

Phase I Trial of the Cryptophycin Analogue LY355703 Administered as an Intravenous Infusion on a Day 1 and 8 Schedule Every 21 Days

James P. Stevenson,¹ Weijing Sun, Maryann Gallagher, Robert Johnson, David Vaughn, Lynn Schuchter, Kenneth Algazy, Stephen Hahn, Nathan Enas, Diane Ellis, Donald Thornton, and Peter J. O'Dwyer

University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania 19104 [J. P. S., W. S., M. G., D. V., L. S., K. A., S. H., P. J. O.], and Eli Lilly Research Laboratories, Indianapolis, Indiana 46285 [R. J., N. E., D. E., D. T.]

ABSTRACT

The cryptophycin analogue LY355703 is a potent inhibitor of microtubule polymerization that displays *in vitro* and *in vivo* activity in cell lines and tumor xenografts displaying the multidrug-resistant phenotype. In a Phase I trial, 25 patients received LY355703 as a 2-h i.v. infusion on day 1 and day 8 repeated every 3 weeks. Doses were escalated from 0.1 to 2.22 mg/m² using a modified continual reassessment method. Neurological toxicity was found to be dose-limiting at 1.84 and 2.22 mg/m². Among four patients treated at these doses, two had grade 4 constipation/ileus, one with severe myalgias, and one had grade 3 motor neuropathy. These findings were reversible. The 1.5 mg/m² dose level was well tolerated. An amended twice-weekly schedule was pursued in 11 patients in an attempt to improve dose intensity and avoid dose-limiting neurotoxicity. Doses of >0.75 mg/m² on a day 1, 4, 8, and 11 schedule every 21 days were not tolerated as a result of nausea/constipation, suggesting that LY355703 toxicity is not schedule dependent and is related to cumulative dose. LY355703 plasma concentrations measured by liquid chromatography with tandem mass spectrometry were evaluated using a population pharmacokinetic model. LY355703 was eliminated rapidly with a short terminal half-life that ranged from 0.8 to 3.9 h. Interpatient variability with respect to plasma clearance and volume of distribution, including covariates, was moderate at 32% and 39%, respectively. Maximum plasma concentration and area under the plasma concentration-time curve were linear over the dose range studied. A patient with

non-small cell lung cancer previously treated with taxanes experienced a partial response lasting 4 months, and five patients had stable disease lasting ≥3 months. LY355703 at a dose of 1.5 mg/m² is recommended for Phase II evaluation on a days 1 and 8 schedule. Twice-weekly dosing did not allow improvement in dose intensity or tolerability.

INTRODUCTION

The synthetic depsipeptide LY355703 (cryptophycin 52; Fig. 1) is an analogue of naturally occurring cryptophycins that have been isolated from *Nostoc* species of blue-green algae (1, 2). Cryptophycins are cytotoxic to cells in the picomolar range, an effect associated with inhibition of microtubular polymerization. Cryptophycin strongly binds microtubule ends ($K_d = 47$ nM) at the *Vinca* alkaloid-binding site and causes G₂-M block in cell cycle progression, leading to apoptosis (3, 4).

LY355703 displays potent cytotoxic activity across a broad spectrum of cell lines, with IC₅₀s in the 10–50 pM range for most lines (5). *In vivo* activity was observed in murine solid tumors (of colon, mammary, and pancreatic origin) and human tumor xenografts [colon, mammary, and prostate (6–8)]. In advanced-stage mammary and prostate xenografts in severe combined immunodeficient (SCID) mice, complete tumor regressions were observed (9). Studies of matched pairs of cell lines with acquired resistance to *Vinca* alkaloids and taxanes or engineered to overexpress the multidrug resistance protein suggested that LY355703 is non-cross-resistant to these agents (10, 11). *In vivo* scheduling studies favored frequent schedules of administration (5).

Preclinical pharmacological studies revealed LY355703 to be highly protein bound (up to 99%, depending on the species; Ref. 5). Elimination half-lives were intermediate (1.5 h for rat and 4 h for dog), with hepatic elimination accounting for about 90% of the drug's disposition in each species. The drug is extensively metabolized, but not all of the metabolites have yet been characterized.

The toxicity of LY355703 in rats and dogs was predominantly myelosuppression, affecting both neutrophils and platelets (5). The dog was the most sensitive species, which led to a starting dose for the clinical trial as one-tenth the MTD² in that species. We describe a Phase I/pharmacokinetic trial of LY355703 administered on a day 1 and day 8 schedule repeated every 21 days as well as an amended schedule of twice-weekly dosing on days 1, 4, 8, and 11 every 21 days.

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¹ To whom requests for reprints should be addressed, at University of Pennsylvania, Presbyterian Medical Center, 51 North 39th Street, MAB-103, Philadelphia, PA 19104. Phone: (215) 662-9671; Fax: (215) 243-3269; E-mail: james.stevenson@uphs.upenn.edu.

² The abbreviations used are: MTD, maximum tolerated dose; DLT, dose-limiting toxicity; ALT, alanine transaminase; BSA, body surface area; C_{max}, maximal plasma concentration; AUC, area under the concentration-time curve; CL, plasma clearance; V, volume of distribution.

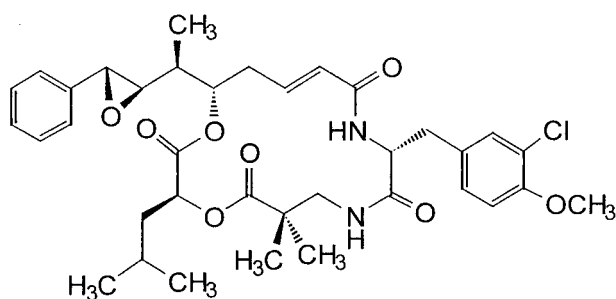


Fig. 1 Structure of LY355703.

PATIENTS AND METHODS

Patients were treated on this trial between May 1998 and March 2001 at the Developmental Therapeutics Program of the University of Pennsylvania Cancer Center. All received therapy as outpatients. Eligible patients were at least 18 years of age with histologically confirmed solid tumors that were refractory to standard therapy or for which no effective therapy was available. An Eastern Cooperative Oncology Group performance status of ≤ 2 and a life expectancy of ≥ 3 months were required. All patients had recovered from prior treatment and had received no cytotoxic therapy or radiation in the previous 4 weeks (6 weeks for mitomycin C or nitrosoureas). Patients had adequate bone marrow (absolute neutrophil count $\geq 1500/\mu\text{l}$; platelets $\geq 100,000/\mu\text{l}$), renal (creatinine < 1.5 -fold upper limit of normal), and hepatic (bilirubin < 1.3 -fold upper limit of normal; transaminases ≤ 2.5 -fold upper limit of normal) function at baseline. The study and all amendments were approved by the Institutional Review Board of the University of Pennsylvania, and all patients received information on the purpose and conduct of the study and gave written informed consent.

Pretreatment evaluation included a history and physical examination, complete blood count, serum electrolytes, creatinine, and biochemical screen within 2 weeks of initiating treatment and documentation of the extent of disease (by computed tomography or magnetic resonance imaging scanning) within 4 weeks. Chest radiograph and electrocardiogram were also performed pretreatment. Blood counts were performed twice weekly, and biochemical profiles were performed weekly for the first cycle, and patients were seen and examined before every course. Disease measurement was performed every other cycle. Toxicity during treatment was graded according to the 1979 WHO criteria. Response criteria were standard (12).

Drug Administration. LY355703 was supplied at 1 mg/m² in 20-ml glass vials that also contained 525 mg of polyoxyl 35 castor oil (cremophor EL) and 395 mg of absolute alcohol per milliliter. The concentrated drug was diluted up to 19:1 in normal saline before use. The final volume was then administered as a zero-order i.v. infusion over 2 h on days 1 and 8. Cycles were repeated every 21 days. After determination of the MTD on this schedule, an amended schedule of LY355703 administration on days 1, 4, 8, and 11 every 21 days was studied at an initial dose of 0.75 mg/m². Because of the presence of cremophor EL, only non-polyvinyl chloride-containing administration set components were used. The finding of multiple hypersensitivity reactions led us to premedicate all patients with

dexamethasone (4 mg, i.v. or p.o.) 30–60 min before every dose. In the event of a hypersensitivity reaction despite this regimen, a more standard pretreatment regimen of dexamethasone (20 mg, i.v.), diphenhydramine (50 mg, i.v.), and either cimetidine (300 mg, i.v.) or ranitidine (50 mg, i.v.) given 30–60 min before dosing was used.

Study Design. A modified continuous reassessment method of dose escalation was used in this Phase I trial (13). This Bayesian statistical methodology combines *a priori* information with dose and toxicity data observed during the study to guide dose escalation as quickly and safely possible. For this study, because little *a priori* information existed on the distribution for the MTD, a uniform prior distribution on the interval from 0.1 to 5.0 mg/m² was selected. The prior dose-toxicity relationship was assumed to be a logistic function, $[1 + \exp(-1.5 \times (\text{dose} - 3.4623))]^{-1}$, assuming *a priori* that a dose of 3 mg/m² was associated with a 33.3% DLT rate. As the study progressed, these prior distributions were updated according to the modified continuous reassessment method, and the mean of the posterior distribution for the MTD was used as the current target dose for future patients, subject to the following rules specified in the protocol. Doses were doubled until a toxicity of \geq grade 2 was observed, followed by a more conservative Fibonacci-like strategy. One patient was accrued to each level until DLT was observed, whereupon expanded accrual to each level was used. The MTD was defined to be the dose at which \geq one-third of the patients experienced drug-related DLT. The recommended Phase II dose was to be a well-tolerated dose below the MTD. DLT was defined as grade 4 neutropenia lasting ≥ 5 days or grade 3/4 neutropenia with sepsis, grade 4 thrombocytopenia, or any nonhematological toxicity grade ≥ 3 (excluding alopecia, allergy, nausea, and vomiting). The day 8 dose was omitted for grade ≥ 3 neutropenia, thrombocytopenia, or nonhematological toxicity or for grade ≥ 2 neurotoxicity. Dose modifications were planned based on toxicity in previous cycles.

Pharmacokinetic Sampling and Analysis. The pharmacokinetics of LY355703 were evaluated as part of a population pharmacokinetic analysis. Blood samples were collected for analysis of LY355703 in plasma from 36 patients during cycle 1. Blood samples (5 ml) were collected in heparinized tubes before infusion and 1, 2, 3, 4, 6, and 8 h after the start of infusion on day 1. Day 8 samples were collected just before the end of LY355703 infusion and 3–6 h after the start of infusion. Samples were centrifuged immediately at room temperature, and the plasma was separated and stored at -80°C . Batched samples were shipped on dry ice to the analytical site.

Plasma samples were assayed for LY355703 concentrations in plasma using a validated liquid chromatography with tandem mass spectrometry method over the concentration range 0.25–200 ng/ml as described by Berna *et al.* (14). The overall relative standard deviation, which is an expression of the precision, was $\leq 17.06\%$ at all concentrations. The overall relative error, which is an expression of the accuracy, was $\leq 12.35\%$ for all concentrations.

Pharmacokinetic analysis was performed using population pharmacokinetic methods with the nonlinear mixed effects modeling program NONMEM (Version 5, PREDPP 5; Ref. 15). An open one-compartment model parameterized in terms of clear-

Table 1 Patient demographics

No. of patients/evaluable	36/34
Age, mean (range) (yrs)	55 (37–89)
Sex, M/F	23/13
Performance status	0/6 1/28 2/2
Prior treatment	
Chemotherapy	35
Radiation	15
None	1
Tumor types	
Renal	6
Lung, non-small cell	7
Head and neck	4
Colorectal	7
Sarcoma	3
Other	9

Table 2 Dose escalation strategy

Dose (mg/m ²)	N	No. of cycles
Schedule 1		
0.1	1	5
0.2	3	11
0.3	1	2
0.45	1	2
0.68	6	15
0.88	1	4
1.3	1	1
1.48	6	12
1.84	3	3
2.22	1	2
Schedule 2		
0.75	3	3
1.0	8	14

ance and volume was determined to be the most appropriate structural model for the available data. A final population pharmacokinetic model including statistically significant covariates was developed. The effect of factors such as age, gender, BSA, body weight, aspartate transaminase, ALT, alkaline phosphatase, total bilirubin, albumin, and calculated creatinine clearance with respect to clearance and volume were evaluated during model building. Of the covariates tested, CL was demonstrated to be a function of ALT and BSA according to the following form:

$$CL = \Theta_1 \times \left(\frac{ALT}{22.8}\right)^{\Theta_2} \times \left(\frac{BSA}{1.84}\right)^{\Theta_3} \quad (A)$$

V was determined to be a function of BSA as follows:

$$V = \Theta_4 \times \left(\frac{BSA}{1.84}\right)^{\Theta_5} \quad (B)$$

The terminal elimination half-life ($t_{1/2}$) was calculated from CL and V by the following relationship:

$$t_{1/2} = \frac{\ln(2)}{\lambda_z} \quad (C)$$

where λ_z is the terminal elimination rate constant. The pharmacokinetic results presented represent an analysis of plasma concentration-time data collected in this study using the final population model.

RESULTS

A total of 36 patients received 76 cycles of therapy with LY355703 (median, 2 cycles; range, 1–8 cycles). All but five patients received one full cycle of therapy. Two patients receiving the once-weekly schedule removed themselves from the study after day 1 of treatment, and three patients on twice-weekly LY355703 developed rapidly progressive disease during the first week of treatment. The demographic characteristics of the patients are listed in Table 1. There was a preponderance of males, with a median age of 55 years. All but two patients had received prior chemotherapy with a median of two regimens. The performance status of these patients was excellent, with

only two patients having performance status of 2. A range of solid tumors was represented among the patients entered, with a preponderance of renal cell cancer.

The dose escalations and the number of patients and cycles for the day 1 and day 8 schedule (schedule 1) and the twice-weekly schedule (schedule 2) are depicted in Table 2.

Schedules

Schedule 1

Minor levels of toxicity led to expansion at 0.2 mg/m², and a single episode of dose-limiting myalgia (grade 3) led to expansion at 0.68 mg/m². When this was well tolerated by other patients, escalation continued to a maximum of 2.2 mg/m². An episode of DLT at this dose resulted in exploration of an intermediate dose (1.84 mg/m²) at which two episodes of DLT (grade 4) were observed among three patients entered. Expansion of the previous level (1.48 mg/m²) to six patients was well tolerated.

Schedule 2

An initial dose of 0.75 mg/m² was administered on the twice-weekly schedule, based on the tolerability of this dose in schedule 1. Escalation to 1.0 mg/m² occurred; however, two episodes of DLT and the inability to deliver doses on time as a result of grade 2 toxicity made further dose escalation unfeasible.

Toxicity

Neurotoxicity

The major toxicity experienced by patients in this trial was neurological (Table 3). Characteristics of this toxicity are described for each schedule below.

Schedule 1. Dose-limiting motor neuropathy occurred at 2.2 mg/m². The patient was a 58-year-old male with metastatic esophageal cancer who had received multiple prior therapies, including cisplatin, paclitaxel, and cervical radiation. At baseline he reported residual grade 1 neuropathic symptoms in the fourth and fifth digits of his right hand. No acute toxicity was observed. However, beginning about 10 h postinfusion on day 1,

Table 3 Highest grade of LY355703 neurotoxicity in cycle 1

Dose (mg/m ²)	N	CTC ^a grade				
		0	1	2	3	4
Schedule 1						
0.1–0.5	6	4	2			
0.68	6	5	1			
0.9–1.1	2		2			
1.48	6	1	4	1		
1.84	2					2
2.22	1				1	
Schedule 2						
0.75	3	1	1			
1.0	8	0	2	4	1	1

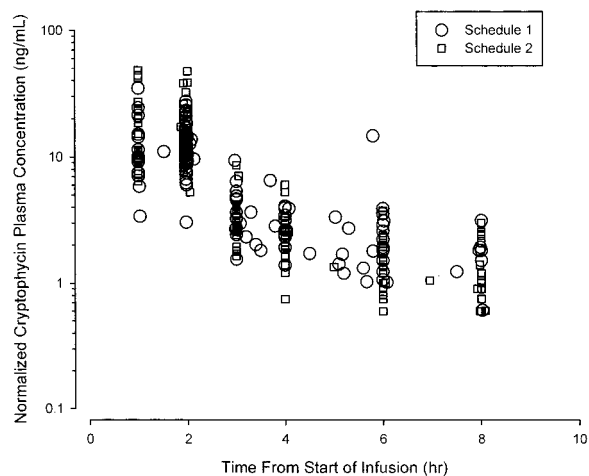
^a CTC, Common Toxicity Criteria.

he developed grade 2 neurosensory and grade 3 neuromotor toxicity characterized by numbness/paresthesias in his fingers and toes, bilateral lower extremity weakness, and loss of strength in his right arm. These symptoms persisted and precluded dosing on day 8; however, they completely resolved within 14 days of his original dose. Electromyography and nerve conduction studies performed before cycle 2 revealed normal sensory and motor conduction. He received his second cycle with a 50% dose reduction and experienced transient grade 1 distal paresthesias on day 1 and day 8 only.

Because of the severity of this effect, and the substantial dose escalation represented by this dose level, it was decided to explore 1.84 mg/m². Two patients were entered, and both required admission to the hospital for management of constipation and abdominal cramping with laxatives and i.v. hydration. Interestingly, these patients experienced no or minimal peripheral neuropathy.

Dosing at 1.5 mg/m² was generally well tolerated. One patient with locally advanced head and neck carcinoma experienced severe tumor pain on day 1 within 1 h of completing LY355703 infusion. The pain persisted for approximately 2 h and required i.v. narcotic administration for relief. Retreatment on day 8 resulted in the occurrence of similar symptoms before completion of the infusion. He declined retreatment on cycle 2 with dose reduction. Another patient with non-small cell lung cancer experienced similar tumor pain at the site of a rib metastasis that was grade 2 in severity. Other neurological toxicity included only transient grade 1 paresthesias and constipation in the six other patients treated at this dose level.

Schedule 2. Dose-limiting neurological toxicity in the form of constipation/ileus occurred in two patients receiving 1.0 mg/m² on the twice-weekly schedule. This occurred despite prophylaxis with an aggressive laxative regimen. One of these patients received only two doses of LY355703 and developed grade 4 constipation in the setting of rapidly progressing disease and was unable to resume treatment. Another three patients experienced grade 2 constipation during cycle 1 with associated nausea that necessitated frequent holding of LY355703 doses. Grade 1/2 neurosensory toxicity occurred in five patients receiving 1.0 mg/m² LY355703, but there were no grade 3 or greater neurosensory events. The constipation described above greatly limited the delivery of LY355703 on this schedule at doses of >0.75 mg/m².



Note: Concentrations were normalized to a dose of 1.5 mg/m².

Fig. 2 Normalized observed LY355703 plasma concentrations versus time. Concentrations were normalized to a dose of 1.5 mg/m².

Hypersensitivity

As expected with a cremophor-containing formulation, hypersensitivity reactions occurred at multiple dose levels and affected 6 of 36 (17%) patients. In five of six patients, the severity was grade 2; it was mild in the remaining patient. Onset was typical for infusion-related hypersensitivity, with symptoms occurring within 15 min of administration. Five reactions occurred on day 1 of cycle 1, and one occurred during the second weekly infusion of cycle 2. In all five of those with grade 2 reactions, the treatment was successfully continued with standard triple therapy (including a single dose of dexamethasone the evening before dosing). Routine premedication was begun with the final three patients treated at 1.5 mg/m², and no reactions were observed in these patients. Based on these findings, we recommend that all patients receive some prophylaxis; we continue to explore minimizing the intensity of this prophylaxis.

Other Toxicity

No significant myelosuppression was observed in this trial on either LY355703 schedule. Two patients experienced grade 1 neutropenia, and there was one episode of grade 1 thrombocytopenia. Nausea and vomiting were uncommon (except when associated with constipation) and responded to antiemetic therapy. Mild alopecia occurred in six patients. Grade 1 hypertension during LY355703 infusion was also observed.

Pharmacokinetics

Fig. 2 shows normalized plasma LY355703 concentrations as a function of time. Plasma concentrations were generally below the minimum quantitation limit of the assay (0.3 ng/ml) within 8 h after start of infusion, suggesting a short terminal elimination half-life. Plasma concentrations from the two administration schedules overlapped, suggesting that the pharmacokinetics were consistent between schedules.

Pharmacokinetic parameter estimates are presented in Table 4. CL was 51.5 liters/h for a typical patient with an ALT

Table 4 Summary of mean LY355703 pharmacokinetic parameter estimates

Parameter description	Population ^a estimate (% SEE)	Interpatient ^b variability (% SEE)
Clearance		
Parameter for CL (liters/h)	51.5 (6.4)	32% (38)
Effect of ALT on CL ^c	-0.132 (84.1)	
Effect of BSA on CL ^c	1.06 (43)	
V		
Parameter for V (liters)	131 (8.9)	39% (29)
Effect of BSA on V ^d	1.93 (29)	
Residual error		
Proportional ^e	51 (10)	

^a Pharmacokinetic database: 36 subjects; 287 observations. SEE, SE of the estimate.

^b Exponential error model; results represented as a percentage coefficient of variation.

$$^c \text{CL} = 51.5 \times \left(\frac{\text{ALT}}{22.8}\right)^{-0.13} \times \left(\frac{\text{BSA}}{1.84}\right)^{1.06}$$

$$^d \text{V} = 131 \times \left(\frac{\text{BSA}}{1.84}\right)^{1.93}$$

^e The difference between model-predicted cryptophycin plasma concentration and observed concentration was modeled as $C_{ij} = C_{sij} \times (1 + (\epsilon_{ij}))$. The value includes intrasubject variability, model misspecification, and any errors in blood sampling (phlebotomy) times.

of 22.8 units/liter and a BSA of 1.84 m² and ranged from 29.3 to 76.1 liters/h. Volume of distribution was 131 liters for a typical patient with a BSA of 1.84 m² and ranged from 68.4 to 285 liters. Interpatient variability with respect to CL and V were moderate at 32% and 39%, respectively. The terminal elimination half-life was short, ranging from 0.8 to 3.9 h. AUC and C_{max} values were shown to be linear with dose (Fig. 3), consistent with modeling results that showed that dose was not a statistically significant covariate with respect to CL.

Patient Benefit

Six patients had objective evidence of benefit on this Phase I trial. There was one partial response in a patient with non-small cell lung cancer treated at 0.1 mg/m². She had previously been treated with three regimens for her disease. The response lasted for a total of 5 cycles. Five patients had stable disease lasting 4–8 cycles. Three of these patients had renal cell cancer [one of these patients had received only interleukin 2 previously; the others had multiple (>3) prior regimens]. A patient with head and neck cancer who had also been treated with multiple prior regimens had stable disease for 6 cycles, and a patient with heavily pretreated colon cancer maintained disease stability for 4 cycles on the twice-weekly schedule.

DISCUSSION

The cryptophycins are a novel family of macrocyclic depsipeptides whose cytotoxic activity is a consequence of inhibition of tubulin polymerization (3). These compounds are of interest because of their broad antitumor activity, their potency in preclinical models, and the established clinical efficacy of compounds directed to tubulin. LY355703 in addition is not a substrate for the MDR efflux pump and is active in cell lines with resistance acquired by this mechanism (10, 11). It was

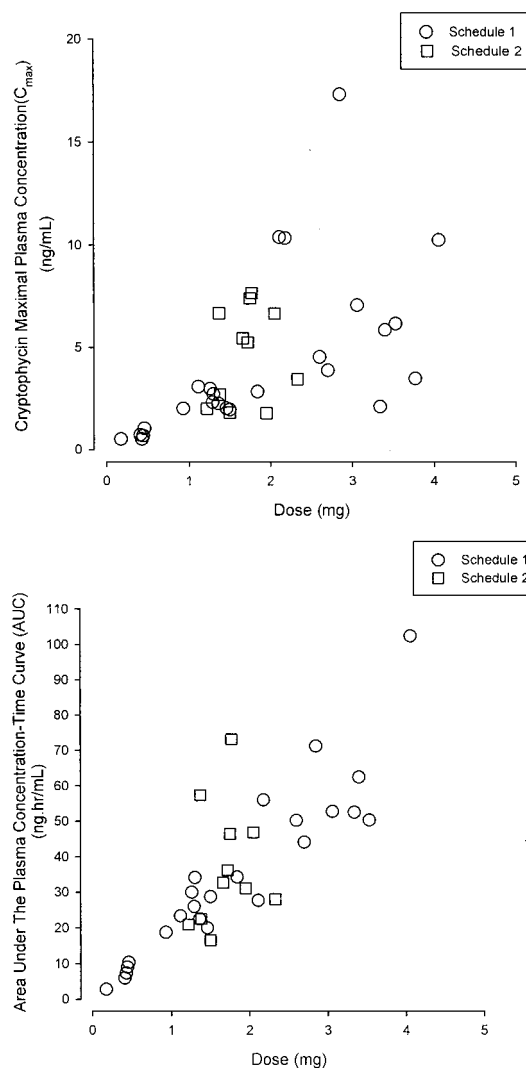


Fig. 3 Predicted LY355703 C_{max} and AUC as a function of dose.

selected for clinical development based on its potency, solubility, and preclinical toxicology profile.

Preclinical antitumor studies *in vivo* suggested that a frequent intermittent schedule may be optimal (5). Toxicological studies indicated that myelosuppression would be dose-limiting. Myelosuppression is the DLT of taxanes and vinblastine both in preclinical models and in the clinic (16, 17). Both of these drug classes are also neurotoxic, but to a lesser degree. LY355703 is dose-limited by neurotoxicity and has minimal myelosuppression at these doses and schedule. The *Vinca* alkaloid vincristine is also dose-limited by neurotoxicity (18). This differs from vinblastine only in the substitution of a formyl group for a methyl group on the dihydroindole ring (19). Although the basis for the differential toxicity between vincristine and vinblastine is not definitely established, it is plausible that the more lipophilic vincristine has greater penetration into neural tissue. This observation may support the investigation of more hydrophilic analogues of LY355703 because vinblastine clearly has greater activity in solid tumors.

Alternatively, one might ask whether the schedule of administration is a determinant of neurotoxicity. Although the symptoms of motor neuropathy and constipation were severe in the patients at high doses, they resolved quickly without long-term sequelae. This is not consistent with axonal death (as with *Vinca* alkaloids and taxanes; Ref. 20) and suggests a reversible, possibly receptor-mediated interaction with the neuron. An approach to understanding the clinical relevance of this observation may be to ask whether its pharmacological basis relates more to C_{max} or to AUC. To that end, we studied twice-weekly dosing and found constipation to be the predominant neurological toxicity with more frequent dosing, whereas the neurosensory effects were not as pronounced. The severity of the constipation did not allow us to administer LY355703 on time or at greater dose intensity than on the day 1 and day 8 schedule (on both schedules, 1.5 mg/m²/week was tolerable), and further exploration of this schedule was not pursued.

The observance of severe pain at tumor site in two patients is not surprising because this entity has been described with therapy with other tubulin-binding agents (21). The mechanism underlying the development of this symptom is unclear; one plausible hypothesis is tumor ischemia, and we plan to study changes in tumor perfusion by serial magnetic resonance imaging in our ongoing studies of LY355703.

The pharmacokinetics of LY355703 were evaluated by using nonlinear mixed effect modeling. An open one-compartment structural model was used to fit the data, even though the plasma concentration-time profiles showed possible biphasic behavior. An attempt to fit the data to a two-compartment model was performed, but some of the parameters were estimated with poor precision. This lack of precision was likely due to a lack of frequent blood samples just after termination of infusion, resulting in insufficient data to characterize the distribution phase. Additionally, because the apparent distribution phase was not pronounced, a one-compartment model was selected for the structural model. The magnitude of the residual variability (51%) likely reflects model misspecification in addition to assay variability and other sources of variability.

Finally, we observed minor evidence of antitumor activity on this study across a wide dose range. Responding and stabilizing tumors included those such as multiply pretreated non-small cell lung cancer, renal cell cancer, and head and neck cancer. These results support further evaluation of this interesting class of compounds.

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