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CLINICAL TRIAL REPORT

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

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Abstract
Purpose Preclinical data suggest that the synthetic retinoid bexarotene may be an effective chemopreventive agent and that it may act synergistically in combination with platinum-based chemotherapy. The primary objective of this study was to determine whether repeated doses of bexarotene capsules affect pharmacokinetic parameters of paclitaxel or carboplatin in patients with advanced non-small cell lung cancer.
Methods Patients received treatment with paclitaxel (200 mg/m^2) and carboplatin to provide a target AUC of 6 mg min/mL (day 1) every 3 weeks. Continuous oral bexarotene therapy (400 mg/m^2/day) was initiated on Day 4, and patients started lipid-lowering therapy prior to beginning chemotherapy. Blood sampling to characterize the pharmacokinetic profiles of the chemotherapeutic agents with or without bexarotene was performed during cycle 1 (without concomitant bexarotene) and during cycle 2 (with concomitant bexarotene).
Results An analysis of drug concentration data from 16 patients indicated that bexarotene did not affect the pharmacokinetics of paclitaxel, free carboplatin, or total carboplatin concentrations. However, both maximal plasma concentrations and total exposure of bexarotene increased by 80% in the presence of paclitaxel–carboplatin by an, as of yet, unexplained mechanism. The toxicities observed resembled those of either the chemotherapy regimen or bexarotene alone, and there was no evidence for an enhancement of any drug-related toxicity with the combined treatment.
Conclusions The administration of bexarotene, paclitaxel, and carboplatin is feasible and safe; however, the increased bexarotene plasma concentrations and exposure warrant further investigation if this combination is to be utilized clinically.

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Introduction

Retinoic acid and its derivatives have been demonstrated to play important roles in the treatment and prevention of various cancers by controlling cell differentiation and death (for review, see [1, 2]). Retinoids bind to the intracellular retinoid (RAR α, β, and γ) and rexinoid (RXR α, β, and γ) receptors, controlling gene expression. Retinoid-based "differentiation therapy", in which retinoids are combined with an anthracycline and cytosine arabinoside have become the standard treatment for patients with acute promyelocytic leukemia [3–6], and the efficacy of this class of agents in other malignancies is under evaluation.

Bexarotene, a synthetic retinoid analog that binds preferentially to RXRs has received regulatory approval in the United States and elsewhere for the treatment for refractory cutaneous T cell lymphoma [7, 8]. The principal toxicity of bexarotene is hypertriglyceridemia, which requires treatment with lipid-lowering agents such as atorvastatin and other agents of this class or fenofibrate and related drugs [7–11].

The combination of bexarotene with chemotherapy for non-small cell lung cancer was undertaken due to the observation of significant RXR signaling in tumor NSCLC biopsies and the activity of bexarotene in xenografts of squamous origin (with subsequent degradation of cyclin D1 and reduction in the expression of TGF-β and EGFR) [12–16]. In combination with chemotherapy, bexarotene produces synergistic growth inhibition in preclinical models including NSCLC cell lines [17–21].

As combination regimens were explored, extensive pharmacokinetic studies of the agents were required as bexarotene is principally metabolized by CYP3A4 with the potential for multiple drug interactions with other CYP3A4-metabolized agents that are used in the treatment for cancer patients [10]. The results of in vitro studies also showed that bexarotene competitively inhibits the CYP2C8-mediated metabolism of paclitaxel (data on file, Eisai Inc.). Additionally, bexarotene was shown to be a modest inducer of CYP3A4 in an in vitro study in human hepatocytes and in vivo (data on file, Eisai Inc.) Based on these data, it was hypothesized that bexarotene could affect the pharmacokinetics and decrease the plasma concentrations of paclitaxel, atorvastatin, and other agents through the induction of CYP3A4 metabolism. It was also hypothesized that bexarotene could increase the plasma concentrations of paclitaxel or other CYP2C8 substrates through the inhibition of CYP2C8 metabolism. Carboplatin elimination is entirely renal, making an pharmacokinetic interaction with bexarotene unlikely. This current study was an open-label phase I study in NSCLC patients designed to assess a number of potential pharmacokinetic drug interactions among bexarotene, chemotherapeutic agents including paclitaxel and carboplatin and lipid-lowering agents including atorvastatin or fenofibrate. This study allowed for the evaluation of the effects of daily oral bexarotene on the kinetics of paclitaxel, carboplatin and atorvastatin, or fenofibrate. This study was run in parallel with a randomized phase III trial of carboplatin/paclitaxel with or without bexarotene in patients with advanced stage NSCLC [22]. Another trial looked at the interactions of bexarotene with cisplatin and vinorelbine chemotherapy in a similar patient population utilizing a trial design nearly identical to that reported here (reported separately).

Patients and methods

Eligibility criteria

Adult patients with histological documentation of NSCLC were eligible for study participation. Additional eligibility criteria included age $\geq$18 years; an Eastern Cooperative Oncology Group performance status of 0–1; no chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or surgery within 4 weeks before the first treatment; no systemic vitamin A exceeding 15,000 IU/day within 14 days prior to initiating study medications; adequate hematopoietic (absolute neutrophic count $\geq$1,000/mm^3, platelet count $\geq$50,000/mm^3, hemoglobin $\geq$8 g/dL), hepatic (total bilirubin, AST, and ALT $\leq$3 times institutional upper normal limit), and renal function (creatinine $<$1.5 time institutional upper normal limit). Fasting serum triglyceride was required to be within normal limits or "normalized" prior to study entry with appropriate intervention such as the use of a lipid-lowering agent specified in this protocol. Patients with known brain metastasis (unless previously treated, stable, and not requiring corticosteroids) or with risk factors for pancreatitis (e.g., prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications associated with pancreatic toxicity) were ineligible.

All patients gave written informed consent before entry into the study in accordance with federal and institutional guidelines. A negative pregnancy test (serum β-HCG) was required for all women of childbearing potential and reliable forms of effective contraception or sexual abstinence during the entire period of treatment with bexarotene were required. Also, patients had to agree to minimize exposure to sunlight and artificial ultraviolet light while receiving bexarotene. Because of a documented drug interaction, treatment with gemfibrozil was prohibited per protocol

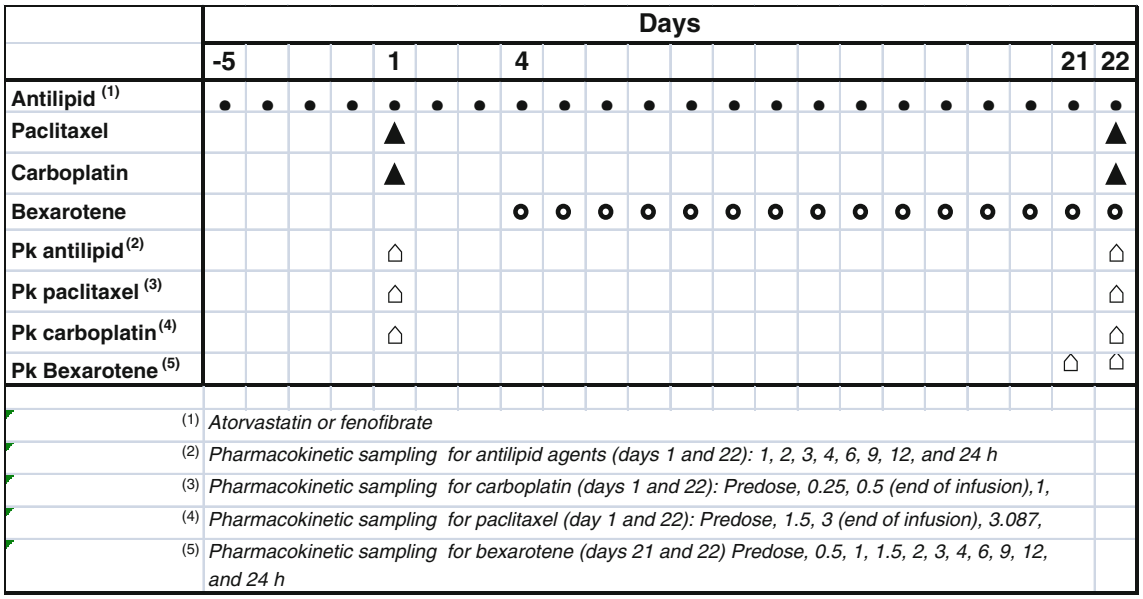

Fig. 1 Treatment and pharmacokinetic sampling plan

[23, 24]. Treatment with known inhibitors or inductors of CYP3A4 was avoided when possible; however, if medically required, use of such agents was carefully monitored. The systemic use of other agents with the potential to interfere, such as other retinoid class drugs, beta-carotene compounds, high vitamin A doses, or agents with the potential to induce hypoglycemia, were also avoided whenever possible.

Treatment plan

At least 5 days prior to the chemotherapy, patients were assigned in an alternating fashion to either daily atorvastatin or fenofibrate. On day 1, patients were treated with carboplatin and paclitaxel, and on day 4 after chemotherapy, patients were started on daily oral bexarotene as depicted in Fig. 1.

Atorvastatin and fenofibrate were started at no less than the highest initial dose (e.g., 10 mg daily of atorvastatin; 134 mg daily of fenofibrate), and, if required, escalated as permitted by the package insert up to 80 mg daily of atorvastatin or 200 mg daily of fenofibrate.

On day 1, paclitaxel was administered at a dose of 200 mg/m^2 IV and infused over 3 h. Following administration of paclitaxel, carboplatin was administered via intravenous infusion over 30 min adjusted to an AUC of 6 mg min/ml according to the Calvert formula [25]. To mitigate possible side effects, premedication with dexamethasone, diphenhydramine, ondansetron, and famotidine 20 mg, was recommended. The chemotherapy regimen was administered every 3 weeks.

Starting on day 5 and continuously thereafter, patients were administered once-daily oral bexarotene at a dose of 400 mg/m^2 rounded to the nearest capsule dose as outlined below. The bexarotene was administered with at least six ounces of water or other fluid, in the morning with food until pharmacokinetic sampling was completed with cycle 2. Treatment with bexarotene was continued concomitantly for at least two cycles in combination with chemotherapy, and it could be continued as long as the patient was felt to be benefiting from the treatment. Bexarotene capsules were supplied as 75 mg soft gelatin capsules with the dose calculated based upon body surface area (BSA), rounded to the nearest 75 mg increment to determine the appropriate number of capsules. Other oral medications were avoided within 1 h before or 1 h after ingesting bexarotene. In the event of a bexarotene-related toxicity, sequential reductions to 300, 200, or 100 mg/m^2/day were permitted. Treatment at doses less than 100 mg/m^2/day was not allowed. Bexarotene capsules were administered at the same time of day as the start of the paclitaxel infusion, in the morning. Blood sampling for pharmacokinetic studies was to occur on Day 1 (for all analytes except bexarotene, after at least 5 days of lipid-lowering pretreatment), Day 21 (for bexarotene only), and Day 22 (for all analytes).

A maximum of 30 patients were planned to be enrolled to provide for at least 15 evaluable patients. A patient was deemed evaluable if the patient had remained on bexarotene through at least two cycles of the combination chemotherapy and had had blood collections sufficient for PK profiling.

Pretreatment and follow-up studies

Medical history, complete physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, concurrent medications, and routine laboratory evaluations were done before treatment and weekly. Routine laboratory evaluations also included thyroid function tests (total T4, thyroid-stimulating hormone (TSH) creatinine phosphokinase (CPK), coagulation profile, and urinalysis.

Pretreatment studies also included a sample for serum lipids after a minimum 8 h fast, an electrocardiogram, a serum pregnancy test, tumor markers, and relevant radiological studies for the evaluation of all sites of malignancy. Radiological studies for disease status assessments were also done after every other course or as needed to confirm response or progression, though there were no protocol specified efficacy endpoints. Toxicity evaluation was assessed using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 3.0.

Post-baseline assessment of the patient's fasting triglyceride level was performed weekly until week 6 and then every 3 weeks thereafter. Patients who developed abnormal triglyceride levels during the study (above 400 mg/dL) had additional laboratory monitoring on a weekly basis until it remained stable. Escalations in the dose of lipid-lowering therapy were permitted for poor control of hypertriglyceridemia, but if unsuccessful, the dose of bexarotene could be reduced. Bexarotene dose reductions and dose suspensions were recommended for triglyceride levels greater than 800 and 1,200 mg/dL, respectively. Only atorvastatin or fenofibrate was allowed to treat bexarotene-induced hypertriglyceridemia. The use of two lipid-lowering agents simultaneously was not permitted due to the potential risks of myopathy, rhabdomyolysis, and acute renal failure.

Plasma pharmacokinetic sampling, assay, and analyses

Blood sampling was obtained from an indwelling venous catheter placed in the arm contralateral to the drug infusion. Blood samples were obtained on day 1, (5 days after the start of atorvastatin or fenofibrate) prior to and immediately following the administration of chemotherapy, and at 2, 3, 4–6, and 8–12 h post-treatment (Fig. 1). Blood samples for the evaluation of bexarotene kinetics were obtained on day 21 (for bexarotene at steady state alone) and on day 22 (in combination with chemotherapy), at the beginning of the second cycle of therapy.

The samples were centrifuged and frozen at −20°C except for the samples for the determination of free platinum, which were immediately centrifuged in Centrifree Micropartition devices (Millipore Corporation) at 4°C at 1,000–2,000×g for 20 min to separate plasma, and then were frozen at −20°C. Paclitaxel, bexarotene, atorvastatin, and fenofibric acid concentrations in heparinized human plasma were determined using validated high-performance liquid chromatography/tandem mass spectroscopy methods (LC/MS/MS) by Cedra Corporation. Total and free carboplatin in heparinized human plasma and plasma ultrafiltrate, respectively, were quantitated using validated atomic absorption methods using a graphite furnace by MDS Pharma Services. All methodologies were developed and validated under standard operating procedures for the laboratory at the time of analysis.

Non-compartmental methods were used to determine single-dose pharmacokinetic (PK) parameters for the chemotherapeutic agents (paclitaxel and carboplatin) and multi-dose (steady state) pharmacokinetic parameters for bexarotene and the lipid-lowering agents. PK parameters were determined for single-dose paclitaxel and carboplatin following intravenous infusions on Day 1 (without bexarotene) and Day 22 (with bexarotene). Parameters included area under the concentration curve (AUC) from Time 0 to the time of last measurable concentration (AUC_{0-t}), AUC from Time 0 extrapolated to infinity ($AUC_{0-\infty}$), $t_{1/2}$, steady-state volume of distribution (V_{ss}), and clearance (CL). 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). These were evaluated on Day 21 (without chemotherapy) and on Day 22 (with chemotherapy).

Assessment of pharmacokinetic drug–drug interactions used linear mixed-effects models with WinNonlin Professional (Version 4.0.1) Bioequivalence Wizard (Pharsight Corporation, Mountain View, CA, USA). Dose normalization was required to compare dose-dependent parameters (AUC and C_{max}) between treatment periods as some patients had protocol-allowable dose adjustments between periods. Values of pharmacokinetic parameters were natural log transformed prior to analysis. The models used subject as a random effect and Day (e.g., without or with bexarotene capsules) as the fixed effect. 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) were included as the statistical assessments for the PK evaluation. The Satterthwaite approximation for degrees of freedom was utilized, and the analyses implemented restricted maximum likelihood estimation. Differences with P values of <0.05 were considered statistically significant.

Results

Safety

Twenty-two subjects were enrolled in this two-center study and received study medication. Seventeen received at least two doses of chemotherapy and sixteen of those were considered evaluable for pharmacokinetic analysis. Subject demographics and baseline classification are presented in Table 1.

Seven patients were withdrawn due to disease progression, five patients due to adverse events (hypertriglyceridemia in three patients, peripheral neuropathy and neutropenia in two patients), and ten due to administrative reasons, withdrawal of consent, or non-compliance.

Seventeen patients (77.3%) received at least two cycles of chemotherapy, and the overall median number of cycles was three. The median duration of exposure to bexarotene was 62.0 days (range: 7–140 days) and the overall average dose for 21 patients was 323.8 mg/m^2/day. Ten patients (45.5%) required dose reduction and/or suspension, primarily secondary to increased triglycerides. During the study, eleven of the 22 patients (50.0%) received atorvastatin only; five (22.7%) received fenofibrate only; one (4.5%) switched from atorvastatin to fenofibrate; and five (22.7%) from fenofibrate to atorvastatin.

The most common related adverse events (all grades) were hypertriglyceridemia (90.9%), fatigue/asthenia (77.3%), neutropenia and nausea (72.7% each), constipation (68.2%), alopecia and anemia (63.6% each), dyspnea (59.1%), diarrhea and neuropathy (40.9% each), hypercholesterolemia, headache, arthralgia, and abdominal pain (36.4% each)—see Table 2.

Hypertriglyceridemia was mild or moderate (grade 1 and 2) in 11 patients (50%) or severe (Grade 3 and 4) in 9 patients (40.9%). Triglyceride and cholesterol levels were elevated within 3 weeks and then stabilized between weeks 3 and 18. There were no reports of pancreatitis, but hypothyroidism was reported in four patients (18.2%).

This phase I study focused on the pharmacokinetics of bexarotene in combination with carboplatin/paclitaxel chemotherapy, and therefore, efficacy data were not collected.

Table 1 Baseline demographic data

Variable	Number (%) of patients ($N = 22$)
Age (years)	
<65 (*n*, %)	13 (59.1)
≥65 (*n*, %)	9 (40.9)
Mean (±SD)	60.6 (±9.5)
Sex	
Male (*n*, %)	14 (63.6)
Female (*n*, %)	8 (36.4)
TNM stage at baseline	
IIIA	2 (9.1)
IIIB	4 (18.2)
IV	16 (72.7)
ECOG PS	
0	4 (18.2)
1	18 (81.8)
Histologic classification	
Adenocarcinoma	12 (54.5)
NSCLC (NOS)	7 (31.8)
Squamous cell carcinoma	2 (9.1)
Bronchoalveolar	1 (4.5)
Baseline metabolic abnormalities	
Hypercholesterolemia	3 (13.6)
Elevated liver enzymes	1 (4.5)
History of hypothyroidism	3 (13.6)
Diabetes mellitus	2 (9.1)

NSCLC non-small cell lung cancer, *NOS* not otherwise specified, *TNM* tumor/node/metastasis, *ECOG PS* ECOG performance status

Effect of bexarotene on paclitaxel and carboplatin pharmacokinetics

Plasma paclitaxel concentration–time data from all 16 evaluable patients were included in the pharmacokinetic evaluation. Results of the statistical analysis of the relevant paclitaxel pharmacokinetic parameters with or without coadministration of bexarotene (day 1 and 22) are presented in Table 3A. The geometric least square mean (GeoLSM) values of the plasma ultrafiltrate clearance (CL) of paclitaxel with or without repeated one-daily dosing of bexarotene were 11.82 and 14.53 L/h/m^2, respectively. The paclitaxel steady-state volume of distribution (Vss) GeoLSM values with or without bexarotene were 81.87 and 111.8 L/m^2, respectively. The GeoLSM values of AUC_{0-t} and AUC_{0-inf} of paclitaxel in the presence/absence of bexarotene were 16,657 versus 13,483 and 16,929 versus 13,761 ng h/mL, respectively. The 90% CI of the GeoLSM for all the paclitaxel PK parameters except Vss were within 0.80–1.20 indicating no statistically significant differences between the two treatment periods (with or without bexarotene).

Evaluation of the effect of bexarotene on carboplatin pharmacokinetics was primarily focused on carboplatin concentrations in plasma ultrafiltrate. Although there were 16 evaluable patients, data from 3 patients were excluded from the evaluation using plasma ultrafiltrate due to an insufficient volume of ultrafiltrate collected. Total carboplatin data from one patient were excluded from PK evaluation because a plasma sample was not obtained at the

Table 2 Hematological and non-hematological adverse events

Adverse event by system organ	Grade 1 *N* (%)	Grade 2 *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)
Hematological toxicity				
Neutropenia	2 (9.1)	1 (4.5)	5 (22.7)	8 (36.4)
Anemia	5 (22.7)	6 (27.3)	2 (9.1)	1 (4.5)
Leukopenia	0 (0.0)	2 (9.1)	2 (9.1)	2 (9.1)
Thrombocytopenia	4 (18.2)	1 (4.5)	1 (4.5)	0 (0.0)
Non-hematological toxicity				
Hypothyroidism	0 (0.0)	**4 (18.2)**	0 (0.0)	0 (0.0)
Hypertriglyceridemia	3 (13.6)	**8 (36.4)**	**7 (31.8)**	2 (9.1)
Hypercholesterolemia	3 (13.6)	**8 (36.4)**	**7 (31.8)**	2 (9.1)
Dyspnea	7 (31.8)	1 (4.5)	**5 (22.7)**	0 (0.0)
Nausea	13 (59.1)	0 (0.0)	**3 (13.6)**	0 (0.0)
Vomiting	5 (22.7)	1 (4.5)	0 (0.0)	0 (0.0)
Constipation	8 (36.4)	**5 (22.7)**	2 (9.1)	0 (0.0)
Diarrhea	5 (22.7)	**3 (13.6)**	1 (4.5)	0 (0.0)
Abdominal pain	5 (22.7)	2 (9.1)	1 (4.5)	0 (0.0)
Neuropathy	7 (31.8)	1 (4.5)	1 (4.5)	0 (0.0)
Headache	8 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	3 (13.6)	**11 (50.0)**	0 (0.0)	0 (0.0)
Rash	6 (27.3)	1 (4.5)	0 (0.0)	0 (0.0)
Arthralgia	5 (22.7)	**3 (13.6)**	0 (0.0)	0 (0.0)
Fatigue (asthenia)	6 (27.3)	**6 (27.3)**	**5 (22.7)**	0 (0.0)

Bold indicates clinically significant values

end of infusion, preventing accurate determination of noncompartmental PK parameters. The carboplatin pharmacokinetic parameters including clearance (CL), volume of distribution at steady state (Vss), and area under the concentration time curve from time zero to last quantifiable concentration collection time (AUC_{0-t}) or to infinity (AUC_{0-inf}) were not significantly altered by the coadministration of bexarotene (Table 3B). The geometric least square mean (GeoLSM) values of the plasma ultrafiltrate clearance (CL) of free (unbound) carboplatin with or without repeated one-daily dosing of bexarotene were 8.27 and 7.38 L/h/m^2, respectively. The free (unbound) carboplatin steady-state volume of distribution (Vss) GeoLSM values with or without bexarotene were 24.62 and 24.61 L/m^2, respectively. The GeoLSM values of AUC_{0-t} and AUC_{0-inf} of free carboplatin in the presence/absence of bexarotene were 79,613 versus 85,715 and 83,180 versus 91,388 ng h/mL, respectively.

Effect of paclitaxel plus carboplatin on bexarotene pharmacokinetics

The effect of the chemotherapeutic agents on bexarotene was studied by comparing its pharmacokinetic profile before and after paclitaxel plus carboplatin (day 21 and 22) in 16 evaluable patients. Five patients needed dose reduction of bexarotene prior to sampling for bexarotene pharmacokinetics, but all except two patients were on a stable dose during days 21 and 22. Data from four patients were excluded for bexarotene concentration analysis due to dosing prior to the scheduled dosing time or not taking bexarotene with food. An assessment of the differences in selected PK parameters across study periods using linear mixed-effect model was described in Table 3C for patients with PK data with and without paclitaxel and carboplatin. Bexarotene C_{max} and AUC_{0-24} were significantly increased 100 and 80%, respectively, when concomitantly administered with paclitaxel and carboplatin ($P < 0.05$). The GeoLSM C_{max} without and with chemotherapy were 721.6 and 1,446.3 ng/mL, respectively, with a % ratio of GeoLSM of 200%, p.006. The AUC_{0-24} (ng h/mL) increased from 3,880.6 to 6,990.1 with a % ratio of GeoLSM of 180%, p.02. The dose-adjusted mean plasma bexarotene concentrations with and without paclitaxel and carboplatin are shown in Fig. 2, reflecting the increase in bexarotene levels with the addition of chemotherapy. The interactions between bexarotene and anti-lipid agents are reported in a separate manuscript.

Discussion

This study was designed to explore potential drug interactions with the combination of carboplatin/paclitaxel and

Table 3 Pharmacokinetic parameters of drug–drug interaction analysis

Comparison	Parameter	Treatment	GeoLSM	(%) ratio of GeoLSM	90% confidence interval	*P* value
A. Effect of bexarotene on paclitaxel PK ($n = 16$)	CL (L/h/m^2)	No bexarotene (day 1)	11.82			
		Plus bexarotene (day 22)	14.53	123	100.75–150.18	0.088
	Vss (L/m^2)	No bexarotene (day 1)	81.87			
		Plus bexarotene (day 22)	111.8	136.55	108–172.02	**0.029**
	AUC_{0-t} (ng h/mL)	No bexarotene (day 1)	16,657			
		Plus bexarotene (day 22)	13,483	80.94	66.24–98.92	0.083
	AUC_{0-inf} (ng h/mL)	No bexarotene (day 1)	16,929			
		Plus bexarotene (day 22)	13,761	81.29	66.58–99.25	0.088
	Free (unbound) carboplatin					
B. Effect of bexarotene on carboplatin PK ($n = 16$)	CL (L/h/m^2)	No bexarotene (day 1)	8.27			
		Plus bexarotene (day 22)	7.38	89.21	72.94–109.10	0.34
	Vss (L/m^2)	No bexarotene (day 1)	24.62			
		Plus bexarotene (day 22)	24.61	99.96	84.32–118.49	0.99
	AUC_{0-t} (ng h/mL)	No bexarotene (day 1)	79,613			
		Plus bexarotene (day 22)	85,715	107.67	92.17–125.77	0.425
	AUC_{0-inf} (ng h/mL)	No bexarotene (day 1)	83,180			
		Plus bexarotene (day 22)	91,388	109.87	95.66–126.19	0.256
	Total (bound and unbound) carboplatin					
C. Effect of chemotherapy on bexarotene ($n = 16$)	AUC_{0-t} (ng h/mL)	No bexarotene (day 1)	115,984			
		Plus bexarotene (day 22)	129,907	112	100.31–125.06	0.091
	*C*max (ng/mL)	No chemotherapy (day 21)	721.6			
		Plus chemotherapy (day 22)	1,446.3	200.42	134.38–298.92	**0.006**
	AUC_{0-24} (ng h/mL)	No chemotherapy (day 21)	3,880.6			
		Plus chemotherapy (day 22)	6,990.1	180.13	118.08–274.78	**0.02**
D. Effect of bexarotene on atorvastatin ($n = 8$)	C_{max} (ng/mL)	No bexarotene (day 1)	60.26			
		Plus bexarotene (day 22)	42.27	70.15	31.42–156.64	0.449
	AUC_{0-24} (ng h/mL)	No bexarotene (day 1)	346.8			
		Plus bexarotene (day 22)	182.78	52.7	31.96–86.90	**0.04**

Bold indicates statistically significant values

GeoLSM geometric least square mean, *CL* clearance, *Vss* volume of distribution at steady state, AUC_{0-t} area under the curve from time zero to last quantifiable concentration collection time, AUC_{0-inf} area under the curve from time zero to infinity, AUC_{0-24} area under the curve from time 0 to 24 h, C_{max} maximum observed concentrations

bexarotene with lipid-lowering agents. Based on a review of the metabolism of the drugs and the potential for drug interactions, the trial was conceived for a direct assessment of the effect of daily administration of bexarotene on paclitaxel, carboplatin, atorvastatin, and fenofibrate pharmacokinetics and the effect of these on bexarotene concentrations. A phase III trial exploring the efficacy of bexarotene when added to carboplatin and paclitaxel as first-line therapy for patients with advanced NSCLC was conducted contemporaneously with this trial to explore the efficacy of the combination. That trial was a randomized phase III study of carboplatin and paclitaxel given with or without bexarotene. The trial reported here was designed specifically to gather detailed PK interaction data on the combination.

There were no new or unexpected toxicities identified in this study. Known toxicities of carboplatin and paclitaxel including alopecia, neuropathy, anemia, and neutropenia were observed, but the incidence of these toxicities does not appear to be greater than that expected in patients who receive combination chemotherapy with carboplatin and paclitaxel without bexarotene [26]. As expected, hypertriglyceridemia was frequent and of the same magnitude as expected when bexarotene is used as a single agent. Three patients were withdrawn from trial due to hypertriglyceridemia, and it remains the most common and most significant toxicity associated with bexarotene. Median total cholesterol also increased after the start of bexarotene therapy, but the relative increase was less pronounced than the change in triglycerides. Prophylactic administration of

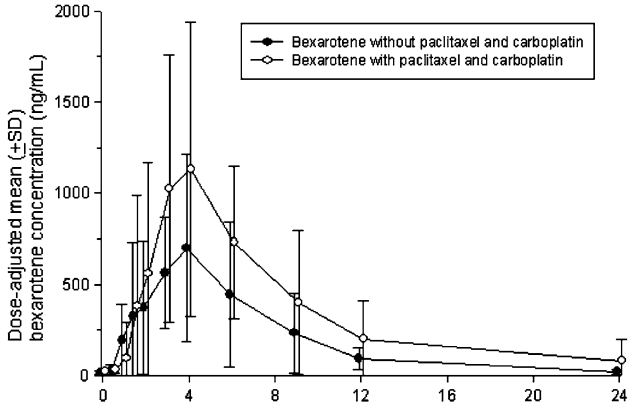

Fig. 2 Mean dose-adjusted (to 400 mg m^{-2}) plasma bexarotene concentrations with and without intravenous paclitaxel and carboplatin in patients ($N = 12$) with NSCLC

lipid-lowering drugs to control triglyceride levels was beneficial for the majority of patients. However, control of cholesterol and triglycerides levels in patients on bexarotene remains a challenge for many patients even with maximal doses of lipid-lowering agents.

The primary endpoint of this trial was the assessment of PK interactions. The results indicate that concomitant administration of bexarotene capsules with paclitaxel, a known CYP2C8 probe substrate [27], did not alter paclitaxel plasma concentrations.

Pharmacokinetic evaluation of drug–drug interactions between bexarotene and the chemotherapy agents determined that paclitaxel, free carboplatin, and total carboplatin concentrations were generally similar with or without bexarotene. Although paclitaxel's AUC was reduced by 19%, the differences were not statistically significant.

Coadministration of chemotherapy did, however, alter bexarotene pharmacokinetics as both the C_{max} and AUC of bexarotene were significantly increased (by 100 and 80%, respectively) with concomitant treatment with paclitaxel and carboplatin. This interaction can be considered a moderate interaction as outlined in the 2006 FDA Draft Guidance for Drug Interaction Studies [28]. Bexarotene is primarily eliminated through the hepatobiliary system, and CYP3A4 is the major cytochrome P450 responsible for the formation of the oxidative metabolites that are the first step in bexarotene metabolism. Paclitaxel is also partially metabolized by CYP3A4 [29]. However, in a clinical study, concomitant administration of bexarotene capsules with multiple doses of ketoconazole, a strong inhibitor of CYP3A4, did not alter bexarotene plasma concentrations (data on file, Eisai Inc.). This suggests that bexarotene elimination is not substantially dependent on CYP3A4 metabolism. Paclitaxel has been noted to be a weak inducer of CYP3A4, and carboplatin elimination is entirely renal. Thus, the increased Cmax and AUC of bexarotene documented in cycle 2 (with chemotherapy) cannot readily be explained. As carboplatin is renally excreted, no effect on bexarotene is expected. The predicted interaction with paclitaxel, which can weakly induce CYP3A4, should have, if anything, lead to a reduction in observed bexarotene C_{max} and AUC, not an increase. No additional toxicity was noted however. In addition, the half-life of bexarotene was decreased approximately twofold, apparent oral volume of distribution (Vz/F) decreased fivefold, and oral clearance (CL/F) decreased twofold suggesting a potential for alteration in bexarotene distribution with concomitant administration of paclitaxel and carboplatin. No significant alteration of bexarotene pharmacokinetics was seen when coadministered with cisplatin and vinorelbine, reported separately [30].

This study expands the current experience in the pharmacology of bexarotene in combination with chemotherapy. Two large randomized phase III trials of chemotherapy with or without bexarotene in advanced stage NSCLC failed to demonstrate an improvement in progression free or overall survival with the addition of the drug [22, 31], nor was substantial single agent activity of the drug seen in a phase II study in the disease [32]. Based on the results of this study, it is unlikely that a PK drug interaction between bexarotene and carboplatin or paclitaxel would explain the lack of efficacy seen in the phase III trial of this combination. The role of bexarotene in NSCLC is uncertain, but several studies are underway to further evaluate the activity of bexarotene in combination with targeted drugs such as erlotinib, rosiglitazone, and histone deacetylase (HDAC) inhibitors such as vorinostat [14, 33–39].

In conclusion, the concern of alteration of either paclitaxel or carboplatin pharmacokinetics when administered with bexarotene were not realized, and no recommendations could be made for changing the doses of paclitaxel or carboplatin when given in combination with bexarotene. On the other hand, bexarotene pharmacokinetics were altered when administered with paclitaxel and carboplatin combination with an increase in both maximum concentration and overall exposure. If this combination is explored further, precautions should be considered such as staggered administration that potentially may decrease or avoid this interaction due to the relatively short half-life of bexarotene (approximately 10 h) [40].

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Conflicts of interest Dr. Arturo Lopez-Anaya was an employee of Eisai, Inc. 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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