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CLINICAL TRIAL REPORT

A phase I pharmacokinetic study of bexarotene with vinorelbine and cisplatin in patients with advanced non-small-cell lung cancer (NSCLC)

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Abstract
Purpose This is a phase I study of the retinoid X receptor agonist bexarotene (Targretin®) in combination with the chemotherapeutic drugs cisplatin and vinorelbine and lipid-lowering therapy. This study looked for pharmacokinetic (PK) interactions between the agents in parallel with a phase III study of the combination.
Methods Patients ($n = 26$) with advanced-stage non-small-cell lung cancer received intravenous cisplatin 100 mg/m^2 on day 1 and at 4-week intervals plus intravenous vinorelbine 25 mg/m^2 weekly. Continuous oral bexarotene therapy (400 mg/m^2/day) was initiated at day 4. Lipid-lowering therapy was initiated in all patients due to hypertriglyceridemia associated with bexarotene use. PK profiles of the chemotherapeutic agents were obtained on day 1 (without bexarotene) and during cycles 2–4 (with bexarotene). Vinorelbine ($n = 18$) and free cisplatin ($n = 17$) PK parameters in evaluable patients were determined using non-compartmental methods.
Results Mean vinorelbine and free cisplatin clearance and dose-corrected AUC values with bexarotene were within 20% of respective values without concomitant bexarotene. Bexarotene levels did not vary with or without co-administration of the chemotherapeutic agents. There was no evidence of increased toxicity when bexarotene was co-administered with the chemotherapeutic agents.
Conclusions Bexarotene does not substantially affect vinorelbine or cisplatin PK, and the combination is well tolerated. The results are consistent with the mechanisms of elimination of vinorelbine (high metabolic clearance) and cisplatin (non-enzymatic and renal elimination).

Keywords Bexarotene · Pharmacokinetics · Cisplatin · Vinorelbine · Non-small-cell lung cancer

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Introduction

Retinoids are crucial for many aspects of cellular function including reproduction, differentiation, immune function, and growth [20, 27] and act by altering gene expression mediated through two families of nuclear receptors: the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs) [7]. Bexarotene belongs to a retinoid class, rexinoids, that selectively activates retinoid X receptor (RXRs), and the drug is approved for the treatment of refractory early- and advanced-stage cutaneous T-cell lymphomas [3, 9].

Single-agent phase I studies demonstrated bexarotene's tolerability with MTDs ranging from 300 to 500 mg/m^2/day and toxicities including transiently elevated liver function tests (LFTs), leukopenia, hypertriglyceridemia (rarely leading to pancreatitis), and hypercalcemia. Toxicities at higher doses included desquamation, hyperbilirubinemia, diarrhea, and elevated prothrombin time [21, 24]. Pharmacokinetic data from the phase I studies demonstrated that daily dosing of bexarotene is adequate with pre-dose bexarotene levels obtained during repeat-dose administration of 300 mg/m^2/day ranging from 6.14 to 22.01 ng/ml, indicative of continuous exposure with once-daily dosing. Peak plasma bexarotene concentrations were generally observed within 3 h of dosing, and the estimated elimination half-life is 7–9 h. Elimination in man is almost entirely hepatobiliary with a very minor renal component, with minimal accumulation with once-daily dosing (results on file, Eisai Inc.). Initial pharmacokinetic results from phase I studies in two patients with daily oral dose of 300 mg/m^2 indicated that mean single-dose and repeated daily-dose plasma concentration profiles (C_{max} and AUC values) were similar, suggesting no alteration in bexarotene pharmacokinetics with repeated dosing or accumulation with repeated daily dosing [9]. However, additional results suggest some decreased in C_{max} and AUC with repeat dosing due to CYP3A4 induction, but this was non-linear and not clinically relevant (data on file, Eisai Inc.).

Investigation of bexarotene treatment of non-small-cell lung cancer (NSCLC) was initiated based on results from non-small-cell lung cancer (NSCLC) patients in the early phase I trial who appeared to have disease stabilization on bexarotene [21, 24]. This was further supported by a linkage between lung cancer progression and retinoid receptor dis-regulation [13, 15]; altered expression of RXR subtypes in lung cancer [4, 5, 22]; and an association between low RXRß gene expression and poor survival in patients with NSCLC [4]. One of the combination regimens investigated was cisplatin/vinorelbine and bexarotene based on preclinical synergism seen with bexarotene and both of these chemotherapeutic agents [11]. The initial phase I/II study utilized full-dose cisplatin and vinorelbine with escalating doses of bexarotene and found 400 mg/m^2 to be the dose for phase II [16]. Promising response and median survival time (MST) in the phase II portion led to the phase III SPIRIT I trial. This study was run in parallel for more complete PK data. The SPIRIT II trial evaluated bexarotene in combination with carboplatin/paclitaxel with an additional phase I trial for more complete PK data completed as well.

Bexarotene is metabolized to oxidative metabolites via the cytochrome P450 enzyme CYP3A4 and may induce CYP3A4 [12, 26]. Bexarotene capsules could affect the pharmacokinetics and decrease the plasma concentrations of vinorelbine and other agents through induction of CYP3A4 metabolism. Therefore, the current study was designed to assess potential pharmacokinetic drug interactions among bexarotene, cisplatin and vinorelbine, and lipid-lowering agents, as well as to evaluate the safety of this combination and the steady-stage pharmacokinetics of bexarotene in patients with NSCLC.

Patients and methods

This was a multicenter, open-label, phase 1 study of NSCLC patients assessing the safety, tolerability, and pharmacokinetics of bexarotene in combination with vinorelbine and cisplatin. Up to 60 patients were to be enrolled in the study to provide at least 15 evaluable patients receiving bexarotene capsules at an initial dose of 400 mg/m^2/day in the study. A patient was deemed evaluable if bexarotene capsules were administered during at least two cycles of the specified combination chemotherapy, and blood samples for pharmacokinetic profiling were collected. Each patient not meeting these criteria for evaluability was replaced with one additional patient. A total of 26 patients were enrolled, and 18 of these patients were considered evaluable.

Eligible patients had confirmed advanced-stage NSCLC, no active brain metastasis, ECOG performance status 0 or 1, adequate organ system function (transaminases and bilirubin <3 times upper limits of normal (ULN), adequate hematologic parameters (hemoglobin > 8 g/dl, absolute neutrophil count > 1,000/mm^3, and platelets > 50,000/mm^3), fasting serum triglycerides within the normal range (baseline lipid-lowering therapy was allowed), no risk factors for pancreatitis, no prior investigational agent for at least 30 days, no prior systemic anticancer therapy for at least 14 days, and no use of vitamin A in excess of 15,000 IU/day within 14 days. Strict contraceptive guidelines were in place for both men and women on the trial, and regular pregnancy tests were given to women of childbearing potential regularly while on study. Use of gemfibrozil or any retinoid class drugs, beta-carotene compounds

or vitamin A doses beyond 15,000 IU per day was strictly prohibited, and caution was advised with all drugs (including grapefruit) with known interaction with cytochrome P450 3A4 as well as with hypoglycemic agents.

All treatment doses of the chemotherapeutics and bexarotene in this phase I study were identical to a parallel phase III trial evaluating the efficacy of this regimen (SPIRIT I) [23]. All patients signed a written informed consent document approved by the local institutional investigational review board (IRB).

Procedures

All patients were started on a lipid-lowering agent (atorvastatin or fenofibrate) prior to beginning bexarotene capsule treatment. Starting on day 1, commercially available vinorelbine was infused intravenously for 15 min at a dose of 25 mg/m^2 once weekly. Commercially available cisplatin (100 mg/m^2) was infused intravenously over 60 min every 4 weeks starting 15 min after completion of the vinorelbine. Patients took once-daily oral bexarotene capsules 400 mg/m^2 with food beginning on day 4. The actual dose of bexarotene was rounded to within 37.5 mg or less of the calculated dose using the available capsule strength of 75 mg. There was no pre-specified limitation to number of cycles of therapy, and patients continued on the combination as long as they were potentially benefiting and were without unacceptable toxicity. In the event of a bexarotene capsule–related toxicity, such as elevated triglyceride levels, the dose of bexarotene capsules for an individual patient was reduced from 400 to 300, to 200, and then to 100 mg/m^2/day. Bexarotene capsules could be suspended at any time, as necessary.

Every patient was seen weekly with adverse event, physical examination, clinical and laboratory data collected. There were no protocol-specified efficacy evaluations. Up to 30 patients were to be enrolled in the study to provide for at least 15 evaluable patients who completed all PK profiling.

Serial blood samples were collected in heparinized tubes on day 1, day 28, and day 29. In addition, for those patients who remained on the study for more than two chemotherapy cycles, a single 5-ml blood sample was collected 45 min following the completion of vinorelbine infusion on the first week of each chemotherapy cycle after cycle 2. Blood samples were centrifuged, and the plasma was removed and then frozen until analysis.

Analytical methods

Bexarotene and vinorelbine concentrations in heparinized human plasma were determined using validated high-performance liquid chromatography/tandem mass spectroscopy (LC/MS/MS) methods as previously reported [28]. Total and free cisplatin in heparinized human plasma and plasma ultrafiltrate, respectively, were quantified using validated atomic absorption methods using a graphite furnace. All methodologies were developed and validated under standard operating procedures for the laboratory at the time of analysis and met the established assay performance criteria.

Data analysis Non-compartmental methods of analysis were used to determine single-dose pharmacokinetic parameters of vinorelbine, and free and total cisplatin, as well as multiple-dose (steady-state) pharmacokinetics of bexarotene. The PK parameters for bexarotene included area under the concentration–time curve for the 24-h dosing interval (AUC_{0-24}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and apparent terminal half-life ($t_{1/2}$), oral clearance (CL/F), and oral volume of distribution for the terminal elimination phase (V_z/F).

PK parameters were determined for single-dose vinorelbine and cisplatin following intravenous infusions on day 1 and during cycles 2 or 3. Parameters included AUC from time zero to the time of last measurable concentration (AUC_{0-t}), AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$), $t_{1/2}$, steady-state volume of distribution (V_{ss}), and clearance (CL).

Assessment of pharmacokinetic drug–drug interactions employed linear mixed-effects models using WinNonlin Professional (version 4.0.1) Bioequivalence Wizard. Values of pharmacokinetic parameters were natural log-transformed prior to analysis, and dose-dependent parameters (AUC and C_{max}) were dose-normalized. Dose normalization was necessary to compare PK parameters between treatment periods for those subjects who required protocol-allowable dose adjustments between periods. The models used period (e.g., without or with bexarotene capsules) as the fixed effect and subject as a random effect. Statistical assessments for the pharmacokinetic evaluation included descriptive statistics of pharmacokinetic parameters, and, for selected parameters, mixed-effect models to contrast mean pharmacokinetic parameter estimates across treatment periods (after natural log transformation). The analyses implemented restricted maximum likelihood estimation and the Satterthwaite approximation for degrees of freedom. Differences with P values of <0.05 were considered statistically significant.

Results

Safety

In total, 26 patients were enrolled in this study of bexarotene, cisplatin, and vinorelbine, but 8 were non-evaluable due to failure to complete the pharmacokinetic

Table 1 All adverse events with overall incidence ≥10% by severity regardless of relatedness ($N = 26$)

Adverse event	Mild *N* (%)	Moderate *N* (%)	Moderately severe *N* (%)	Severe *N* (%)
Neutropenia[a]	4 (15.4)	6 (23.1)	5 (19.2)	7 (26.9)
Anemia	0	8 (30.8)	3 (11.5)	0
Leukopenia	0	1 (3.8)	2 (7.7)	2 (7.7)*
Hypertriglyceridemia[b]	5 (19.2)*	6 (23.1)*	5 (19.2)*	1 (3.8)*
Anorexia	0	5 (19.2)	0 (0.0)	0 (0.0)
Insomnia	4 (15.4)	2 (7.7)	0 (0.0)	0 (0.0)
Dizziness	1 (3.8)	4 (15.4)	0 (0.0)	0 (0.0)
Headache	5 (19.2)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	4 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Tinnitus	3 (11.5)	5 (19.2)	1 (3.8)	0 (0.0)
Deafness	1 (3.8)	2 (7.7)	0 (0.0)	0 (0.0)
Flushing	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory disorders	2 (7.7)	4 (15.4)	1 (3.8)	1 (3.8)
Nausea	7 (26.9)	6 (23.1)	1 (3.8)	0 (0.0)
Constipation	6 (23.1)	5 (19.2)	0 (0.0)	0 (0.0)
Vomiting	6 (23.1)	3 (11.5)	2 (7.7)	0 (0.0)
Dyspepsia	5 (19.2)	2 (7.7)	0 (0.0)	0 (0.0)
Diarrhea	2 (7.7)	1 (3.8)	1 (3.8)	0 (0.0)
Alopecia	4 (15.4)	1 (3.8)	1 (3.8)	0 (0.0)
Rash	3 (11.5)*	2 (7.7)*	0 (0.0)	0 (0.0)
Fatigue	1 (3.8)	5 (19.2)	1 (3.8)	0 (0.0)
Chest pain	0 (0.0)	1 (3.8)	2 (7.7)	0 (0.0)
Lethargy	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (7.7)	0 (0.0)	1 (3.8)	0 (0.0)

Patients are counted at most once in each preferred term row and at most once in each system organ class row. Patients are classified by the highest severity within each row

* Related to bexarotene (related comprises the categories of yes, related; probably related; and possibly related)

[a] Combined neutropenia (neutropenia and neutrophil count decreased)

[b] Combined hypertriglyceridemia (blood triglycerides increased and hypertriglyceridemia)

sampling. All patients enrolled and exposed to at least one dose of bexarotene capsules were evaluated for safety and toxicity. Of the 26 patients, 19 were men and 7 were women, with a median age of 61 years (range, 35–70), and the majority (80%) was of non-Hispanic white ethnicity. One patient with mesothelioma was inadvertently enrolled, and the remainder had NSCLC. Toxicity data and the pharmacokinetic data for bexarotene, vinorelbine, and cisplatin are discussed below. The data on interactions with atorvastatin and fenofibrate were pooled from this study and a related study of bexarotene with carboplatin and paclitaxel and will be published separately [25, 30].

There was no evidence of enhancement in toxicity with this combination regimen, and toxicities were as would be expected from the chemotherapeutic agents or bexarotene alone. All adverse events for the 26 enrolled patients, regardless of relatedness to treatment, are presented in Table 1. Toxicities at least possibly related to bexarotene include hypertriglyceridemia (17/26 patients), headache (5/26), and various rashes including folliculitis (5/26). Seven serious adverse events (SAEs) were noted in 5 patients. SAEs, including vomiting ($n = 2$), constipation ($n = 1$), and neutropenic sepsis ($n = 1$), were related to cisplatin/vinorelbine. SAEs not felt to be related to study therapy included 1 episode each of hemoptysis (fatal), and embolic stroke (fatal). Eight patients withdrew from study due to adverse events including one patient who withdrew due to hypertriglyceridemia that was related to bexarotene. Median serum triglyceride levels increased to four times baseline levels over the first 4 weeks of bexarotene use with 5 patients developing grade 3 and 1 patient grade 4 hypertriglyceridemia. Eight patients required dose reductions of bexarotene due to hypertriglyceridemia or increased blood triglycerides. No trends toward elevations of any liver function tests or thyroid function tests were seen in this study, and pancreatitis was not reported.

Pharmacokinetics

Bexarotene

Bexarotene capsule doses in six patients were reduced from the 400 mg/m^2/day initial dose to 300 mg/m^2/day ($n = 2$), 200 mg/m^2/day ($n = 2$), or 100 mg/m^2/day ($n = 2$) prior to either sampling period for bexarotene PK. All 18 patients received the same respective dose of bexarotene capsules with and without cisplatin and vinorelbine. Bexarotene C_{max} and

Table 2 Steady-state bexarotene pharmacokinetic parameters with and without intravenous cisplatin and vinorelbine chemotherapy

	No cisplatin and vinorelbine			With cisplatin and vinorelbine		
	N	Mean	SD	*N*	Mean	SD
Dose (mg/m^2)	18	333	108	18	333	108
$t_{1/2}$ (h)	18	6.53	5.12	18	5.21	4.16
Oral CL (l/h/m^2)	18	113.2	70.8	18	128.5	86.2
t_{max} (h)	18	2.91	1.84	18	2.94	2.51
Dose adjusted[a] to 400 mg/m^2						
C_{max} (ng/ml)	18	1,190.7	892.5	18	1,060.7	578.6
AUC_{0-24} (ng h/ml)	18	5,632.5	4,227.5	18	4,303.7	2,576.7

AUC_{0-24} area under the plasma concentration–time curve over the interval of time zero to 24 h, C_{max} maximum observed plasma concentration, *Oral CL* plasma clearance divided by bioavailability, $t_{1/2}$ terminal elimination half-life, t_{max} time to C_{max}

[a] Bexarotene capsules were administered orally once daily to steady state at doses from 100 to 400 mg/m^2

AUC values with vinorelbine and cisplatin were similar to respective values without concomitant chemotherapy (Table 2). Least-squares mean bexarotene C_{max} were essentially identical, and AUC values without concomitant chemotherapy were within 17% of respective values with concomitant chemotherapy. This AUC difference was not statistically significant ($P = 0.4249$) (Table 5). Mean plasma bexarotene concentrations versus time with and without concomitant chemotherapy were similar (Fig. 1).

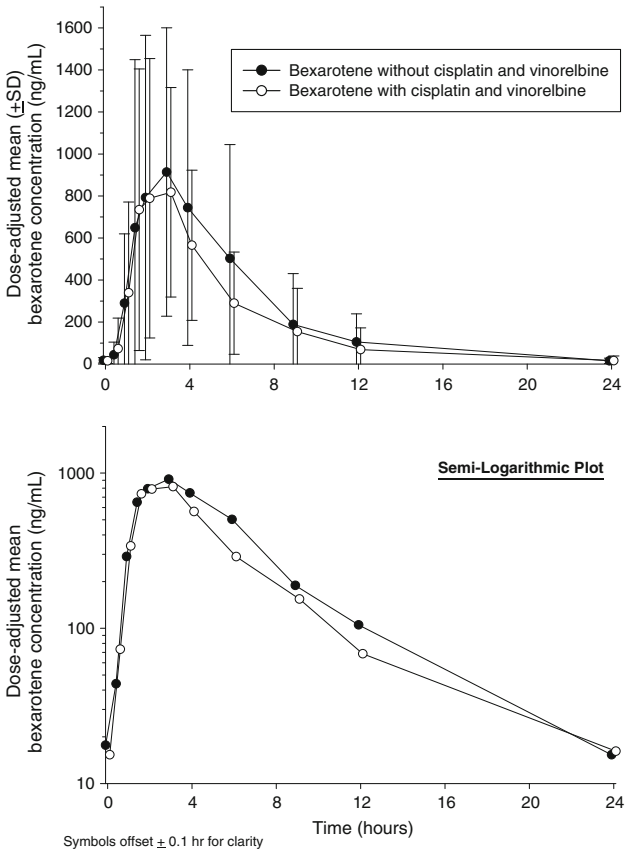

Fig. 1 Mean dose-adjusted (to 400 mg/m^2) plasma bexarotene concentrations with and without intravenous cisplatin and vinorelbine in patients ($N = 18$) with NSCLC

Vinorelbine

All eighteen patients received single intravenous infusions of 25 mg/m^2 of vinorelbine on day 1. Fourteen patients received an identical single intravenous infusion of 25 mg/m^2 on day 29. Two patients received a dose of 18.75 mg/m^2, 1 patient received a dose of 20 mg/m^2, and 1 patient received a dose of 12.5 mg/m^2 during the PK period with bexarotene capsules (day 29). Descriptive statistics of mean vinorelbine PK parameters with and without concomitant bexarotene capsules for evaluable patients are summarized in Table 3. A statistical assessment of the effect of bexarotene capsules on select dose-normalized vinorelbine PK parameters using linear mixed-effects models was conducted for patients with PK data both with and without bexarotene capsules. Vinorelbine PK parameters were generally similar with or without co-administration of bexarotene capsules. The geometric least-squares mean of the AUC values with or without bexarotene were within 20% of each other. An approximate 15% decrease in AUC parameters was observed with bexarotene capsule administration (Table 5). No statistically significant differences were observed in PK parameters ($t_{1/2}$, CL and AUC) between the two periods with the exception of V_{ss} ($P = 0.0108$) with an approximate 59% increase (data not shown).

The magnitude and direction of individual changes in dose-adjusted vinorelbine AUC with and without bexarotene capsule co-administration were quite variable with some decreases and some increases with bexarotene co-administration (data not shown). Mean dose-adjusted plasma vinorelbine concentrations versus time are presented in Fig. 2a and were similar with or without concomitant bexarotene capsules.

Table 3 Vinorelbine pharmacokinetic parameters with and without repeated once-daily concomitant bexarotene capsules

	No bexarotene			With bexarotene		
	N	Mean	SD	*N*	Mean	SD
Dose (mg/m^2)	18	25.0	0.0	18	23.3	3.5
Infusion time (h)	18	0.232	0.065	18	0.222	0.091
$t_{1/2}$ (h)	18	42.9	14.2	18	57.1	20.1
V_{ss} (l/m^2)	18	1,134	453	18	1,907	926
CL (l/h/m^2)	18	47.7	9.15	18	56.9	16.0
Dose adjusted[a] to 25 mg/m^2						
AUC_{0-t} (ng h/ml)	18	511.8	96.2	18	449.9	149.5
$AUC_{0-\infty}$ (ng h/ml)	18	541.2	96.6	18	477.8	152.5

AUC area under the plasma concentration–time curve over the interval of time zero to time of last measurable concentration ($0-t$) or from time zero to infinite time ($0-\infty$), *CL* plasma clearance, $t_{1/2}$ terminal elimination half-life, V_{ss} steady-state volume of distribution

All patients ($n = 18$) also received a single dose of intravenous cisplatin and steady-state oral lipid-lowering agent (atorvastatin or fenofibrate)

[a] Vinorelbine was administered by intravenous infusion over approximately 15 min at 25 mg/m^2, except patients 62, 64, 65, and 221 who received 18.75, 12.5, 18.75, and 20.0 mg/m^2, respectively, during the bexarotene phase

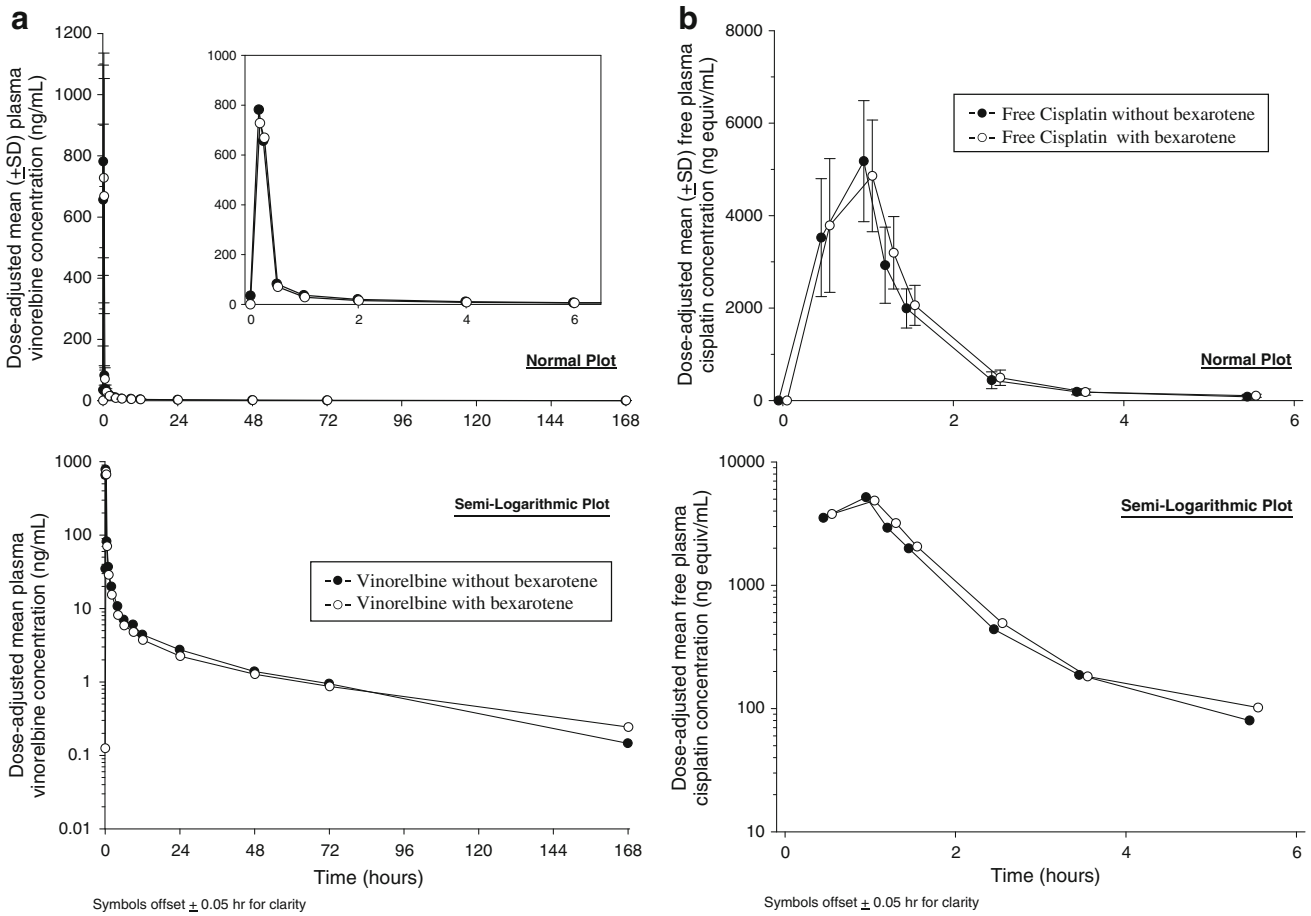

Fig. 2 **a** Chemotherapy with or without bexarotene/vinorelbine mean dose-adjusted (to 25 mg/m^2) plasma vinorelbine concentrations with and without repeated once-daily concomitant bexarotene capsules in patients ($N = 18$) with NSCLC. **b** Chemotherapy with or without bexarotene/cisplatin mean dose-adjusted (to 100 mg/m^2) free plasma cisplatin concentrations with ($N = 17$ patients) and without ($N = 15$ patients) repeated once-daily concomitant bexarotene capsules in patients with NSCLC

Cisplatin

Due to insufficient plasma ultrafiltrate volumes, free cisplatin PK parameters were only determined for 15 patients without bexarotene and 17 patients with bexarotene. Plasma and plasma ultrafiltrate samples for the determination of cisplatin concentrations were received from all 18 evaluable patients.

The effect of bexarotene on cisplatin pharmacokinetics was primarily assessed with cisplatin concentrations in plasma ultrafiltrate (i.e., free cisplatin). Individual patient and descriptive statistics of free and total cisplatin PK with and without bexarotene capsules for evaluable patients are summarized in Table 4. All PK ($t_{1/2}$, CL, Vss and AUC) parameters were similar with and without bexarotene capsules. The geometric least-squares mean of the free cisplatin AUC values with bexarotene were within 10% of respective values without bexarotene (Table 5). No statistically significant difference between treatment periods was observed for the PK parameters. There was no observable trend in the individual subject changes in free cisplatin AUC values. Mean free plasma cisplatin concentration versus time profiles are presented in Fig. 2b and were not altered by concomitant bexarotene capsules. Comparable results were also seen with mean total cisplatin concentration and total cisplatin exposure ($AUC_{0-\infty}$), which was similar with and without bexarotene capsule treatment (Table 5).

Discussion

In this phase I study of the combination of bexarotene (400 mg/m^2/day orally), cisplatin (100 mg/m^2/every 4 weeks IV), and vinorelbine (25 mg/m^2/weekly IV), detailed PK analyses in 18 patients revealed that concomitant administration of bexarotene capsules generally had no effect on the PK of vinorelbine or free or total cisplatin. Plasma vinorelbine, free and total cisplatin concentrations were similar (mean differences in AUC $\leq$ 15%) with or without concomitant administration of bexarotene capsules.

No unexpected toxicity or laboratory abnormalities were seen in this study. Plasma bexarotene exposure (C_{max} and AUC_{0-24}) was similar with and without concomitant administration of cisplatin and vinorelbine. Plasma bexarotene peak concentrations were essentially identical, and AUC_{0-24} values were within 17% during concomitant cisplatin and vinorelbine chemotherapy relative to values without chemotherapy. There was no evidence of vinorelbine reducing bexarotene clearance due to competitive inhibition of CYP3A4 or any other mechanism. Bexarotene pharmacokinetic data in the current study are similar to values observed in other bexarotene capsule studies in other patient populations [24].

Though an approximate 15% decrease in vinorelbine AUC parameters was observed with bexarotene capsule administration, corresponding with an increase in clearance, this was not statistically significant. The V_{ss} was the

Table 4 Free and total cisplatin pharmacokinetic parameters with and without repeated once-daily concomitant bexarotene capsules

	No bexarotene			With bexarotene		
	N	Mean	SD	*N*	Mean	SD
Dose (mg/m^2)	15	100.0	0.0	17	98.82	4.85
Infusion time (h)	15	1.01	0.04	17	1.02	0.06
Free (unbound) cisplatin						
$t_{1/2}$ (h)	15	1.38	0.90	17	1.49	0.83
CL (l/h/m^2)	15	16.95	3.90	17	15.60	2.92
V_{ss} (l/m^2)	15	17.79	8.73	17	16.64	5.71
Dose adjusted[a] to 100 mg/m^2						
AUC_{0-t} (ng equiv h/ml)	15	6,004.5	1,586.1	17	6,398.4	1,360.6
$AUC_{0-\infty}$ (ng equiv h/ml)	15	6,232.4	1,578.9	17	6,640.4	1,369.6
Total (bound and unbound) cisplatin						
Dose adjusted[a] to 100 mg/m^2						
AUC_{0-t} (ng equiv h/ml)	17	72,497	9,458	16	78,586	11,142

AUC area under the plasma concentration–time curve over the interval of time zero to time of last measurable concentration (0−t) or from time zero to infinite time (0−∞), *CL* plasma ultrafiltrate clearance, *ng equiv* equivalent mass of cisplatin, $t_{1/2}$ terminal elimination half-life, V_{ss} steady-state volume of distribution

All patients also received a single dose of intravenous vinorelbine and steady-state oral lipid-lowering agent (atorvastatin or fenofibrate)

[a] Cisplatin was administered by a 60-min intravenous infusion at a dose of 100 mg/m^2, except patient 221 who received a dose of 80 mg/m^2 during the bexarotene capsule period

Table 5 Statistical comparison between drugs alone versus combined for $AUC_{(0-\infty)}$ and C_{max}

Treatment	Analyte	Statistic	AUC Ratio combined/alone[a]	C_{max} Ratio combined/alone[a]
Cisplatin plus vinorelbine	Bexarotene[d]	Geometric mean	83.83* ($n = 18$)	99.62 ($n = 18$)
		P value[b]	0.4249	0.9856
		(90% CI)[c]	(57.95, 121.28)	(69.73, 142.31)
Bexarotene	Free unbound cisplatin[e]	Geometric mean	107.6 ($n = 14$)	NA
		P value[b]	0.3501	NA
		(90% CI)[c]	(94.38, 122.72)	NA
Bexarotene	Total cisplatin[e]	Geometric mean	106.2 ($n = 15$)	NA
		P value[b]	0.1163	NA
		(90% CI)[c]	(99.61, 117.63)	NA
Bexarotene	Vinorelbine[f]	Geometric mean	85.8 ($n = 18$)	NA
		P value[b]	0.0725	NA
		(90% CI)[c]	(74.6, 98.67)	NA

* *AUC* area under the plasma concentration–time curve from 0 to 24 h for bexarotene, C_{max} maximum observed plasma concentration

[a] % Ratio of GeoLSM for drugs combined over drug(s) alone

[b] For difference between GeoLSM

[c] The 90% confidence interval (CI)

[d] For bexarotene, dose was normalized to 400 mg/m^2/day

[e] All patients also received a single dose of intravenous vinorelbine and steady-state oral lipid-lowering agent (atorvastatin or fenofibrate)

[f] All patients also received a single dose of intravenous cisplatin and steady-state oral lipid-lowering agent (atorvastatin or fenofibrate)

only statistically significant vinorelbine PK parameter to vary with the addition of bexarotene. While vinorelbine is metabolized by CYP3A4, it is also a high plasma clearance (Table 3; mean data, 47.7 l/h/m^2) compound close to the human liver blood flow [approximately 50 l/h/m^2 (for a 70-kg man)] [18]. Any potential induction of CYP3A4 metabolism of vinorelbine by bexarotene would be limited since vinorelbine appears to be limited by liver blood flow. The modest increase in vinorelbine clearance observed in the current study is consistent with induction of metabolism of an intravenously administered high-clearance compound. The plasma vinorelbine clearance observed in the current study is consistent with published values [14, 17, 19]. Vinorelbine exhibits a blood-to-plasma ratio of approximately 1.9, supporting the high blood clearance value for this compound [10].

No effect was seen on any free or total cisplatin PK parameters with the addition of bexarotene. This lack of effect of bexarotene on cisplatin PK is consistent with the proposed elimination mechanism of cisplatin through a chemical degradation process, and not enzymatic hydrolysis [6]. Free cisplatin clearance observed in the current study is similar to values reported in the literature [1].

Interestingly, a subanalysis from the SPIRIT I trial and the related SPIRIT II trial (with carboplatin and paclitaxel) did indicate that those patients who had a significant rise in triglyceride levels while on bexarotene may have had a survival benefit [2, 23]. In this study and a similar PK study of carboplatin/paclitaxel and bexarotene at these doses, no correlation was seen between serum triglyceride levels and bexarotene AUC, arguing against a direct connection between higher levels of hypertriglyceridemia and higher bexarotene exposure [29]. So the correlation between hypertriglyceridemia and better survival found in the phase III SPIRIT trials [2, 23] is unlikely to be related to variable exposure to bexarotene manifesting as variable triglyceride levels. Instead, a differential response is likely, with certain individuals having increased sensitivity to bexarotene as reflected by elevated triglycerides and associated survival benefit. An ongoing BATTLE study currently utilizes bexarotene in a subset of NSCLC patients and will provide comparative efficacy data looking at multiple biomarkers that may predict for benefit with the drug [8].

The parallel randomized phase III trial of cisplatin and vinorelbine with or without bexarotene for the first-line therapy of advanced NSCLC (SPIRIT I) failed to show an overall survival advantage with the addition of bexarotene [23]. The results from this phase I study indicate that a PK interaction between bexarotene and the chemotherapeutic agents is highly unlikely. In conclusion, there was only a minor decrease in vinorelbine AUC, which was non-statistically significant with the addition of bexarotene, and there were no PK changes for cisplatin with the addition of bexarotene.

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Conflict of interest Dr. Arturo Lopez-Anaya was an employee of Eisai Pharmaceuticals at the time of his work on this manuscript. All other authors have no conflict of interest with regard to financial or personal relationships with other people or organizations that could inappropriately influence this work.

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