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Phase I clinical and pharmacology study of 502U83 given as a 24-h continuous intravenous infusion

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Summary. 502U83 is an arylmethylaminopropanediol that displays significant antitumor activity in a number of murine and human tumor-model systems. In the present phase I study, a 24-h continuous intravenous infusion of this agent was given every 28 days to patients with advanced or refractory solid tumors. In all, 46 patients received a total of 96 cycles of 502U83 at doses ranging from 25 to 8,000 mg/m^2. No significant hematologic, gastrointestinal, or neurologic toxicity was observed. At doses of 2,000 mg/m^2 and higher, prolongation of the corrected QT interval on ECG was evident in most patients but was completely reversible, was not associated with arrhythmias, and was not dose-limiting. Dose-limiting pulmonary toxicity characterized by acute onset of dyspnea, severe hypoxemia, interstitial pulmonary edema, and death occurred in three patients treated at the highest dose levels. Plasma concentrations of 502U83 and its metabolites were measured by high-performance liquid chromatography. The 502U83 maximal concentration (C_{max}) and area under the concentration-time curve (AUC) were proportional to the delivered dose; however, substantial interpatient variability in total body clearance was noted at all dose levels. Significant conversion of 502U83 to two glucuronide metabolites was detected. Metabolite concentrations were highest in the three patients who succumbed to pulmonary toxicity, although the precise contribution of these metabolites to the observed toxic effects is unknown. In view of the unfavorable clinical profile of QTc prolongation and pulmonary toxicity produced by 502U83, further clinical development of this agent has been suspended.

Introduction

502U83 is one of a series of novel synthetic compounds, arylmethylaminopropanediols (AMAPs), that display significant antitumor activity in a number of murine and human tumor-model systems. Although their mechanism of action has not been determined with certainty, AMAPs are believed to interact with DNA by intercalation [1, 2]. 502U83 is one of four such compounds selected for clinical evaluation. It contains a carbocyclic nucleus bearing methylaminopropanediol and ethylene glycol ether substituents on opposite sides of the central ring (Fig. 1) and is the least lipophilic of the compounds in clinical trial.

Like the other congeners, 502U83 exhibits in vitro and in vivo antitumor activity against P388 leukemia, L1210 leukemia, B16 melanoma, Lewis lung carcinoma, M5076 sarcoma, and colon 38 carcinoma. It does not show significant antitumor activity against human breast-, lung-, or colon-tumor xenografts in immune-deficient mice. 502U83 is active against P388 sublines resistant to alkylating agents, antimetabolites, vincristine, cisplatin, actinomycin D, and mitoxantrone but exerts no activity against amsacrine- or doxorubicin-resistant lines. In a human tumor colony-forming assay, it has exhibited activity against breast, colon, and non-small-cell lung cancer as well as melanoma; overall, responses were seen in 53% of human tumors exposed continuously to 502U83 at a concentration of 10 μg/ml [5].

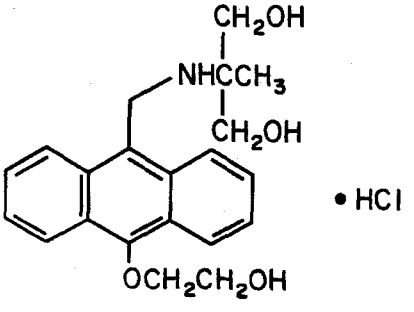

Fig. 1. Structure of 502U83

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Animal toxicology studies have been conducted in mice, rats, and dogs using single-dose and daily $\times 5$ schedules. Mouse lethality studies identified the single-dose LD_{10} (dose lethal to 10% of the population) as 81 mg/kg and the LD_{90} as 119 mg/kg; for rats these doses were about 20% higher. Dogs received single intravenous doses of 502U83 at 30 and 60 mg/kg. The primary toxic effects were emesis, bone marrow suppression, lymphoid atrophy, and enteritis. No neurologic, cardiac, or pulmonary toxicity was observed [3].

We conducted a phase I clinical trial of 502U83 given as a 24-h continuous intravenous infusion. The starting dose for humans was 1/10 of the mouse LD_{10} as adjusted on a surface-area equivalence basis.

Patients and methods

Eligibility criteria. To be eligible for entry into the present study, patients were required to have a histologically confirmed diagnosis of cancer that was refractory to standard treatment or for which there was no known effective therapy. The presence of measurable or evaluable disease was desired but not required. Other eligibility criteria included a Karnofsky performance status of at least 60%; a life expectancy of at least 12 weeks; and adequate organ function, including a WBC of $\geq 3{,}000/mm^3$, a granulocyte count of $\geq 1{,}500/mm^3$, a platelet count of $\geq 100{,}000/mm^3$, a hemoglobin level of >9 g/100 ml, a bilirubin value of ≤ 2.5 mg/100 ml, a creatinine level of ≤ 2 mg/100 ml, and serum glutamic oxaloacetic transaminase and alkaline phosphatase values of less than twice the upper limit of normal. Patients were also required to have normal levels of electrolytes, calcium, phosphorus, and uric acid and a blood glucose value of ≤ 200 mg/100 ml. Patients must have been off previous anticancer therapy for at least 3 weeks (6 weeks if prior therapy included a nitrosourea or mitomycin) and must have recovered from the toxic effects of all prior therapy. Patients were excluded from the study if they had a history of recent myocardial infarction or cardiac arrhythmia or if the pretreatment ECG demonstrated heart block or arrhythmia. All patients were more than 18 years of age and provided written informed consent for participation in the study in compliance with institutional and federal guidelines.

Treatment plan. Patients were hospitalized for the administration of each dose of 502U83. The drug was supplied by the Burroughs Wellcome Co. as a sterile lyophilized powder in an amber 10-ml vial containing 502U HCl equivalent to 100 mg 502U free base. The vials were reconstituted with 10 ml bacteriostatic water for injection, and the drug was further diluted in 5% dextrose in water for administration. The drug was given to patients as a 24-h continuous intravenous infusion via an indwelling central venous catheter. At doses of up to 2,000 mg/m^2, the total daily dose was given in 1,000 cc 5% dextrose in water. At doses ranging from 2,500 to 4,000 mg/m^2, one-half of the daily dose was diluted in 1,000 cc 5% dextrose in water and infused over 12 h. At doses exceeding 4,000 mg/m^2, one-third of the daily dose was diluted in 500 cc 5% dextrose in water and infused over 8 h. Cycles of chemotherapy were given every 21–28 days in the absence of severe toxicity or rapid tumor progression.

The starting dose was 25 mg/m^2. Doses were escalated by increments of 100% in cohorts of at least three patients until a dose of 1,600 mg/m^2 was reached. At that time we became aware of data from another phase I study of 502U83 that demonstrated significant prolongation of the QTc interval on the ECG of patients receiving 2,000 mg/m^2 infused over 1 h. We therefore reduced the magnitude of all subsequent dose escalations to approximately 25% of the preceding dose level. At least three evaluable patients were entered at each dose level. The first patient at each dose level was observed for at least 2 weeks. If no severe toxicity was observed, subsequent patients were entered at weekly intervals. If toxicity of grade 2 or greater occurred in one of three patients at a given dose level, three additional patients were enrolled at that dose. Patients who exhibited stable disease or a response to therapy after completing at least two cycles could be escalated to the next higher dose level, provided that that level had previously been shown to produce acceptable levels of toxicity in at least three patients.

Study parameters. Pretreatment examinations included a baseline medical history and physical examination; a complete blood count; a platelet count; serum chemistries; determinations of prothrombin time, partial thromboplastin time, and creatinine clearance; urinalysis; a chest X-ray; an ECG; and appropriate baseline scans or X-rays for evaluation of the extent of disease. Patients were seen weekly in the clinic once treatment had begun. At each visit, a medical history was obtained, a physical examination was performed, and any toxicity was noted. In addition, a complete blood count, a platelet count, and serum chemistries were carried out. Creatinine clearance determination, ECG, and chest X-ray were repeated on day 22 of each cycle, and evaluation of the extent of disease was performed after two cycles of therapy or sooner if clinically indicated.

During the 24-h drug infusion, the patient's vital signs were monitored every 15 min for the first 2 h, every hour for the next 2 h, and then every 4 h until the end of the infusion. Initially, an ECG was obtained pre- and postinfusion. Beginning at the 2,000 mg/m^2 dose level, ECGs were obtained prior to infusion; at 4, 8, 16, and 24 h during the infusion; and at 2 and 4 h postinfusion. Standard response criteria and WHO toxicity criteria were used for evaluation of patients.

Blood sampling. Blood samples for pharmacokinetic studies were obtained from an indwelling heparin lock prior to initiation of the drug infusion; at 2, 6, and 12 h during the infusion; at the end of the infusion; and at 10, 20, 40, and 60 min and 1.5, 2, 4, 6, 8, 12, and 24 h postinfusion. Serial 8-ml samples were collected in tubes containing ethylenediaminetetraacetic acid which were centrifuged at 2,000 rpm for 20 min. The plasma was decanted, divided into two aliquots, flash-frozen, and stored at –20° C in polyethylene tubes. At the completion of each cycle of chemotherapy, all samples were shipped frozen on dry ice by overnight mail to the Burroughs Wellcome Co. for analysis.

High-performance liquid chromatographic analysis. A reverse-phase high-performance liquid chromatographic (HPLC) analytical method was used for determination of 502U83 and its metabolites in plasma. Plasma samples were thawed to room temperature, vortexed, and centrifuged (Beckman, Microfuge 12) at 12,000 *g* for 10 min to remove particulates. A portion of the supernatant was transferred to a limited volume insert within an amber injection vial of an autosampler (Hewlett Packard model 1090 Solvent Delivery System), which was then sealed. Aliquots of 20 µl were injected directly onto a hexyl HPLC analytical column (Phase Sep; Spherisorb S5C6, 100×4.6 mm) protected by a guard cartridge (Brownlee Newguard RP-8). The HPLC mobile phase contained 0.2 or 0.6 M ammonium acetate and a methanol gradient ranging from 0–50% produced by a system controller and data-analysis software (Hewlett Packard Series 310 Chemstation). The flow rate was 2 ml/min, and detection was accomplished using a fluorescence detector (Shimadzu Model RF-530) set to excitation and emission wavelengths of 254 and 442 nm, respectively.

For each set of patient samples run, a calibration curve was constructed from plasma spiked with 502U83 over a concentration range of 0.12–35 µg/ml and was processed and analyzed concurrently. Plasma samples that contained drug or metabolite concentrations that exceeded the upper limits of the calibration curve were diluted with blank human plasma and reassayed. The coefficient of variation of the assay was 5%–7% over the linear range of the assay, and the lower limit of quantitation was 120 ng/ml.

Analysis of the standard calibration curves was performed using the Statistical Analysis System (SAS version 82) licensed from the SAS Institute (Cary, N.C.). A least-squares regression of the natural log of the 502U83 chromatographic peak areas versus the natural log of the known concentrations of 502U83 was carried out for each curve. Residual plots were evaluated for evidence of lack of fit, and the mean square error of

Table 1. Patient's characteristics

Total number of patients	46
Sex:	
M	26
F	20
Median age (years)	60 (range, 34–76)
Karnofsky performance status:	
100	6
90	20
80	10
70	6
60	4
Prior therapy:	
Chemotherapy	23
Chemotherapy + radiation	20
Radiation therapy	0
Biologic therapy	1
None	2

Table 2. Dose-escalation scheme

Entry dose (mg/m^2)	Number of patients	Number of cycles	Dose escalation[a]
25	3	5	–
50	3	5	–
100	3	5	–
200	3	9	400 mg/m^2 ×2 cycles
400	3	5	–
800	4	5	2,000 mg/m^2 ×1 cycle
1,600	3	8	2,500 mg/m^2 ×1 cycle
2,000	3	9	–
2,500	3	6	–
3,200	3	5	–
4,000	3	16	–
5,200	4	7	–
6,500	6	9	–
8,000	2	2	
Totals	46	96	

[a] Dose escalation was carried out as indicated for one patient in each cohort

each regression was monitored to detect significant changes in the precision of the assay. The regression parameter estimates were used to calculate 502U83 and metabolite concentrations in the patients' samples. The metabolite concentrations were expressed as equivalents of 502U83 since no pure stocks of these compounds were available. The two major metabolites detected were isolated from patients' urine samples and identified by nuclear magnetic resonance (NMR) and mass spectroscopy (T. L. Allsup, Burroughs Wellcome Co., personal communication).

Pharmacokinetic analysis. The C_{max} value represented the highest 502U83 plasma concentration observed during the infusion. The area under the concentration-time curve (AUC) was calculated using nonlinear least-squares regression analysis with a weighting function of 1/concentration.

Results

Overall, 46 patients received a total of 96 cycles of 502U83. The characteristics of the patients are shown in Table 1 and the doses given are listed in Table 2. In all, 24 of the patients had advanced colorectal or pancreatic cancer; the remainder had a variety of other solid tumors. All patients were evaluable for toxicity.

The drug was very well tolerated at doses below 6,500 mg/m^2. One of three patients treated at both 2,000 and 4,000 mg/m^2 developed facial swelling during the drug infusion that resolved without sequelae within 24 h after the completion of the infusion. One of four patients treated at 5,200 mg/m^2 developed grade 2 leukopenia of short duration. Mild nausea and vomiting occurred in 50% of patients treated at 6,500 mg/m^2, and one of six patients treated at this dose experienced grade 1 diarrhea. Leukopenia and thrombocytopenia occurred in two of six patients treated at 6,500 mg/m^2; in one patient, this toxic effect was of grade 2 severity and short duration; in the other, grade 4 toxicity occurred in the setting of catheter-related sepsis, azotemia, and elevated bilirubin levels (14 mg/dl).

Cardiac conduction-system changes

When given as a 1-h or 4-h infusion, 502U83 has been shown to produce prolongation of the corrected QT (QT_c) interval on ECG [11]. Beginning at doses of 2,000 mg/m^2, all patients in this study were carefully monitored for cardiac conduction abnormalities by means of frequent 12-lead ECG and rhythm strips. Some prolongation of the QT_c interval occurred during the drug infusion in most patients, with the median percentage of increase over baseline values being 10%–12% at the highest dose levels. In all cases, the QT_c interval returned to baseline levels within 4 h of the end of the drug infusion and no arrhythmia was noted. No significant relationship was found between the dose or AUC of 502U83 and the extent of QT_c prolongation. No consistent or significant prolongation of the PR or QRS intervals was noted in these patients.

Pulmonary toxicity

The most clinically significant and dose-limiting toxicity observed in this study was severe respiratory distress. Three patients died of this apparently treatment-related complication. The first patient had advanced colon cancer but normal pulmonary function at study entry at the 6,500 mg/m^2 dose level. At 12 h after the beginning of the 24-h infusion of 502U83, she was found on the floor of her room, mildly lethargic but completely oriented and showing normal neurologic function. A computerized tomographic (CT) head scan was performed and revealed no evidence of metastasis or infarct. At approximately 2 h after the completion of the 24-h infusion of 502U83, she exhibited increasing lethargy and suffered a respiratory arrest. Room-air arterial blood gases revealed severe hypoxemia (PO_2, 31 mmHg) and a chest X-ray demonstrated bilateral perihilar edema. Despite intubation and mechanical ventilation, her respiratory status progressively deteriorated and she expired approximately 9 h after completing

Table 3. Plasma concentrations of 502U and its metabolites

Dose (mg/m²)	C_{max} (μg/ml)		
	502U	502U-Gluc	Acid-Gluc
25	ND		
50	0.08 ± .02		
100	0.082		
200	0.198 ± .04		
400	0.411 ± .18		
800	0.963 ± .58		
1,600	1.37 ± .62		
2,000	1.91 ± .34		
2,500	1.98 ± .12		
3,200	2.69 ± .38		
4,000	3.31 ± .95	7.06 ± 6.7	5.79 ± 1.4
5,200	3.77 ±1.1	8.74 ± 6.0	10.74 ± 6.3
6,500	5.04 ±1.7	47.9 ±75	16.5 ± 7.8
8,000	5.74 ±1.9	68.2 ±86	11.3 ±11.9

502U-Gluc, 502U-glucuronide; Acid-Gluc, acid glucuronide; ND, not detectable

Table 4. 502U AUC and clearance values

Dose (mg/m²)	Number of cycles	AUC[a] (μg ml⁻¹ h⁻¹)	Clearance[a] (ml min⁻¹ m⁻²)
50	2	1.9 ± 0.9	844 ± 643
100	1	2.2	846
200	2	4.4 ± 0.6	750 ± 206
400	2	9.8 ± 2.7	795 ± 427
800	4	21.5 ±16	912 ± 512
1,600	3	28.0 ±12	1,872 ±1,016
2,000	3	41.4 ± 9.5	1,031 ± 321
2,500	3	45.9 ± 5.4	1,356 ± 269
3,200	3	65.8 ± 8.7	904 ± 84
4,000	3	74.6 ±20	1,270 ± 513
5,200	4	79.3 ±22	1,504 ± 363
6,500	6	103.4 ±22	1,426 ± 432
8,000	2	85.1 ±13	1,259 ± 328

[a] Data represent mean values ± SD

the infusion of 502U83. Postmortem examination revealed no cardiac disease or pulmonary embolus. The lungs were found to be normal on examination by both light and electron microscopy, and no specific cause of death was determined.

The second patient was a man with extensive liver metastases from pancreatic cancer whose performance status was excellent and who was treated at 6,500 mg/m². A venous access device was implanted several days before the initiation of chemotherapy, and on the patient's admission to the hospital, the skin surrounding this area was noted to be tender and erythematous. Approximately midway through the chemotherapy infusion, the patient was found to be febrile. Blood cultures as well as cultures of skin surrounding the catheter site obtained at that time were positive for *Staphylococcus aureus*. The patient completed the 24-h infusion but soon thereafter became hypotensive and hypoxic. He was treated vigorously with intravenous fluids, antibiotics, and mechanical ventilation, after which the fever subsided and blood cultures were negative. However, he remained severely hypoxic and chest X-ray findings were consistent with pulmonary edema. ECG revealed a normal ejection fraction, normal cardiac valves, and no regional wall abnormality, suggesting that the pulmonary edema was not cardiogenic. Over a period of several days, the patient's renal and liver function progressively deteriorated and he developed grade 4 leukopenia and thrombocytopenia. Myelosuppression was first noted on day 5 of the treatment cycle, and the nadir WBC of 0.5 cells/μl occurred on day 9. He expired 10 days following the infusion of 502U83. Postmortem examination of the lungs revealed hyperplasia of type II pneumocytes, hyaline membranes, and interstitial hemorrhage consistent with adult respiratory distress syndrome. At autopsy the bone marrow was hypocellular, consistent with a chemotherapy effect.

The third patient was a 56-year-old woman with colon cancer metastatic to the liver who was treated at 8,000 mg/m². She tolerated the 24-h drug infusion well, complaining only of mild nausea. However, at approximately 2 h after the completion of the drug infusion, she developed acute dyspnea and was noted to be tachypneic, with an arterial PO_2 of 52 mmHg. Her condition rapidly deteriorated and she was moved to the intensive care unit and intubated. The arterial PO_2 was 90 mmHg with an inspired O_2 concentration of 100%. Her chest X-ray revealed interstitial pulmonary edema. Despite vigorous therapy, she became progressively hypotensive and expired about 5 h after completing the 24-h infusion of 502U83. An autopsy was not obtained.

It is noteworthy that four other patients treated at 6,500 mg/m² and another patient treated at 8,000 mg/m² tolerated the therapy well without showing signs of respiratory distress. However, in view of the three respiratory deaths described above, the study was closed.

Response to therapy

No complete or partial response was observed.

Pharmacokinetics

The pharmacokinetic results of the present study are summarized in Tables 3 and 4. The increase in 502U83 C_{max} and AUC was proportional to the increase in dose over the range of doses studied ($r = 0.995$ and 0.95, respectively). Substantial interpatient variability in total body clearance was noted at all dose levels, with the mean coefficient of variation being 42%.

A significant correlation was noted between total body clearance of the drug and body surface area ($r = 0.469$, $P = 0.0029$). Clearance was also found to display a weak but significant positive correlation with dose ($r = 0.339$, $P = 0.040$; Fig. 2). Plasma samples obtained from patients treated at 502U83 doses of 4,000 mg/m² and higher were analyzed for the presence of two glucuronide metabolites,

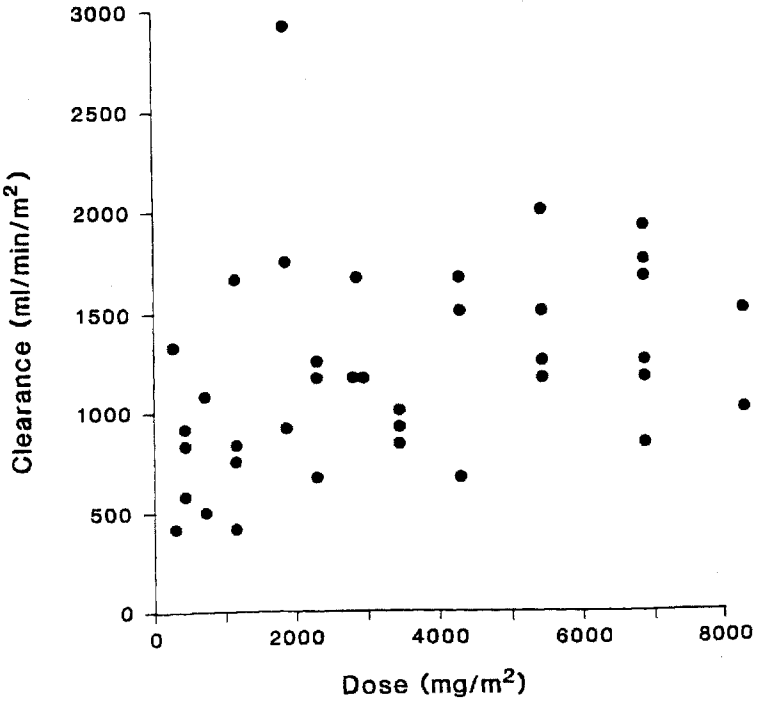

Fig. 2. Relationship between the delivered dose of 502U83 and total body clearance ($r = 0.33$, $P = 0.040$)

identified as a 502U glucuronide and an acid glucuronide. As shown in Table 3, maximal concentrations of both metabolites exceeded the C_{max} of 502U83. The mean ratios of the maximal concentrations of 502U-glucuronide and acid glucuronide to that of 502U83 were 5.38 and 2.96, respectively. Maximal concentrations of both metabolites were noted in the plasma samples obtained at the completion of the 24-h infusion of 502U. The highest concentrations of 502U-glucuronide were detected in the three patients who died of apparent respiratory toxicity. In these individuals, the ratios of the C_{max} of 502U-glucuronide to that of 502U83 were 23.3, 12.9, and 18.1, respectively.

Discussion

502U83 is the least lipophilic of a number of AMAP compounds recently brought to clinical trial. The related compound crisnatol (770U) is highly lipophilic and produced dose-limiting neurologic toxicity during initial clinical trials [4]. When given as a 1-h or 4-h intravenous infusion, 502U83 has been found to produce dose-limiting prolongation of the QT_c interval on ECGs of patients treated at a dose of 2,000 mg/m^2 [11]. At this dose level, QT_c prolongation of 15%–72% above baseline levels was noted but was not complicated by cardiac arrhythmias or symptoms. No relationship was found between the QT_c increase and the AUC of 502U83. In the present study we also observed QT_c interval prolongation, but the median percentage of increase over baseline values did not exceed 12.7% at any dose level. This more moderate effect may be related to the lower peak concentrations of 502U83 that occurred during the 24-h infusion employed in the present study. At a dose of 2,000 mg/m^2, the C_{max} observed following short-term infusion of 502U83 ranged from 10- to 22 μg/ml [11] as compared with the 1.91-μg/ml value obtained following 24-h infusion of the same dose. Indeed, during the 24-h infusion, the C_{max} of 502U83 did not exceed 10 μg/ml, even at doses as high as 8,000 mg/m^2. Although we cannot conclude with certainty that the lower peak concentrations of 502U83 resulted in less cardiac toxicity, it is clear that the cardiac effects of the drug are not dose-limiting on the 24-h infusion schedule.

The present study was terminated following the occurrence of three deaths at the highest dose levels studied. Each case was characterized by acute onset of dyspnea, severe hypoxemia, and interstitial pulmonary edema, which began during the infusion or soon after its completion. Although the interpretation of one patient's course was complicated by the occurrence of *Staphylococcus aureus* sepsis, his respiratory condition failed to improve even after he had become afebrile and his blood cultures had become negative. Postmortem examination of the lungs of two patients revealed no abnormality in one case and findings consistent with adult respiratory distress syndrome in the other. The clear temporal relationship between the administration of 502U83 and the occurrence of pulmonary toxicity strongly suggests a causal relationship.

Of particular interest was the finding of very high levels of 502U-glucuronide in the plasma of the patients who died. High levels of this metabolite were noted in the plasma of each patient prior to the onset of clinical symptoms of respiratory distress, and peak concentrations had occurred by the time of completion of the drug infusion, suggesting that accumulation of this metabolite was not the result of impaired clearance in critically ill, hypotensive patients. All three patients who died had extensive liver metastases prior to treatment, although the pretreatment liver function of each patient was adequate to meet the eligibility criteria for protocol entry; their total bilirubin

levels at study entry were 0.4, 1.5, and 0.6 mg/dl, respectively. It is not possible to say whether the high concentrations of 502U-glucuronide contributed directly to the observed pulmonary toxicity or whether they were a manifestation of some as yet unknown alteration of 502U83 metabolism that resulted in the production of a toxic metabolite.

Few examples exist of antineoplastic agents that are metabolized extensively to glucuronide forms. One notable example is 4′-epidoxorubicin, the metabolism of which is characterized by the conversion of the drug to epirubicin glucuronide [9, 12]. Glucuronidation of epirubicin is unique to humans and has not been observed in preclinical pharmacology studies in a number of animal species [6]. Recent clinical studies have demonstrated marked interpatient variability in the formation of epirubicin glucuronide [7, 8]. Robert and colleagues [10] retrospectively analyzed clinical and pharmacologic data of 48 patients treated with epirubicin. Two populations of patients were identified on the basis of the concentration ratios of epirubicin glucuronide to parent drug. Interestingly, patients with high concentration ratios experienced significantly more hematologic toxicity but showed a lower rate of tumor response than did patients with low ratios. This observation is difficult to explain, particularly since epirubicin glucuronide has not been demonstrated to have biological activity. Preclinical pharmacology studies of 502U83 also failed to demonstrate metabolism of this drug to glucuronide forms, although glucuronide metabolites of other AMAPs were detected. Toxicology studies performed in both rodents and dogs also failed to predict either cardiac or pulmonary toxicity from this agent. Whether the lack of such toxicity is related to a failure to generate glucuronide metabolites in these species in presently unknown.

The pharmacokinetic results of this study are similar to those previously reported by Von Hoff and colleagues [11] for a 1- or 4-h infusion of the drug. In both studies, the AUC was found to be proportional to the delivered dose. However, our results also revealed a modest but significant positive correlation between total body clearance and dose. This relationship might not have been apparent in the previous study, since dose escalation was discontinued at 2,000 mg/m^2, whereas we were capable of giving doses as high as 8,000 mg/m^2. At these very high doses, it is possible that saturation of either plasma protein binding, enterohepatic circulation, or renal tubular reabsorption of the drug occurred, resulting in higher systemic clearance.

This study clearly illustrates the difficulties that can be encountered in the study of new drugs when preclinical pharmacology and toxicology are not representative of the drug's effects in humans. The maximal tolerated dose (MTD) in this study was 320 times the starting dose and required 14 dose-escalation steps to define. The unusual toxicities observed were not predictable from animal toxicology and their pathogenesis remains largely unexplained at present. However, the unfavorable clinical profile of QT_c prolongation and pulmonary toxicity produced by 502U has resulted in the suspension of further clinical trials of this agent.

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