.D.	2.38	—	41
				Mean oral	5.72	75	—
				± S.D.	2.04	56	—

F = systemic bioavailability.

Pharmacokinetic analysis

The results of the pharmacokinetic analysis of patient plasma samples for PTX are summarized in Tables 4 and 5. PTX plasma mean concentrations at the end of infusion and at 2 h and 4 h post-infusion are presented in Fig. 2. The drug plasma concentration at the end of the infusion is dependent on the duration of infusion and the rate of infusion. For the 311 and 400 mg/m^2 dosage groups, the durations of infusion were variable and were dependent on the rate of infusion adjusted so as not to exceed 2.5 mg/min. The PTX plasma concentrations at the end of infusion cannot be considered to be at the steady state, based on drug concentration–time simulation which predicts that infusion must persist for 18 h before steady state is reached. The total body clearance, Cl_{tot}, can be calculated by the following equation:

$$Cl_{tot} = \text{dose/AUC}.$$

The Cl_{tot} values were 136 and 173 ml/min/1.73 m^2 for the 311 and 400 mg/m^2 dosage groups, respectively. In a study of PTX administered by i.v.

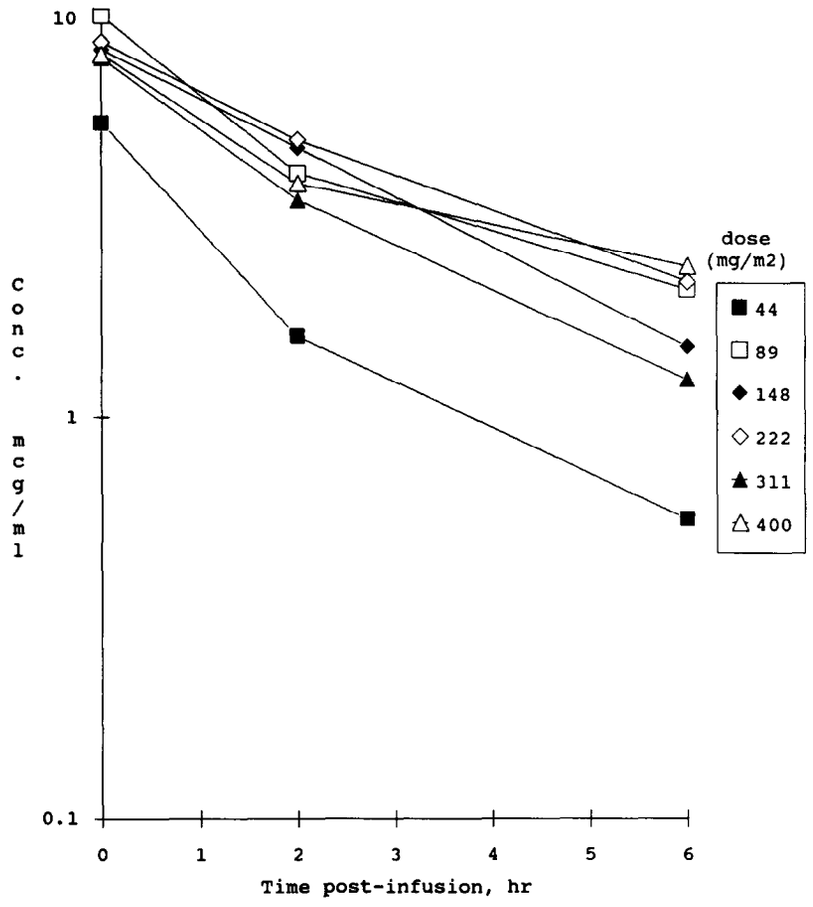

Fig. 2. Piritrexim mean plasma concentrations (mcg/ml) *following intravenous infusion.*

infusion, the mean Cl_{tot} value was 140 ml/min/70 kg and the mean half-life was 4.5 h [10]. For those patients participating in the absolute oral bioavailability (F) studies (fourth patient at each dosage level with first weekly dose administered orally), mean oral bioavailability was 75% (±56% S.D.; range 23–168%). There was no dose-related difference in terminal half-lives whether the drug was administerd by the intravenous or oral route (mean $t_{1/2}$: 5.61 vs. 5.72 h, respectively).

DISCUSSION

This phase I study of PTX administered in four weekly intravenous infusions to patients with advanced chemotherapy-resistant malignancies was concluded with the onset of an increasingly frequent and severe (but admittedly not dose-limiting) peripheral vein phlebitis at the drug infusion site. It became clear that this toxicity could not be ameliorated without disruptive adjustments to drug formulation, concentrations of infused drug, infusion rates and infused volumes. Although other hematological and non-hematological toxicities began to emerge with increasing dosage, none approached dose-limiting proportions at any dosage level. Indeed, the adjustments to the infusion technique rendered the application of a weekly treatment schedule an increasing burden on patient time. Consequently, this treatment schedule cannot be recommended as one which has wide applicability in future studies. Central venous catheters may be necessary to avoid this toxicity. Antitumor activity was observed in one sarcoma patient at the 400 mg/m^2 dosage level.

The pharmacokinetic data demonstrate that, following oral administration, PTX elimination half-life was the same as that following intravenous administration. The estimated systemic bioavailability of PTX in patients receiving both oral and intravenous doses was 75 ± 56%. These data suggest that PTX may have important utility when administered by the oral route. Indeed, a recently published clinical trial of oral PTX administered to patients with non-small cell lung cancer utilized a dosage of 160 mg/m^2 twice daily for 5 consecutive days [11]. A partial response of 4 months' duration was observed in one of 33 treated patients on this phase II trial.

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