Phase I and Clinical Pharmacology Trial of 502U83 Using a Monthly Single Dose Schedule


Division of Oncology, Department of Medicine and School of Pharmacy, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284-7884

ABSTRACT

502U83 is an arylmethylaminopropanediol derivative exhibiting significant antineoplastic activity in a number of murine and human tumor models. In this Phase I trial, a 1-hr or 4-hr infusion of the agent was administered i.v. in 250 ml of 5% dextrose in water every 28 days. Fifty-three courses at doses of 25 to 2000 mg/m² were administered to 36 patients with refractory solid tumors. Prolongation of the PR, QRS, and QT intervals on electrocardiograms was dose limiting at 2000 mg/m². This prolongation appeared dose related and was reversible upon discontinuation of the infusion. No hematological toxicity was observed. Other toxicities included only sporadic and mild to moderate nausea and vomiting. No tumor responses were noted.

502U83 plasma concentrations were determined by high-pressure liquid chromatography. Complete pharmacokinetic profiles were obtained for 21 of the 36 patients. After infusion, plasma concentrations declined in a biexponential or in a triexponential manner with a harmonic mean terminal t½ of 8.83 h. Using a three-compartment model, the mean apparent volume of distribution at steady state and total-body clearance were 195 liters and 42.5 liters/h/m², respectively, indicative of extensive tissue distribution. No correlation could be found between the pharmacokinetic parameters and prolongation of the cardiac conduction intervals. Because of the cardiac effects with the drug, the schedule of administration of 502U83 used in this study cannot be recommended.

INTRODUCTION

The group of molecules collectively known as AMAPs has shown a broad spectrum of antitumor activity in murine and human tumor systems. To explore the potential utility of this novel series, four of the congeners have been selected for clinical development on the basis of antitumor activity, physicochemical properties, and drug disposition differences. In this study, we report results of a Phase I trial with one of the congeners, 502U83.

Biophysical studies have shown that 502U83 (Fig. 1) is the most hydrophilic of the four clinical candidates and binds relatively weakly to DNA (1). However, the precise mechanism of action of 502U83 is unknown. Like the other congeners, it showed in vitro and in vivo activity against P388 leukemia (with a high percentage of long-term survivors), L1210 leukemia, B16 melanoma, M5076 sarcoma, Lewis lung carcinoma and colon 38. It is active against P388 sublines that are resistant to mitoxantrone and actinomycin D but not against acridinyl anisidide or doxorubicin-resistant lines. It is orally active and produces resistance of P388 implanted in the footpad. The agent also has activity against a variety of human tumor colony-forming units growing in soft agar, including breast, colon, non-small cell lung, and renal cell colony-forming units (2).

One of the most attractive features of 502U83 was that in animals it did not have any acute central nervous system effects that were noted with the other two congeners brought into clinical trials (crisnatol and A773U). Rodent lethality studies identified the single-dose LD₁₀ to be 81 mg/kg and the LD₉₀ as 119 mg/kg in the mouse; for rats, the doses were about 20% higher (3). In dogs, emesis was the only acute effect noted. Dose-related antiproliferative effects included hypopcellular marrow, atrophic lymphoid tissue, and maturation arrest enteritis at peak plasma concentrations ranging from 7.3 to 17.3 μg/ml. Electrocardiograms performed on the dogs at nonmogentic doses of 502U83 showed no significant changes. The human starting dose was 1/10 of the murine LD₁₀ adjusted on a surface area equivalence basis.

MATERIALS AND METHODS

Patient Selection. The clinical characteristics and diagnoses for patients in this trial are displayed in Table I. Thirty-six patients were entered into the study. All patients had histologically documented advanced solid tumors, for which there were no forms of more effective therapy. Measurable or evaluable disease was not required for admission. Patients were required to have adequate organ function, including the following: bone marrow: WBC, ≥3,000/mm³ (granulocytes, ≥1,500/mm³), platelets, ≥100,000/mm³, hemoglobin, ≥10 g/100 ml; hepatic: bilirubin, ≤2.5 mg/100 ml, serum glutamic oxaloacetic transaminase, ≤2.0 times normal, alkaline phosphatase, ≤2.0 times normal (higher values of serum glumatic oxaloacetic transaminase and alkaline phosphatase were allowed if due to patient’s tumor), prothrombin time and partial thromboplastin time, normal; renal: normal urinalysis, creatinine, ≤2.0 mg/100 ml; cardiac: no history of recent myocardial infarction or uncontrolled arrhythmia; metabolic: normal electrolytes, including calcium, phosphorus, and uric acid, and blood glucose, <200 mg/100 ml.

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Treatment Plan. Patients were hospitalized for each dose of 502U83. The formulation of the drug for clinical use was supplied by Burroughs Wellcome Co. as a sterile powder in 100-mg vials. The vials were reconstituted with 10 ml of bacteriostatic water for injection. The solution was then passed through a 0.22-μm filter and further diluted in 250 ml of 5% dextrose in water. The drug was administered to patients through a free-flowing i.v. line, using an infusion pump over 1
Doses were escalated by doubling the dose until a biological effect was seen, at which point they were increased by 50% until Grade 1 toxicity was noted. At that point the escalations were reduced to 33% (Table 2). At least three evaluable patients were entered at each dose level. The first patient at each level was observed for 4 wk. If toxicity was acceptable, two additional patients were entered. When a dose of 2000 mg/m² given as a 1-h infusion was reached, prolongation of the PR, QRS, and QT intervals became significant (15 to 71% increase). In an attempt to decrease this effect, three additional patients were treated at 2000 mg/m² using a 4-h infusion. There was no intrapatient dose escalation.

Study Parameters. Baseline studies on all patients included history and physical examination, complete blood count, serum chemistries, prothrombin time, partial thromboplastin time, urinalysis, chest X-ray, ECG, and appropriate baseline scans or X-rays needed to measure tumor response. After treatment, patients were seen in the clinic weekly for 4 wk. At each visit, evaluations included history, physical examination, toxicity notation, complete blood counts, serum chemistries, prothrombin time, partial thromboplastin time, and urinalysis. In addition, studies for tumor measurement or evaluation were performed prior to each course. Standard response criteria and WHO toxicity criteria were used in the evaluation.

Termination of Study. Patients were taken off study after completion of follow-up evaluations if their disease was found to be progressing by Day 29 of any course. Patients were also free to terminate their participation in the study at any time.

Blood Sampling. Blood samples for pharmacokinetic studies were obtained via an indwelling i.v. heparin lock in the arm contralateral to the infusion line. Serial 8-ml specimens were obtained in EDTA tubes before infusion, 30 min (1, 2, and 4 h with the 4-h infusion) into infusion, and at the end of infusion. Postinfusion samples were collected 10, 20, 40, and 60 min and 1.5, 2, 4, 6, 8, 12, 24, and 48 h postinfusion. The samples were centrifuged, and the plasma was collected, flash frozen, and stored at −20°C in polyethylene tubes. A baseline urine specimen was obtained, and several urine samples were collected during and after infusion with the last collection period ending at 48 h. The total volume of each sample was recorded; the urine sample was shaken; and a 20-ml aliquot was removed, labeled, and stored at −20°C. The concentration of drug in each specimen was measured by HPLC.

HPLC Analysis. A reverse-phase HPLC method was developed for the analysis of 502U83 in plasma and urine samples. Samples (0.5 ml) were acidified with 50 µl of 12 N NaOH and extracted with 5.0 ml of methyl tert-butyl ether. The samples were then mixed on a multipurpose rotator (protected from light) for 10 min, and 4.5 ml of the organic layer were transferred to a 16- x 125-mm disposable glass tube. A volume of 50 µl of formic acid was added to ensure that 502U83 was in the salt form. The samples were evaporated to dryness under a stream of nitrogen. The extraction procedure yielded 90% recovery of 502U83 from plasma. The residue was reconstituted with 250 µl of mobile-phase HPLC consisting of HPLC-grade water, acetonitrile, and 0.1 M monobasic potassium phosphate (57:33:10). The HPLC system consisted of a pump (Model 950; Waters, Milford, MA), variable wavelength UV detector (Model 841; Waters), and autosampler (Model 710B Wisp; Waters), and chromatography control module (LDC, Riviera Beach, FL). The elution system consisted of a 2-cm Pelliguard LC-8 guard column (Supelco, Bellefonte, PA) and a Spherisorb S-5 C6 HPLC column, 10 cm x 4.6 mm (Anspec, Ann Arbor, MI). The mobile phase was pumped at a flow rate of 2.0 ml/min, and the detector wavelength was 254 nm. The coefficient of variation for the assay was less than 4 to 11% over the linear range of the assay (0.03 to 15.0 µg/ml), and the lower limit of the assay was set at 30 ng/ml for a 1.0-ml sample.

Pharmacokinetic Analysis. The 502U83 plasma concentration-time data were analyzed using a 2- or 3-compartment model with zero-order infusion. Nonlinear least-squares regression analysis was performed using NONLIN (4) with a weighting function of 1/concentration. The estimates of the intercompartmental rate constants and the \( V'_S \) were used to calculate the terminal-phase \( t_{1/2} \), \( V_{\text{ss}} \), AUC, and total-body CL. The \( C_{\text{max}} \) observed in blood was the highest 502U83 plasma concentration.
Table 3  Changes in QTc intervals in patients receiving 502U83

| Patient | Infusion time (h) | Dose (mg/m²) | QTc baseline (ms) | QTc at end of infusion (ms) | % of increase in QTc
|---------|------------------|--------------|------------------|-----------------------------|----------------------|
| 20      | 1.75             | 1600         | 420              | 460                         | 9.5
| 21      | 1.05             | 1600         | 420              | 460                         | 9.5
| 22      | 1.00             | 1600         | 420              | 460                         | 9.5
| 23      | 1.05             | 1600         | 420              | 460                         | 9.5
| 24      | 1.00             | 1600         | 420              | 460                         | 9.5
| 25      | 1.05             | 1600         | 420              | 460                         | 9.5
| 26      | 1.00             | 1600         | 420              | 460                         | 9.5
| 27      | 1.05             | 1600         | 420              | 460                         | 9.5
| 28      | 1.00             | 1600         | 420              | 460                         | 9.5
| 29      | 1.75             | 1600         | 420              | 460                         | 9.5
| 30      | —                | 2000         | 420              | 636                         | 15.1
| 31      | 1.67             | 2000         | 420              | 636                         | 15.1
| 32      | 1.00             | 2000         | 420              | 636                         | 15.1
| 33      | 1.00             | 2000         | 420              | 636                         | 15.1
| 34      | 4.00             | 2000         | 420              | 636                         | 15.1
| 35      | 4.08             | 2000         | 420              | 636                         | 15.1
| 36      | 3.92             | 2000         | 420              | 636                         | 15.1

* At end of infusion, compared with baseline.
* Patients on whom pharmacokinetic studies were performed.
* ND1, end of infusion ECG could not be found for review; ND2, infusion not completed secondary to gastrointestinal bleed, and patient did not have follow-up ECG.
* —, patient did not complete infusion secondary to gastrointestinal bleed during infusion.

Fig. 2. QTc interval prolongation measured in three patients during infusion of 2000 mg/m² over 4 h. EOI, end of infusion.

RESULTS

Thirty-six patients received a total of 53 courses of 502U83. One patient (patient 30 with hepatoma at 2000 mg/m²) had to have the drug discontinued because of bleeding esophageal varices unrelated to 502U83. All other patients were evaluable for toxicity. Overall, 502U83 was well tolerated, and the toxicity which halted the trial was a consistent prolongation of conduction intervals found on electrocardiography.

Cardiac Conduction System Changes. No changes in cardiac conduction were noted up to doses of 800 mg/m². At that level, the 12-lead computerized ECG reader (Marquette, Marquette, WI) began to show prolongations in the PR, QRS, QT, and QTc (corrected QT) intervals. After that discovery, computerized ECGs were systematically performed pretreatment and at the end of infusion. All ECGs were reviewed by a reference cardiologist (G. L. F.). To quantify the ECG changes, the variations in the intervals were expressed as a maximum percentage of increase. Table 3 details the changes in the QTc intervals. The values detailed in Table 3 were then used to explore the relation between ECG changes, drug dose, and a variety of pharmacokinetic parameters. Since significant ECG interval changes were noted at doses ≥800 mg/m² and no significant changes were noted below that dose level, there was a suggestion of a greater prolongation of the QTc with increasing doses of 502U83 which, in turn, suggested the possibility of a peak plasma effect of 502U83. In an attempt to decrease a peak plasma level effect, a 4-h infusion of the agent was explored. As can be seen in Fig. 2 (and Table 3), patients receiving 2000 mg/m² over 4 h (with 12-lead ECGs performed hourly) still had QTc prolongations. The percentage of QTc prolonga-

Table 4  502U83 pharmacokinetic parameters (two compartment)

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<th>Patient</th>
<th>Infusion time (h)</th>
<th>Dose (mg/m²)</th>
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<th>C(0) (µg/ml)</th>
<th>AUC (h·µg/ml)</th>
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* I.E., index of exposure.
* Excluded from mean.
* Harmonic mean.
Table 5 502U83 pharmacokinetic parameters (three compartment) (1- and 4-h infusion schedule)

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<th>C_max (µg/ml)</th>
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Mean ± SD 12.56 ± 6.75 42.5 ± 10.50 22.10 ± 19.60 195.1 ± 74.93 3.94 ± 2.13

* Harmonic mean.

Fig. 3. Representative plasma concentration versus time profiles for individual patients. Patient 18 receiving 400 mg/m² of 502U83. Inset is Patient 5 receiving 50 mg/m² of 502U83.

The pharmacokinetic results are summarized in Tables 4 and 5. Plasma concentration versus time profiles for two representative individual patients are shown in Fig. 3. The plasma concentrations declined biexponentially and fit a 2-compartment model for the first nine patients up to and including doses of 100 mg/m² (see data for Patient 5, Fig. 3 inset). However, the data from the rest of the patients at >100 mg/m² were best fitted using a 3-compartment model (see data for Patient 18, Fig. 3). For these patients the harmonic mean terminal t_max was 8.83 h (see Table 5). The mean apparent volume of distribution at steady state was 195.1 liters/m², and the mean similar to the QTc (data not shown). Thus, it appears that this agent has a global influence on transmembrane depolarization and repolarization in the heart. All of the interval prolongations were reversible. For example, in one patient, after a 4-h infusion, the QTc increased from a baseline of 495 ms to 647 ms at the end of the infusion. By 15 h after the infusion the QTc had returned to baseline (501 ms). Despite these prolongations no arrhythmias were noted, and no episodes of multifocal ventricular tachycardia ("torsades des pointes") occurred. Since, however, this had been previously described as happening for another chemotherapeutic agent which caused QTc prolongation, it was felt safest to abandon this schedule (5).

Serial serum potassium levels were obtained from patients at the highest dose level. There were no consistent changes in the potassium values to explain the ECG interval prolongations. However, prolongation of QT intervals was seen in the two patients who had potassium levels below 3 meq/liter. Some patients were receiving concomitant phenothiazines for nausea and vomiting, but the interval prolongations noted in these patients were no greater than the prolongations noted in patients not receiving concomitant phenothiazines.

Other Toxicities. The other toxicities noted with 502U83 included sporadic mild to moderate nausea and vomiting which did not appear dose related. Grade 1 leukopenia was noted in 2 patients at 2000 mg/m² (nadir on Days 12 and 14, respectively). One patient had a minor extravasation of drug without consequence.

Antitumor Effects. No partial or complete tumor responses were noted in this Phase I study. Seven patients had stable disease for two to five monthly courses of therapy with all others having progressive disease after one course. The longest duration of stable disease (5 mo) was noted in a woman with renal cell carcinoma at the 800-mg/m² dose level.

Pharmacokinetics. The pharmacokinetic results are summarized in Tables 4 and 5. Plasma concentration versus time profiles for two representative individual patients are shown in Fig. 3. The plasma concentrations declined biexponentially and fit a 2-compartment model for the first nine patients up to and including doses of 100 mg/m² (see data for Patient 5, Fig. 3 inset). However, the data from the rest of the patients at >100 mg/m² were best fitted using a 3-compartment model (see data for Patient 18, Fig. 3). For these patients the harmonic mean terminal t_max was 8.83 h (see Table 5). The mean apparent volume of distribution at steady state was 195.1 liters/m², and the mean
total-body clearance was 42.5 liters/h/m². The increase in the AUC was proportional ($r^2 = 0.96$) to the increase in dose over the entire dosage range (50 to 2000 mg/m²).

**DISCUSSION**

This study reports on the second AMAP brought to clinical trial. The first AMAP in clinical trial was crisnatol [2-(6-chrysensy1methyl)amin0]-2-methyl-1,3-propanediol] or BW77-0U82 mesylate. In Phase I clinical trials with that agent, reversible neurological toxicity was dose limiting (6). The agent is now undergoing Phase II trials at a dose of 2250 mg/m². In trials with that agent one patient developed reversible sinus node arrest. No other hints of cardiac effects with crisnatol were noted, although preclinical studies had shown it to be a negative chronotrope.

In the present study the maximum tolerated dose of 502U83 was determined to be 2000 mg/m². At that dose level, significant prolongation of PR, QRS, and QT was noted. Prolongation of the QT interval is a well-known effect of quinidine and other antiarrhythmic drugs such as procainamide and disopyramide (7–9). Other drugs causing this effect include phenothiazines, tricyclic antidepressants, and amantadine overdoses (9, 10). Electrolyte disturbances such as hypokalemia and hypomagnesemia have also been reported to cause QT interval prolongation (7, 9). Of major interest is the prolongation of the QT interval described by Trump et al. (5) when they used the cern. QT prolongation and either the incidence of serious arrhythmia or ventricular fibrillation resulting from single extrasystoles during which the ventricle is vulnerable to ventricular tachycardia: a complication of disopyramide showed with quinidine. J. Electrocardiol., 14: 301-308, 1981.

The potential consequence of QT interval prolongation seen in these patients is clearly a cause for concern. QT interval prolongations have been noted at the highest doses (800, 1200, 1600, and 2000 mg/m²) of 502U83. Given the potential consequence of QT interval prolongation seen with other agents (i.e., serious ventricular arrhythmias), we did not feel that further increases in doses of 502U83 on this schedule were justified.

It is of note that ECGs previously performed as part of the initial dog toxicology studies with 502U83 were within normal limits. However, those ECG studies had been done at nonmetogenic (low) doses of 502U83. After the cardiac effects were noted in patients, dogs were given a surface area equivalent dose to match the dose in humans. The dogs were more sensitive to other high-dose effects of the drug (i.e., emesis) that meaningful ECGs could not be recorded.

Doses of 502U83 which do not produce QT interval prolongations are unlikely to achieve cytotoxic effects. Therefore, the use of a 1- or 4-h infusion cannot be recommended. Other Phase I trials, using 24- or 72-h infusions may provide a useful schedule for Phase II studies. Clearly, if schedule changes in the clinic do not allow bypassing of the conduction toxicity, development of a preclinical model will be necessary to try to find AMAP analogues which do not have this side effect.

**ACKNOWLEDGMENTS**

The authors thank Clair Waggoner and Julia Perkins for their excellent preparation of this manuscript as well as the nurses and personnel of the Special Diagnostic and Treatment Unit of the Audie Murphy VA Hospital.

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Phase I and Clinical Pharmacology Trial of 502U83 Using a Monthly Single Dose Schedule

Daniel D. Von Hoff, John G. Kuhn, Kathleen A. Havlin, et al.


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