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ORIGINAL ARTICLE

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Phase I study of the multidrug resistance inhibitor zosuquidar administered in combination with vinorelbine in patients with advanced solid tumours

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Abstract *Background*: Zosuquidar (LY335979) is an oral P-glycoprotein modulator. This phase I study was designed to determine the maximum tolerated dose (MTD) of zosuquidar in combination with vinorelbine. The effects of zosuquidar on vinorelbine pharmacokinetics were also examined. *Design*: Patients with advanced solid tumours were treated with escalating doses of zosuquidar administered every 8–12 h on days 7–9 and 14–16 during cycle 1 then days 0–2, 7–9, and 14–16 from cycle 2 onwards, with vinorelbine 22.5–30 mg/m^2 IV on days 1, 8 and 15 every 28 days. *Results*: Of 21 patients registered, 19 were treated at four dose levels (zosuquidar 100–300 mg/m^2). Two patients had prolonged and febrile neutropenia at the second dose level resulting in a reduction of the dose of vinorelbine in subsequent dose levels. There was another patient with dose-limiting febrile neutropenia at dose level four which resulted in the expansion of the dose level three. Eight patients had stable disease and no objective responses were seen. Vinorelbine pharmacokinetic studies showed reduced clearance when given with zosuquidar. *Conclusions*: The MTD was zosuquidar 300 mg/m^2 orally every 12 h for 3 days weekly for 3 weeks with vinorelbine 22.5 mg/m^2 IV weekly for 3 weeks every 28 days. Zosuquidar may inhibit vinorelbine clearance to a modest degree.

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Introduction

Multidrug resistance (MDR) is one of the most widely studied mechanisms of anticancer drug resistance. The *mdr*-1 gene encodes for the efflux pump P-glycoprotein (P-gp) [1]. P-gp transports a wide variety of hydrophobic drugs out of cells, including cytotoxic drugs derived from natural products (e.g. taxanes, vinca alkaloids, anthracyclines, epipodophyllotoxins, and topotecan). P-gp is a member of the ATP-binding cassette (ABC) family of cell membrane transporters which includes other proteins thought to be involved in drug resistance [e.g. multidrug resistance protein (MRP), canalicular multiorganic anion transporter (CMOAT), and breast cancer resistance protein (BCRP)] [2]. While P-gp is only one of a number of described drug resistance mechanisms [3, 4], data suggest a role in prognosis [3–6] and clinical drug resistance [7–9].

Zosuquidar is a potent (K_i 59 n *M*) and effective "third-generation" modulator of P-gp (Fig. 1) [10]. This class of P-gp modulators is not thought to affect cytochrome P450 3A4 (CYP3A4) as earlier agents do. It does not appear to be a substrate for P-gp efflux and has a relatively long duration of effect. Preclinical animal studies have demonstrated excellent in vivo activity. Several phase I studies of zosuquidar as a modulator of P-gp have been undertaken. In one, a continuous intravenous infusion (CIVI) of zosuquidar with doxorubicin was used [11]. In this trial, 40 patients were treated in nine cohorts to a maximal zosuquidar dose of 640 mg/m^2 and a doxorubicin dose of 75 mg/m^2. The zosuquidar was well tolerated with no dose-limiting toxicity (DLT). Pharmacokinetic analysis did show that zosuquidar at doses greater than 500 mg caused a small reduction in clearance and a small increase in the area

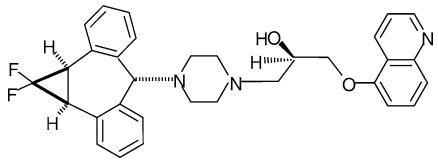

Fig. 1 Chemical structure of zosuquidar (LY335979) (MW 637.0 Da)

under the curve of doxorubicin. A phase I study of oral zosuquidar with doxorubicin in 38 patients at nine dose levels defined the maximally tolerated dose (MTD) of zosuquidar as 300 mg/m^2 every 12 h for 4 days [12]. DLT was neurotoxicity characterized by cerebellar dysfunction, hallucinations and palinopsia. No worsening of doxorubicin toxicity or change in doxorubicin pharmacokinetics was demonstrated.

There is preclinical and clinical evidence that 300 mg/m^2 per day of zosuquidar may achieve peak plasma concentrations of 100–200 n *M*. In vitro studies have shown that complete reversal of drug resistance requires concentrations around 100 n *M* [10]. The protein binding properties of zosuquidar have not been described but should be considered in determining effective concentrations in vivo. The plasma half-life in humans had been initially determined to be less than 6 h, supporting the 8-hourly dosing used in this study [13]; however, subsequent studies have shown a plasma half-life of closer to 20 h [11, 12].

Vinorelbine, a drug most commonly used in the management of breast and lung cancer, was paired with zosuquidar in this study since it is known that resistance to vinca alkaloids is associated with MDR-1 [14]. The starting dose of vinorelbine, 30 mg/m^2 IV on days 1, 8 and 15, is an established single-agent treatment dose [14]. Preclinical studies had not shown any major pharmacokinetic interaction between zosuquidar and coadministered cytotoxic compounds, and thus the dose of vinorelbine was not reduced at the start of this trial [10]. The primary objective was to determine that MTD of zosuquidar given orally, according to an intermittent dosing schedule, in combination with vinorelbine given intravenously as a weekly dose for 3 weeks out of every 4 weeks. Secondary objectives were to determine the toxicity profile of this particular combination, to compare the pharmacokinetics of vinorelbine with and without zosuquidar, and to obtain preliminary data regarding antitumour activity in patients with measurable disease.

Patients and methods

Patient eligibility

Patients were treated at the Princess Margaret Hospital in Toronto, Canada. Eligible criteria for this trial were: age ≥18 years; histologically or cytologically confirmed diagnosis of inoperable metastatic or locally advanced solid cancer and not eligible for curative surgery or radiotherapy; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; use of adequate birth control; previous treatment with no more than two chemotherapy regimens (including adjuvant therapy); no previous exposure to vinca alkaloids or MDR/MRP modulator treatment; and absolute granulocytes ≥1.5×10^9 l^{-1}, platelets ≥100×10^9 l^{-1}, serum creatinine less than 1.5 times the upper limit of normal (ULN) or creatinine clearance > 50 ml/min, bilirubin not more than 1.5 times the ULN and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) not more than 2.5 times the ULN. Patients were ineligible if they had a haematologic malignancy not in remission, were pregnant or lactating, had a systemic infection requiring parenteral antibiotics, had a serious concomitant illness, had a prior history of seizure disorders, had unstable CNS metastases (previously treated patients with stable brain metastases for 3 months were eligible), were on concurrent treatment with other investigational or conventional anticancer therapies, or had grade 2 or worse peripheral neuropathy. All chemotherapy, radiotherapy or surgery had to be completed at least 3 weeks prior to registration (6 weeks if treated with nitrosourea or mitomycin C). The protocol was approved by the Princess Margaret Hospital and the University of Toronto Human Experimentation Committees and all patients gave written consent.

Clinical study design

This was an open-label phase I trial of zosuquidar plus vinorelbine to determine the recommended doses for the combination. The initial plan was to administer vinorelbine 30 mg/m^{2}intravenously over 6–10 min on days 1, 8, and 15 of each 28-day cycle with reduction to 22.5 mg/m^2 for toxicity. Zosuquidar was given in oral solution every 8 h for 2 days and the morning of the 3rd day (seven doses). Patients were requested not to eat for 2 h before and 1 h after each dose. Subjects kept a diary to track compliance with the oral medication. During cycle 1, zosuquidar was given on days 7–9 and 14–16. For cycle 2 and all subsequent cycles, zosuquidar was given on days 0–2, 7–9, and 14–16, where day 0 was day 28 of the previous cycle. A dosing schema is presented in Fig. 2. Each cohort consisted of a minimum of three evaluable patients. The starting dose of zosuquidar was 100 mg/m^2 every 8 h and in the absence of DLT the dose of zosuquidar was to be escalated by 100 mg/m^2 every 8 h in each subsequent cohort up to a planned maximum dose of zosuquidar of 300 mg/m^2 (three planned cohorts).

DLT was defined as an absolute granulocyte count of < 0.5×10^9 l^{-1} for 7 days or more, febrile neutropenia, platelets < 10×10^9 l^{-1}, thrombocytopenic bleeding requiring transfusion, or any grade 3 or worse nonhaematologic toxicity excluding nausea and vomiting as defined by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0. DLT had to

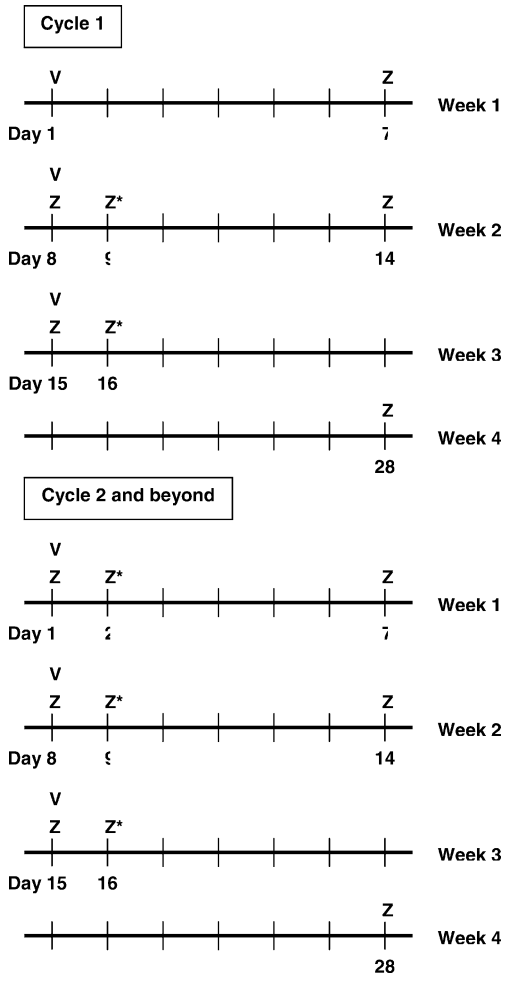

Fig. 2 Dosing schema *V*: vinorelbine 22.5–30 mg/m^{2}IV; *Z*: zosuquidar 100–300 mg/m^{2}PO q8–12 h; *Z**: single dose of zosuquidar in the morning

occur in the first cycle of treatment. If DLT occurred in one of three patients at a given dose level, an additional three patients were treated at the same dose level. If dose escalation proceeded to dose level 3 and no DLT occurred, then nine additional patients would be enrolled at that dose. If DLT occurred in two of six patients, the next lower dose would be the recommended dose for future phase II studies and an additional nine patients would be enrolled. Patients could have their treatment discontinued upon their request, or due to intercurrent illness that would affect assessment or treatment, unacceptable toxicity, tumour progression, or disease recurrence. Patients would also have their treatment discontinued if they had a complete response (CR) for at least two cycles after their CR was confirmed or stable disease for a maximum of six cycles.

Pretreatment assessment and follow-up studies

Patients and treatment toxicity were assessed just prior to each 4-week cycle. Routine haematology and biochemistry were performed weekly. Tumour evaluation was done at baseline and after every second cycle thereafter. A CR was defined as disappearance of all evidence of measurable disease as recorded on two assessments at least 4 weeks apart. A partial response was defined as shrinkage by ≥50% of the overall sum (i.e. sum of largest diameter × perpendicular diameter of bidimensional lesions + sum of unidimensional measurements) of measurable lesions on two assessments at least 4 weeks apart, with no progression in any site. Progression was defined as ≥25% increase in the overall sum of any measurable lesions or the appearance of new lesions. Patients not satisfying any of the above were considered to have stable disease, which was determined from the time of initiation of the study agent.

Pharmacokinetic samples

The pharmacokinetics of zosuquidar and/or vinorelbine were studied during the first 2 weeks of cycle 1 in all patients entered at each dose level. Pharmacokinetic blood samples for vinorelbine alone were collected starting on day 1 and day 8 of cycle 1 at time 0 (predose), just prior to the end of the infusion, and then at 0.5, 1, 2, 4, 8, 24, 48, and 72 h from beginning of the infusion. The zosuquidar pharmacokinetic blood samples were taken at time 0 (prior to the dose of vinorelbine on day 8), and then 1, 2, 4, 6, and 8 h after the 8 a.m. dose of zosuquidar on day 8 of cycle 1. Blood (5 ml for vinorelbine-alone samples and 7 ml for both compounds) was collected into heparinized tubes, centrifuged at 2000–3000 rpm for 15 min, and the plasma was frozen at −70°C.

Vinorelbine and zosuquidar pharmacokinetic analysis

Vinorelbine concentrations were measured at PPD Development (Richmond, Va.) using a validated HPLC method over the concentration range 2.00–500 ng/ml [15]. Zosuquidar concentrations were measured at Oneida Research Services (Whitesboro, N.Y.) using a validated HPLC/fluorescence detection method over the concentration range of 20.0–2000.0 ng/ml [12]. Pharmacokinetic analyses consisted of noncompartmental assessments of zosuquidar and vinorelbine plasma concentration data using WinNonlin Professional version 2.1. The actual recorded sample times after administration of the doses were used for all parameter estimations. For vinorelbine, the following parameters were determined: area under the plasma concentration versus time curve from zero to infinity (AUC), AUC from the last time point where plasma concentration was above the limit of quantification [AUC(t_n–∞)], AUC from time 0 to the last time point where plasma concentration was above the limit of quantification [AUC(0–t_n)], observed plasma concentration at the end of the infusion (C_{endinf}), half-life

associated with the terminal rate constant ($t_{1/2}$), terminal rate constant (λ_z), total body clearance of drug from plasma calculated after IV administration (CL), and volume of distribution in steady state (V_{ss}). The following parameters were assessed for the repeated oral dosing of zosuquidar: AUC from time 0 on day 8 to the last time point where plasma concentration was above the limit of quantification [$AUC(0–t_n)_{day\ 8}$], maximum plasma drug concentration on day 8 of dosing interval ($C_{max,\ day\ 8}$), and time to reach maximum plasma drug concentration on day 8 of dosing interval ($t_{max,\ day\ 8}$). $C_{max,\ day\ 8}$ and $t_{max,\ day\ 8}$ were determined directly from observed concentration-time data. $AUC(0–t_n)_{day\ 8}$ was calculated by a combination of linear and logarithmic trapezoidal methods as described previously for vinorelbine pharmacokinetic analysis.

Statistics on pharmacokinetic parameters were to be calculated by cohort when the number of assessable subjects was six or more. For dose-independent pharmacokinetic parameters, statistics were calculated on all assessable subjects pooled across cohorts.

Results

Patients

Of 21 patients registered on study between March 1999 and November 2000, 19 were treated and all were evaluable for toxicity (Table 1). Two patients were cancelled and replaced (one developed an infection resulting in death prior to treatment, and the other experienced seizures before treatment began). Four patients were inevaluable for response—one patient with prostate cancer with no radiologically measurable disease, and the other three had no repeat imaging to reassess their disease.

Table 1 Patient characteristics ($n = 19$)

Characteristics		Number of patients
Age (years)		
Median	56	
Range	40–73	
Gender		
Female		6
Male		13
ECOG performance status		
0		4
1		14
2		1
Primary site		
Prostate		4
Colon		2
Head and neck		2
Other[a]		11
Prior therapy		
Chemotherapy for metastatic disease		19
One line		10
Two lines		9
Radiotherapy		9
Adjuvant chemotherapy		4
Hormone therapy		3

[a] Single cases of: adrenal, bladder, breast, endometrial, gall bladder, gastric, non-small cell lung cancer, ovary, renal, soft tissue sarcoma, and unknown primary

Dose escalation and toxicity

The 19 patients were treated in four dose levels. Dose level 1 was zosuquidar oral solution 100 mg/m^2 every 8 h orally and vinorelbine 30 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle. Three patients were treated without DLT. At this point, the manufacturer changed the formulation of zosuquidar to capsules in order to improve the taste. The trial design was not changed because limited pharmacokinetic data showed that the bioavailability of the capsules were within the same range as the oral solution [13]. The second dose level was zosuquidar 200 mg/m^2 orally every 8 h with vinorelbine 30 mg/m^2. Two patients had DLTs reported out of the three patients treated. Both patients had prolonged neutropenia with one having associated fever. In both cases, the vinorelbine was thought to be the cause of the DLT resulting in the third dose level having a reduced dose of vinorelbine at 22.5 mg/m^2. In addition to that, the dosing interval of zosuquidar was increased to every 12 h, which was in keeping with other concurrent chemotherapy studies. To better evaluate this dose level, five patients were treated; none experienced DLT. The study then proceeded to a fourth dose level that combined zosuquidar 300 mg/m^2 orally every 12 h with vinorelbine 22.5 mg/m^2. One patient had dose-limiting febrile neutropenia. A second patient required hospital admission for grade 3 stomatitis and neutropenia; however, they were not considered DLT since they occurred during cycle 2. This led to a decision to abandon this dose level and treat an additional five patients at dose level 3. Again, no DLTs were reported. Fatigue was seen in all dose levels ranging from grade 1 to 3. Other common toxicities included nausea, vomiting, anorexia, constipation, and muscle or joint pains (Tables 2 and 3). The most common severe toxicity was neutropenia. This is reflected by the number of missed day-15 doses—9 doses omitted out of 19 scheduled day-15 doses during cycle 1 (47.4%) and 8 doses omitted out of 23 scheduled day-15 doses during subsequent cycles (34.8%).

Antitumour responses

Of the 15 patients evaluable for response, none had either a CR or a partial response. There were eight patients with a best response of stable disease. The median duration was 4.5 months, with a range of 2.1–10.2 months. The remaining seven patients had progressive disease.

Table 2 Most commonly reported drug-related nonhaematologic toxicity

Toxicity	Grade			
	1	2	3	4
Dose level 1: zosuquidar 100 mg/m^2 every 8 h; vinorelbine 30 mg/m^2 ($n=3$)				
Anorexia	2	–	–	–
Constipation	–	2	–	–
Fatigue	–	2	–	–
Muscle weakness	1	–	1	–
Myalgia	1	1	1	–
Nausea	2	–	–	–
Dose level 2: zosuquidar 200 mg/m^2 every 8 h; vinorelbine 30 mg/m^2 ($n=3$)				
Abdominal pain	1	–	1	–
Constipation	2	–	1	–
Dizziness	1	1	–	–
Fatigue	–	2	–	–
Febrile neutropenia	–	–	2	–
Myalgia	–	1	1	–
Nausea	1	1	–	–
Dose level 3: zosuquidar 200 mg/m^2 every 12 h; vinorelbine 22.5 mg/m^2 ($n=10$)				
Anorexia	4	1	–	–
Arthralgia	3	1	1	–
Constipation	1	1	2	–
Fatigue	–	5	2	–
Nausea	4	1	–	–
Vomiting	4	–	–	–
Dose level 4: zosuquidar 300 mg/m^2 every 12 h; vinorelbine 22.5 mg/m^2 ($n=3$)				
Anorexia	–	2	–	–
Constipation	–	2	–	–
Stomatitis	1	–	1	–
Vomiting	2	–	–	–

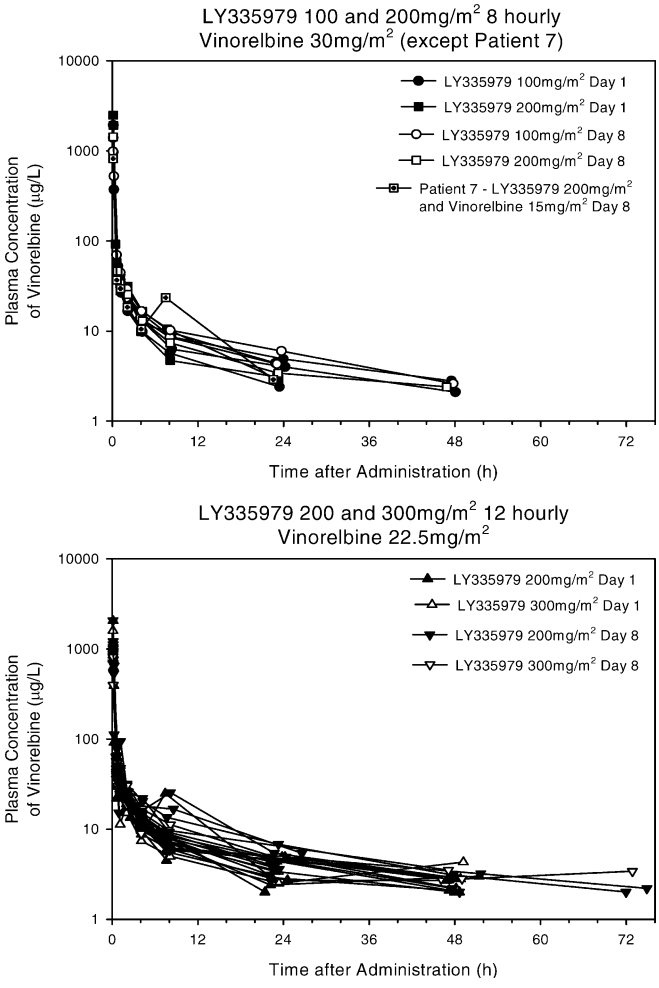

Fig. 3 Plasma concentration of vinorelbine versus time after administration (*LY335979* zosuquidar)

Pharmacokinetics

After a rapid infusion, vinorelbine showed triexponential disposition characterized by three successive half-lives of approximately 3.5 min, 1.5 h, and 10.5–73 h (Fig. 3). The clearance of vinorelbine decreased by 20–24% in the presence of zosuquidar (Table 4). Plasma clearance was independent of vinorelbine dose suggesting that the pharmacokinetics of over this dose range are linear (Fig. 4). The volume of distribution of vinorelbine at steady state increased by 32–37% in the presence of zosuquidar.

The zosuquidar plasma concentration profiles were generally highly variable with both the 8- and 12-hourly regimens. For example, for both the 8- and 12-hourly 200 mg/m^2 dose regimens, the C_{max} ranged from 115 to 429 µg/l and 118 to 310 µg/l, respectively. The study was designed to perform statistical analysis on pharmacokinetic parameters only when the number of assessable patients was six or more per cohort. Unfortunately, none of the cohorts met this criterion and therefore no firm conclusions could be made about the pharmacokinetics of zosuquidar (Table 5). However, it should be noted that the zosuquidar plasma concentrations reported here are consistent with those observed previously [11, 12]. The terminal half-life ($t_{1/2}$) was 13.3–20.1 h which is much longer than the 6 h reported previously, but in keeping with findings from other

Table 3 Haematologic toxicity

Dose level	No. of patients	ANC nadir (/µl), median (range)	Grade 3 ANC	Grade 4 ANC	No. of patients with DLT
1 (zosuquidar 100 mg/m^2 every 8 h; vinorelbine 30 mg/m^2)	3	300 (100–500)	1	2	0
2 (zosuquidar 200 mg/m^2 every 8 h; vinorelbine 30 mg/m^2)	3	200 (100–1100)	0	2	2
3 (zosuquidar 200 mg/m^2 every 12 h; vinorelbine 22.5 mg/m^2)	10	850 (200–5000)	4	2	0
4 (zosuquidar 300 mg/m^2 every 12 h; vinorelbine 22.5 mg/m^2)	3	600 (100–600)	2	1	1

Table 4 Vinorelbine pharmacokinetic parameters with and without zosuquidar. The data presented are geometric means (CV%)

Parameter	Vinorelbine 22.5 mg/m^2 without zosuquidar (day 1) ($n=10$)[a]	Vinorelbine 22,5 mg/m^2 with zosuquidar 200–300 mg/m^2 (day 8) ($n=11$)	Percent change
AUC (μg h/l)	451 (46.4)	585 (36.5)	+30
CL (l/h)	89.0 (43.5)	67.4 (33.9)	−24
V_{ss}(l)	873 (72.2)	1155 (68.7)	+32
$t_{1/2}$(h)	13.3 (117)	20.1 (68.1)	+51

[a] Inadequate number of samples for analysis of vinorelbine 30 mg/m^2

phase I studies in which the mean $t_{1/2}$ for oral zosuquidar was found to be 17 h [12] and for CIVI zosuquidar 24.4 h [11].

Discussion

Intrinsic or acquired resistance to cytotoxic drugs often hinders the successful treatment of many different types of cancer. One of the key mechanisms of MDR involves P-gp and zosuquidar is one of the most potent modulators of P-gp. In this dose-finding phase I clinical trial, zosuquidar was combined with a known substrate of P-gp, the vinca alkaloid vinorelbine. In contrast to other clinical trials combining cytotoxic agents with zosuquidar, we noted a decrease in vinorelbine clearance. Vinorelbine pharmacokinetics have been well documented previously [16]. The cumulative biliary excretion of vinorelbine (0–48 h) is estimated to be 25.8% of the dose [16], and the major cytochrome P450 enzyme involved in vinorelbine metabolism is CYP3A4 [17]. This could account for some part of the decrease in vinorelbine CL in the presence of zosuquidar if parent drug is directly eliminated. Inhibition of CYP3A4 could potentially explain the reduction in vinorelbine plasma concentrations (apparent in vitro K_I of zosuquidar for CYP3A4 was 3.8 μ*M*), which contrasts with the K_I for inhibition of the equilibrium binding of [^{3} H]-vinblastine to P-gp, which is 0.059 μ*M*. However, the zosuquidar plasma concentrations reached in this study were much lower than those required for CYP3A4 inhibition in vitro. This degree of reduction in the clearance of vinorelbine may explain the toxicity observed and the need to lower the dose of vinorelbine. However, the limited results generated here are inadequate to say whether this reduction is clinically relevant. The clearance of doxorubicin is affected to a similar degree by the coadministration of CIVI zosuquidar [11].

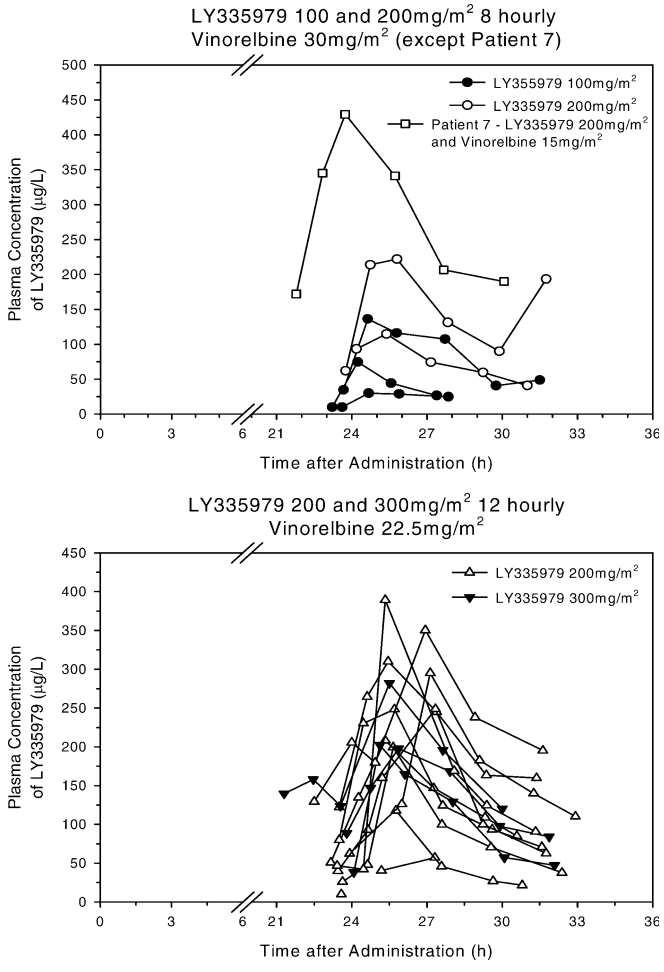

Fig. 4 Plasma concentration of zosuquidar (*LY335979*) versus time after administration

Table 5 Zosuquidar pharmacokinetic data (day 8)

Zosuquidar dose	Patient	AUC(0–t_n) (μg h/l)	C_{max} (μ*M*)	t_{max} (h)
100 mg/m^{2}every 8 h	1	107	0.05	0.950
	2	178	0.12	0.900
	3	656	0.21	0.900
200 mg/m^{2}every 8 h	4	1184[a]	0.35	1.97
	5	584	0.18	2.22
	7	2366[a]	0.67	1.90
200 mg/m^{2}every 12 h	8	755	0.31	1.97
	9	NC	NC	NC
	10	1696	0.49	1.87
	11	1004	0.33	2.13
	12	378	0.18	2.17
	16	1346	0.46	2.13
	17	1154	0.39	2.12
	19	2036	0.55	3.93
	20	1094	0.39	3.87
	21	1355	0.61	1.87
300 mg/m^{2}every 12 h	13	867	0.32	0.983
	14	1587	0.44	4.17
	15	1111	0.31	2.03

[a]AUC(0–t_n) may be overestimated due to the administration of the next dose before the last pharmacokinetic sample time

The steady-state volume of distribution of vinorelbine appeared to increase in the presence of zosuquidar. However, the V_{ss} data were highly variable, with high coefficient of variation (approximate geometric CV of 70% in the presence or absence of zosuquidar). The zosuquidar plasma concentration profiles were generally highly variable with C_{max} ranging from 115 to 429 μg/l and 118 to 310 μg/l following the 8- and 12-hourly 200 mg/m^2 regimen, respectively. In the previously reported trial with oral zosuquidar, the C_{max} for the 160 mg/m^2 dose given 12-hourly was 132.6 μg/l (range 126.6–139.7 μg/l) [12], while for CIVI zosuquidar given at 320 mg/m^2 per day, the C_{max} was 234 μg/l (range 196–283 μg/l) [11]. The concentrations seen in this study represent molar concentrations between 0.18–0.67 μ*M*, which are within the range 0.1–0.5 μ*M* of zosuquidar that is required to completely inhibit P-gp in vitro [10].

The results of this clinical trial indicate that oral zosuquidar can be given using a 3-day dosing schedule and can be delivered safely in combination with vinorelbine. The observed DLTs were neutropenia with or without fever. These were probably caused by vinorelbine. However, the delivery of zosuquidar was changed from every 8 h to every 12 h concomitantly with a decrease in the dose of vinorelbine after DLT was observed. The change in zosuquidar dosing frequency was acceptable based upon extrapolation of preclinical data [13]. The combination of zosuquidar 200 mg/m^2 orally every 12 h on days 0–2, 7–9 and 14–16 with vinorelbine 22.5 mg/m^2 IV on days 1, 8, and 15 every 28 days was well tolerated with no DLT observed, and could be developed further. Consideration could be made for vinorelbine to be given at 30 mg/m^2 once every 21 days or only on days 1 and 8 as is more commonly done currently. The best responses observed were stable disease, but there were numerous dose omissions, delays and reductions during this trial due to toxicity, which may account for the lack of objective responses. Future development of this combination should be considered for disease sites known to respond to vinorelbine in patients who are not as heavily pretreated.

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