

A phase I trial of liposomal doxorubicin, paclitaxel and valspodar (PSC-833), an inhibitor of multidrug resistance

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Purpose: The aim of this study was to determine (i) the maximum tolerated dose (MTD) of liposomal doxorubicin (L-DOX) and paclitaxel (DP), (ii) the MTD of DP plus valspodar (DPV) and (iii) pharmacokinetic (PK) interactions of valspodar with L-DOX and paclitaxel.

Methods: Twenty-three patients with metastatic cancers received DP, followed 4 weeks later by DPV. Dose levels of DP were (mg/m² for L-DOX/paclitaxel): 30/135 (*n* = 7), 30/150 (*n* = 4), 35/150 (*n* = 8) and 40/150 (*n* = 4). Dose levels of DPV were 15/70 (*n* = 10) and 15/60 (*n* = 10). Serial, paired PK studies were performed.

Results: The MTD of DP was 40/150. For DPV at 15/70, five of 10 patients experienced grade 4 neutropenia. In the next cohort, a reduced dose of 15/60 was well tolerated. Valspodar produced reversible grade 3 ataxia in seven patients, requiring dose reduction from 5 to 4 mg/kg. Paired PK studies indicated no interaction between L-DOX and valspodar, and a 49% increase in the median half-life of paclitaxel. Two partial and one minor remissions were noted.

Conclusions: The use of valspodar necessitated dose reductions of DP, with neutropenia being dose limiting. Valspodar PK interactions were observed with paclitaxel but not L-DOX.

Key words: doxorubicin, liposome, multidrug resistance, paclitaxel, valspodar

Introduction

Drug resistance is a major obstacle to effective cancer therapy. One of the best described mechanisms is multidrug resistance (MDR) caused by expression of the *MDR1* gene, which encodes for the P-glycoprotein (P-gp) multidrug transporter [1]. P-gp is an efflux pump for anthracyclines, taxanes and many other drugs [1, 2]. *MDR1* expression is a determinant of both intrinsic and acquired drug resistance in many human cancers [1, 2–4]. Cyclosporine has been shown to inhibit P-gp expressing murine leukemias and has resulted in clinical benefit in some trials in acute myeloid leukemias [5–7].

Valspodar (PSC-833), a non-immunosuppressive, non-nephrotoxic cyclosporine analog, is more potent than cyclosporine in its ability to modulate MDR [8, 9]. However, significant pharmacokinetic (PK) interactions have been observed when valspodar is given in combination with paclitaxel or doxorubicin, necessitating dose reductions of these drugs [10].

Another method to partially overcome P-gp-mediated resistance is liposomal encapsulation of drugs [11–13]. Liposomal doxorubicin (L-DOX) has been used in combination with paclitaxel, with encouraging clinical results [14–16].

We hypothesized that substitution of L-DOX for free doxorubicin would reduce the drug interactions produced by valspodar [10], and report here results of a phase I study of the combination of L-DOX, paclitaxel and valspodar, with serial studies of PK interactions.

Patients and methods

Patient selection

Patients were eligible for this study if they had an incurable malignancy; measurable disease; no chemotherapy for 3 weeks prior to study entry; no radiation therapy 4 weeks prior to study entry; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; anticipated survival >3 months; serum creatinine <1.5 mg/dl; bilirubin <1 mg%; serum aspartate aminotransferase <3× normal; white blood cell count >3500/mm³; platelet count >100 000/mm³. Prior doxorubicin treatment could not exceed a cumulative 300 mg/m². Left ventricular ejection fraction (LVEF) was required to be >45% at rest. The protocol was approved by the Stanford University Human Subjects Committee, and all patients provided informed consent.

Study design

Patients received L-DOX and paclitaxel (DP) during cycle 1; and L-DOX, paclitaxel and valspodar (DPV) during cycle 2, with a 4-week interval between cycles 1 and 2 to minimize potential overlapping myelosuppression and other toxicities.

Dose-limiting toxicity (DLT) was defined as: (i) grade 4 neutropenia or grade 3 neutropenia with fever; (ii) grade 3 thrombocytopenia; (iii) grade 3

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mucositis; and (iv) other grade 3 or 4 toxicity (except hyperbilirubinemia and nausea and vomiting). The maximum tolerated dose (MTD) was defined as that dose level which produced no more than a 30% incidence of DLT. Because of safety concerns about potential concurrent mucositis and neutropenia, any grade 4 neutropenia was considered a DLT regardless of the duration of the neutropenia.

The initial starting doses for DP (mg/m^2) alone were 30/135 and for DP with valspodar 15/70. Dose escalation by cohort and determination of the MTD were based on DLTs observed during the first cycles of DP or DPV, respectively. Patients were initially enrolled in cohorts of three. If one patient developed a DLT, the cohort was expanded to six or more patients.

Valspodar in liquid formulation (Novartis Pharmaceutical Corporation, Basle, Switzerland) was administered at 5 mg/kg orally four times daily for 12 doses. Cerebellar ataxia was graded as previously described [10]. The dose of valspodar was decreased to 4 mg/kg for grade 3 ataxia. If grade 3 ataxia persisted, valspodar was withheld until resolution of symptoms. Chemotherapy was administered on day 2 after the fifth or sixth dose of valspodar. Patients were scheduled to receive DPV every 4 weeks with assessment of toxicities and tumor response.

Chemotherapy administration

All patients received pre-medication to prevent hypersensitivity reactions (dexamethasone 20 mg, famotidine 20 mg and diphenhydramine 25 mg intravenously) and an anti-emetic (ondansetron 10 mg intravenously) 30 min prior to chemotherapy. L-DOX (DoxilTM; Alza Pharmaceuticals, Mountain View, CA, USA) was administered as a 30-min infusion. Paclitaxel (Taxol injectionTM; Bristol-Myers Squibb Oncology, Princeton, NJ, USA) was administered as a 1-h infusion. Patients received full dose L-DOX followed by paclitaxel intravenously for the first cycle. Four weeks later, patients received reduced doses of L-DOX and paclitaxel, in combination with valspodar.

Criteria for response

Partial remission was defined as a 50% reduction in the sum of products of the two largest perpendicular diameters of all measurable lesions for at least 4 weeks, and no new lesion. Minor response was defined as partial regression <50%. Tumor progression was defined as a 25% or greater increase in tumor size measured as the bidimensional product of perpendicular diameters.

Monitoring and criteria for discontinuation of therapy

All patients had a baseline radionuclide ventriculogram (MUGA) to determine the LVEF. In patients who had received prior doxorubicin, this test was repeated after every two cycles. Patients were taken off study if there was a decrease in the absolute LVEF >10% or a decline in the resting LVEF fraction to <45%.

Toxicity was assessed by ECOG criteria [17]. Tumor measurements were performed after every two cycles of treatment. Patients were removed from study if there was tumor progression, or after six cycles of the combination treatment had been administered for stable disease.

PK studies of L-DOX and paclitaxel

PK studies of L-DOX and paclitaxel were performed on all patients during their first cycle of DP and DPV. Plasma samples were analyzed for doxorubicin, doxorubicinol and paclitaxel by high performance liquid chromatography [18, 19]. Blood samples were obtained prior to the paclitaxel infusion (end of L-DOX infusion), and then 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 and 96 h after initiation of the paclitaxel infusion.

L-DOX assay. The determination of doxorubicin was linear from 0.001 to 25 $\mu\text{g}/\text{ml}$, with intra-day and inter-day coefficients of variation and percent

error $\leq 10\%$. The recovery of doxorubicin from plasma was >69%, with a liposomal dispersion efficiency of >96%.

Paclitaxel assay. The coefficient of determinations (r^2) for all standard curves was >0.95. The lower limit of quantitation was 0.01 mM and the inter-day and intra-day coefficient of variations were <8%.

PK analyses. Non-compartmental PK calculations [20] were performed using the XLPHARM M-IND program (Dr V. K. Piotrovskij, Turnhout, Belgium). Volume of distribution at steady state (V_{ss}) and clearance (CL) were derived from equations, where $V_{ss} = (\text{dose} \times \text{AUMC}/\text{AUC}^2) - (\text{dose} \times \text{T})/(2 \times \text{AUC})$, where T is the duration of the infusion. CL was determined by dividing the dose by the plasma AUC. The mean residence time (MRT) was calculated using the equation $\text{MRT} = (\text{AUMC}/\text{AUC}) - \text{T}/2$, where T is the duration of drug administration. Time above threshold concentrations for paclitaxel (i.e. >0.05 or 0.025 μM) were determined by simulating the decay of terminal first-order time point concentrations over a range of time points, using the terminal elimination rate constant K_z , fitted to the equation: $\text{Cp}_2 = \text{Cp}_1 \cdot \exp^{-(K_z \cdot \text{T})}$. The terminal elimination rate constant was determined by log-linear regression of a minimum of three concentration time points in the terminal phase of the elimination curve.

Results

Patient characteristics

Twenty-three patients with a variety of advanced cancers were entered into the trial: lung ($n = 8$), gastric ($n = 4$), sarcoma ($n = 3$), gallbladder ($n = 2$), ovarian ($n = 2$), esophageal ($n = 2$) and one each for gastrointestinal stromal and mesothelioma. There were nine women and 14 men with a median age of 58 years (range 39–82 years). Prior to study entry patients had received a mean of three chemotherapy regimens. Twenty-one of 23 patients had an ECOG performance status <0–1.

Determination of MTD

MTD of DP. Seven patients were entered on the starting dose of 30/135 mg/m^2 , which was well tolerated (Table 1). Paclitaxel was increased from 135 to 150 mg/m^2 , and this cohort also had no DLTs. In the third cohort, the dose of L-DOX was increased from 30 to 35 mg/m^2 (35/150; $n = 8$). One of the first three patients developed grade 4 neutropenia with fever. This led to the expansion of the cohort to eight patients. Three patients developed grade 3 neutropenia, but there were no additional DLTs. In cohort 4, the dose of L-DOX was increased further (40/150), and four patients were treated. One patient developed a DLT with fever and neutropenia. Further accrual to this dose level of DP without valspodar was halted because the study had reached two primary end points, the MTD of DPV, and determination of the PK interactions of valspodar with L-DOX and paclitaxel.

MTD of DPV. Two dose levels of DP combined with valspodar (DPV) were evaluated (Table 2). In the first cohort, because of our previous experience with non-liposomal doxorubicin [10], attenuated doses of L-DOX and paclitaxel were utilized. In cohort 1, patients were treated at a dose level of 15/70 mg/m^2 . Despite these reduced doses, five of 10 patients experienced

Table 1. Hematologic toxicity of L-DOX and paclitaxel and L-DOX, paclitaxel and valsopodar regimens

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
DP regimen				
Dose (mg/m ² DP)	30/135	30/150	35/150	40/150
Number in cohort	7 ^{a,b}	4 ^b	8 ^b	4 ^c
Number with neutropenia ^d				
Grade 4	0	0	1	1
Grade 3	1	1	3	1
Grade 2	2	1	1	2
Febrile neutropenia (<i>n</i>)	0	0	1	0
ANC nadir (cells/mm ³) (mean)	1.99	1.4	1.1	0.96
Platelet nadir (cells/mm ³) (mean)	359	298	255	275
DPV regimen				
Dose (mg/m ² DP)	15/70	15/60	–	–
Number in cohort ^e	10	10	–	–
Number with neutropenia ^d				
Grade 4	5	1	–	–
Grade 3	2	2	–	–
Grade 2	1	5	–	–
ANC nadir (cells/mm ³) (mean)	0.95	1.18	–	–
Platelet nadir (cells/mm ³) (mean)	224	277	–	–

^aOne grade 3 mucositis.

^bOne patient off study due to disease progression prior to 28-day observation period.

^cThis dose level is the MTD with a <30% incidence of a dose-limiting toxicity.

^dNeutropenia grades were: grade 4, ANC <500/mm³; grade 3, ANC 501–1000/mm³; grade 2, ANC 1001–1500/mm³.

^eThree patients did not receive DPV because of disease progression after DP alone.

L-DOX, liposomal doxorubicin; DP, L-DOX and paclitaxel; DPV, L-DOX, paclitaxel and valsopodar; ANC, absolute neutrophil count.

DLTs with grade 4 neutropenia. In the next cohort, the dose of paclitaxel was reduced further to 60 mg/m². Ten patients were treated at this dose. This dose level was the MTD, with only one DLT (grade 4 neutropenia).

Toxicities

The most common toxicity for both DP and DPV was hematologic, as shown in Tables 1 and 2. Grade 4 neutropenia was observed in two of 23 patients treated with DP alone and six of 20 patients treated with DPV. Fever associated with this neutropenia was observed in one of 23 patients on DP alone and none of 20 treated with DPV.

Non-hematological toxicity (grades 2 or 3) for DP alone or DPV are shown in Table 2. No grade 4 non-hematological toxicity was observed. Transient reversible hyperbilirubinemia,

Table 2. Non-hematological toxicity of the L-DOX and paclitaxel and L-DOX, paclitaxel and valsopodar regimens

Cohort	DP				DPV	
	1	2	3	4	1	2
Dose (mg/m ²)	30/135	30/150	35/150	40/150	15/70	15/60
Number in cohort	7	4	8	4	10	10
No. with grade 2 or 3 toxicity ^a						
Nausea/vomiting	0	0	0	0	1	1
Stomatitis	2	0	1	0	1	0
Esophagitis	0	1	0	0	0	1
Anorexia	2	0	0	0	1	0
Constipation	2	2	2	3	5	4
Abdominal pain	0	0	1	0	0	1
Bilirubin	0	0	0	0	2	2
Flushing	1	0	0	0	0	0
Ataxia ^b	0	0	0	0	5	2
Othostasis	0	0	0	0	4	2
Hypotension	1	0	0	0	0	0
Chest discomfort	2	0	0	1	1	0
Confusion	0	1	0	0	0	1
Neuropathy	0	0	1	0	1	1
Headache	0	0	0	0	0	1
Rash	0	1	1	0	4	0
Fatigue	2	1	2	0	2	1
Arthralgias	1	2	1	1	2	2

^aRepresents number of patients with toxicity during first cycle of treatment.

^bAtaxia rapidly reversible with a dose reduction of valsopodar to 4 mg/kg. L-DOX, liposomal doxorubicin; DP, L-DOX and paclitaxel; DPV, L-DOX, paclitaxel and valsopodar.

an anticipated side-effect of valsopodar, as previously reported [21], was seen in four of 20 patients. One patient developed a grade 3 stomatitis. Other reversible side effects reported were constipation (*n* = 10 for DP, *n* = 10 for DPV), fatigue (*n* = 5 for DP, *n* = 3 for DPV), neurological, i.e. confusion/neuropathy (*n* = 0 for DP, *n* = 2 for DPV), and skin rash (*n* = 2 for DP, *n* = 4 for DPV). No hand–foot syndrome was observed. Seven patients developed grade 3 ataxia, which rapidly reversed following a dose reduction of valsopodar to 4 mg/kg.

Antitumor responses

Twenty of the 23 patients were assessable for response. Three patients progressed after the first cycle of DP and did not receive DPV. Of the 20 assessable patients with DPV, partial remissions were observed in two ovarian carcinomas, lasting 5 and 7 months. One patient with non-small-cell lung cancer had a minor response lasting 9 months. Stable disease lasting at least for 6 months was noted in four patients (two non-small-cell lung, one each gastrointestinal stromal tumor and mesothelioma) and for 4 months in one patient with gastric cancer.

Pharmacokinetics

Paired PK analyses with and without valspodar were performed during 18 courses of L-DOX and nine courses of paclitaxel. The reasons for inability to perform paclitaxel PK were incomplete sampling ($n = 3$) and electronic data loss ($n = 9$). Valspodar resulted in an alteration of paclitaxel PK behavior but no apparent interaction with L-DOX (Table 3). Combining valspodar with paclitaxel resulted in larger median V_{ss} (72 versus 108 l/m²) and median $t_{1/2}$ values (10.2 versus 14.9 h) of paclitaxel. The 50% dose reduction in paclitaxel dose during valspodar administration resulted in lower C_{max} values when compared with full dose paclitaxel without valspodar. However, median duration above 0.05 μ M concentrations, thought to be a determinant of pharmacodynamic response for paclitaxel, was 17% higher (18 versus 21 h) during valspodar treatment.

Paired PK analysis during treatment with L-DOX with and without valspodar showed no apparent alteration in L-DOX PK. Table 2. With an average 50% dose reduction of L-DOX during valspodar administration, proportional decreases in C_{max} and AUC values were observed. Time-dependent parameters of L-DOX, such as $t_{1/2}$, MRT and CL were not affected.

Discussion

Many attempts to circumvent MDR in cancer chemotherapy have utilized P-gp blocking agents that are co-administered with cytotoxic drugs [1]. This approach is based on the premise that inhibiting P-gp function will result in increased accumulation of anticancer drugs in the tumor cells and restore full antitumor activity. Attempts to modulate MDR with inhibitors of P-gp, particularly with cyclosporine and valspodar, have been complicated by PK interactions [1, 9, 10, 22–24]. These interactions are thought to arise from inhibition by cyclosporins of multiple metabolic and excretory pathways in normal tissues, particularly the liver, involving P-gp and other drug transporters, as well as the mixed function oxidase CYP 3A4.

Liposomal encapsulation of drugs also appears to partially overcome P-gp-mediated resistance [11, 12]. Pegylated lipo-

somes confer a reduced clearance with prolonged circulation half-life. Their size and structure prevent drug extravasation and result in selective drug accumulation in tissues with increased vascular permeability such as tumors [25]. L-DOX has shown reduced toxicity compared with free doxorubicin, while retaining or even improving antitumor efficacy [21, 26].

We and others have previously reported that valspodar decreases the clearance of several anticancer drugs and necessitates dose reductions to achieve similar drug exposure and toxicity [10, 23, 24, 27]. Based on our previous experience using similar agents, we anticipated substantial PK interactions between valspodar and the MDR substrate agents, and therefore designed the trial to use low initial doses of L-DOX and paclitaxel when given with valspodar.

In our study, the MTD of DP without valspodar was 40/150 mg/m². The addition of valspodar to DP (DPV) resulted in anticipated hematological toxicity, and the MTD of the combination was L-DOX 15 mg/m² and paclitaxel 60 mg/m². The degree of dose reduction of cytotoxins required during co-administration of valspodar in our study is not surprising. Previous studies with valspodar also produced marked alterations in PK, necessitating dose reduction of the cytotoxins [10, 23, 24, 27]. The main toxicity of both DP and DPV in our trial was neutropenia. The mechanism for valspodar-induced cerebellar toxicity is not well understood, but this side-effect was rapidly reversible.

This study is the first to evaluate the effect of valspodar on L-DOX PK in humans. Consistent with observations in animal models [13], our PK analyses showed no drug interaction between valspodar and L-DOX. The lack of effect of valspodar on L-DOX is in contrast to our previous experience with free doxorubicin, where valspodar produced a marked effect on the disposition of the doxorubicin and the major metabolite doxorubicinol [10]. Consistent with our previous findings, the addition of valspodar to paclitaxel resulted in a prolongation of median $t_{1/2}$ and median time above 0.05 μ M concentration [10]. The observed increase in myelosuppression when valspodar was combined with DP may be attributable in large part to these PK effects on paclitaxel. The dose reduction of L-DOX in the DPV combination is not explained by any PK interaction of this agent with valspodar, but may reflect either a pharmacodynamic effect or increased myelosuppression because of the interaction of valspodar with paclitaxel.

Laboratory studies indicate that liposomes may circumvent valspodar-induced doxorubicin PK changes by reducing the rate of drug excretion in liver and kidney tissue to a level that is within the renal and biliary excretion capacity in the presence of P-gp blockade [28, 29]. To further define the PK interactions of L-DOX and valspodar, we are performing a study with L-DOX without paclitaxel, and with and without valspodar.

Because only four patients were treated at the highest doses of L-DOX (40 mg/m²) and paclitaxel (150 mg/m²) without valspodar in our study, it is possible that slightly higher doses of these drugs would be tolerable without the MDR modulator. A recent phase I and II study of L-DOX with paclitaxel recommended doses of 40 mg/m² L-DOX and 175 mg/m² of paclitaxel by 3-h infusion [30]. In that study, when L-DOX was given at 45 mg/m²

Table 3. Effect of valspodar on L-DOX pharmacokinetics

PK parameter	Alone [mean (SD)]	With valspodar [mean (SD)]	% change	<i>P</i> value ^a
L-DOX (as total doxorubicin) ($n = 18$)				
Dose (mg/m ²)	33.1 (3.9)	15.0 (0)	-55	0.0002
C_{max} (μ g/ml)	25.8 (8.8)	13.6 (8.5)	-47	0.0002
AUC (h* μ g/ml)	2675 (1082)	1159 (480)	-57	0.0002
CL (ml/h/m ²)	14.5 (6.0)	14.9 (5.7)	+3	0.3958
$t_{1/2}$ (h)	92 (42)	79 (25)	-14	0.0979
MRT (h)	132 (59)	113 (36)	-14	0.3604
V_{ss} (l/m ²)	1.7 (0.5)	1.5 (0.4)	-12	0.0451

^aTwo-sided *P* value, Wilcoxon sign rank test.

L-DOX, liposomal doxorubicin; SD, standard deviation; CL, clearance; MRT, mean residence time; V_{ss} , volume of distribution at steady state.

with 175 mg/m² of paclitaxel, three of five patients experienced febrile neutropenia.

In 23 patients assessable for response, tumor regression was observed in three of 20 patients, while another five patients had stabilization of disease for at least 4 months. This study was not designed to assess the role of MDR modulation in these responding patients. However, it is notable that these patients had received a mean number of three prior chemotherapy treatments.

In conclusion, valspodar can be administered safely in combination with liposomal doxorubicin and paclitaxel, but requires dose reductions of the cytotoxins. Valspodar significantly increases the paclitaxel exposure secondary to decreased clearance, accounting for the need to reduce doses ~50% to achieve equivalent myelosuppression. To the extent that P-gp expression may play a role in clinical drug resistance, further studies of MDR modulation strategies are warranted, and will continue to require careful PK and pharmacodynamic assessments of drug interactions.

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