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ORIGINAL ARTICLE

Tanespimycin pharmacokinetics: a randomized dose-escalation crossover phase 1 study of two formulations

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Abstract
Purpose This crossover phase 1 study compared the pharmacokinetics and safety of tanespimycin, an HSP90 inhibitor, when administered as a suspension for injection and tanespimycin injection, a Cremophor-based formulation.
Methods Two sequential dose groups (275 mg/m^2 [$n = 5$] and 340 mg/m^2 [$n = 12$]) were randomized to first receive tanespimycin as a suspension or Cremophor-based formulation infusion followed 7 days later by the other formulation. Serial blood samples were collected over a 24-h period on days 1 and 8 to measure pharmacokinetics of tanespimycin and its major metabolite 17-AG. Patients completing the crossover phase continued treatment with the suspension formulation twice weekly for 2 out of 3 weeks.
Results Estimates for tanespimycin CLT (12.76 to 17.28 L/h/m^2), Vz (69.54 to 78.51 L/m^2) and t1/2 (3 to 4 h) were consistent across doses and formulations. AUC ratio of 17-AG to tanespimycin was approximately 60% in the 275 mg/m^2 treatment arm and 93% to 117% in the 340 mg/m^2 treatment arm. For the 340 mg/m^2 treatment arm, AUC(INF) was similar between both formulations; Cmax was 17% lower for the suspension versus the injection formulation. The most common adverse events were diarrhea, nausea, vomiting, dizziness, headache, fatigue, and elevated aspartate aminotransferase. Drug-related myelosuppression was not observed. The best response was stable disease in 7 of 11 evaluable patients.
Conclusions The pharmacokinetics of tanespimycin and its major metabolite 17-AG were similar for the tanespimycin suspension for injection and the tanespimycin injection, a Cremophor-containing product. Tanespimycin was well tolerated when administered as a suspension formulation.

Keywords Pharmacokinetics · HSP90 · Tanespimycin · Suspension · Safety

Introduction

Heat shock protein 90 (HSP90) is a molecular chaperone for proteins involved in cell signaling, proliferation, and survival. Many HSP90 client proteins including BCR-ABL, FLT3, B-Raf, KIT protein, epidermal growth factor receptor (EGFR), and androgen receptor are closely involved in the oncogenic process [14]. Selective depletion of these molecules with HSP90 inhibitors can result in growth arrest and apoptosis and increase the vulnerability of cancer cells to chemotherapeutic interventions. HSP90 has therefore emerged as an important target for the treatment of cancer because of its ability to affect multiple oncogenic pathways and involved proteins [2, 28]. In preclinical models, tanespimycin has antitumor activity against a wide range of solid and hematologic malignancies [4, 12, 15, 25, 27, 30].

Geldanamycin is a natural product that binds a conserved region of HSP90 and inhibits its ATPase function. This prevents the binding and release of chaperone proteins, leading to destabilization and degradation of client proteins and interference with cell survival [1, 10, 23, 24,

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31]. Tanespimycin (17-allylamino-17-demethoxygeldanamycin, 17-AAG) is a less toxic geldanamycin derivative that binds to and inhibits the activity of HSP90 [25]. Tanespimycin is metabolized by CYP3A4 to 17-aminogeldanamycin (17-AG), an active metabolite that also binds HSP90 and disrupts its chaperone function [6, 7, 11]. Tanespimycin is administered as an intravenous infusion with absolute bioavailability of 100%. Ex vivo experiments using plasma from cancer patients demonstrated that tanespimycin and 17-AG were approximately 94 and 92% protein bound, respectively [9]. Tanespimycin is primarily excreted in the bile with <3% of the administered dose excreted in the urine.

Phase 1 clinical studies in patients conducted by the National Cancer Institute with advanced cancer using a dimethyl sulfoxide (DMSO)/egg phospholipid formulation of tanespimycin as monotherapy have evaluated different treatment schedules including once weekly [3, 8, 13, 18], 2 days a week [16, 17], and 5 days a week [9, 26]. These studies demonstrated the safety of tanespimycin as monotherapy, and antitumor activity was observed. Initial studies of tanespimycin in combination with other antitumor agents have yielded encouraging results. The combination of tanespimycin and trastuzumab showed meaningful antitumor activity in women with HER2-positive, trastuzumab-refractory metastatic breast cancer [13], and early studies with tanespimycin alone or in combination with bortezomib showed clinical benefit in patients with relapsed or refractory multiple myeloma [19, 21].

To improve aqueous solubility, parenteral formulations of tanespimycin contain organic excipients such as polyoxyl castor oil (Cremophor EL®, BASF Corporation, Ludwigshafen, Germany), DMSO, or ethanol. Cremophor can cause mild to potentially life-threatening hypersensitivity reactions, and its use requires pretreatment with antihistamines and steroids [5], whereas DMSO is associated with systemic toxicity, including gastrointestinal, cardiac, and pulmonary side effects [22]. These excipients may confound the true maximum tolerated dose of tanespimycin in clinical trials, and hence alternative formulations have been investigated. The Cremophor-based tanespimycin formulation was manufactured by Kosan Biosciences, Hayward, CA. The decision to use a suspension-based formulation consisting of tanespimycin in polysorbate 80, lecithin, and sucrose (suspension formulation) was based on the extensive known safety issues of Cremophor hypersensitivity reaction. The cremophor hypersensitivity would create a disadvantage for tanespimycin in myeloma where many drugs are oral.

This comparison study was performed to evaluate the safety and pharmacokinetics of the suspension formulation in patients with advanced solid tumors. The primary objective was to compare the safety and pharmacokinetics of the tanespimycin suspension with the Cremophor-based formulation. Secondary objectives were to evaluate the safety of the tanespimycin suspension formulation after single and repeat doses and to determine plasma concentrations and single-dose pharmacokinetics of tanespimycin and its major metabolite 17-AG following administration of each formulation.

Patients and methods

Study design

This was a single-center, open-label, randomized, dose-escalating, crossover trial with a continuation phase (Fig. 1). During the crossover phase, patients were randomized to receive tanespimycin intravenously as either a Cremophor-based formulation or as a suspension formulation as their first infusion. After a 7- to 10-day rest, the patients received the other formulation. Two dose groups were investigated: in cohort 1, the 275 mg/m^2 tanespimycin dose was administered over 1 h; in cohort 2, the 340 mg/m^2 tanespimycin dose was administered over 2 h. The 340 mg/m^2 dose was chosen because it was well tolerated, modulated Hsp90 and 20S proteosome biomarkers, and demonstrated antitumor activity. If the lower dose was tolerated in a group of 3 to 6 evaluable patients without dose-limiting toxicity (DLT), a second group of 6 to 12 evaluable patients received the higher dose of each formulation in a randomized crossover manner. Patients were considered evaluable if they received 1 infusion of each formulation and had undergone 24-h postinfusion pharmacokinetic sampling.

Patients completing the crossover phase were eligible to continue to receive treatment with the suspension formulation twice weekly on days 1, 4, 8, and 11 of each 21-day cycle for as long as they derived benefit from treatment. Continuation treatment was initiated 7 to 14 days after completion of the crossover phase. Patients in the low-dose cohort of the crossover phase continued to receive 275 mg/m^2 until the safety of the higher dose was demonstrated in at least 6 patients, after which they could receive the higher dose. All patients received prophylaxis with H_1 and H_2 antagonists and dexamethasone before infusion of the Cremophor-based formulation. No prophylaxis preceded administration of the suspension formulation.

Patients were screened for eligibility no more than 28 days prior to the start of treatment, and baseline assessments were performed within the 10 days preceding initiation of treatment. Safety assessments were performed prior to and after each infusion and at each visit. Laboratory tests (hematology, chemistry, coagulation tests, and urinalysis) were performed prior to and 48 h after each

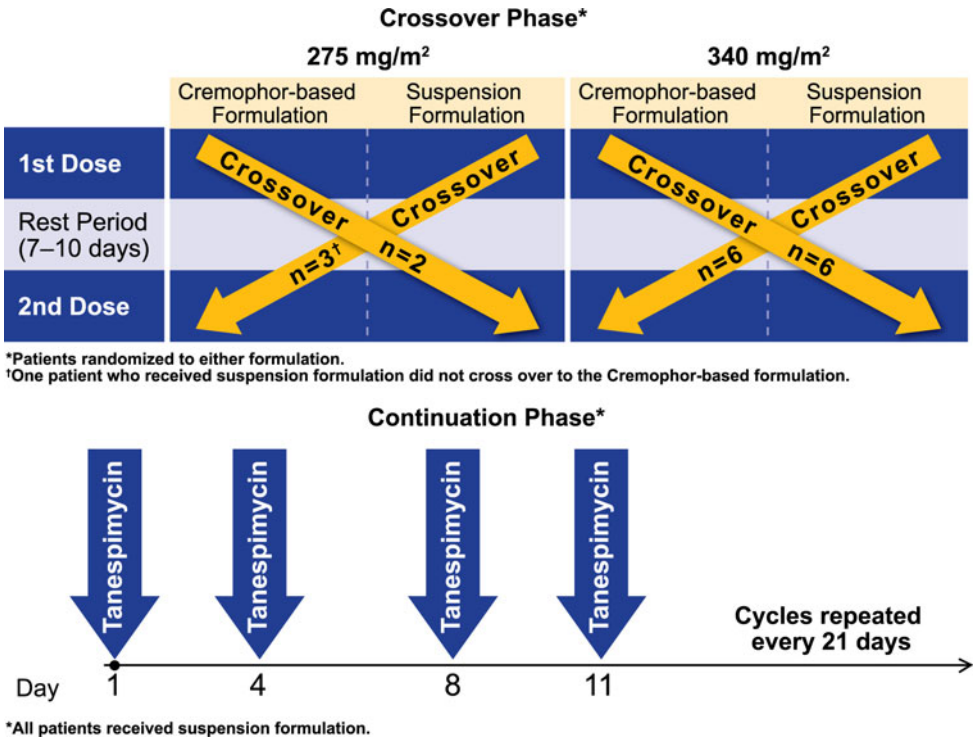

Fig. 1 Study design

infusion during the crossover phase and prior to each treatment cycle and on day 11 during the continuation phase.

The study was approved by the Ethics Committee and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients gave written informed consent to participate in the study.

Tanespimycin formulations

The Cremophor-based formulation contained tanespimycin 10 mg/mL dissolved in 30% propylene glycol, 20% Cremophor EL, and 50% ethanol with further dilution of 1:7 in water for injection prior to administration. Tanespimycin suspension contained tanespimycin 50 mg/mL dissolved in 1% polysorbate 80, 0.25% lecithin, and 10% sucrose; this formulation was further diluted 1:10 in 5% dextrose prior to administration. Both formulations were manufactured and provided by Kosan.

Patient population

The study included adult patients with histologically confirmed solid tumors, Karnofsky performance status $\geq$70%, and with adverse events (AEs) from previous therapies resolved to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0 Grade 2 or lower (with the exception of alopecia). Other eligibility requirements were serum bilirubin $\leq$ upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 $\times$ ULN, hemoglobin $\geq$8.5 g/dL, absolute neutrophil count (ANC) $\geq$ 1.5 $\times$ 10^9/L, and platelet count $\geq$75 $\times$ 10^9/L, all measured within 10 days of tanespimycin administration.

Patients were excluded if they had prior severe hypersensitivity reaction to Cremophor or polysorbate 80; central nervous system metastases; received any anticancer agents within 14 days of the study or nitrosourea within 6 weeks; major surgery in preceding 14 days; cardiovascular disease including New York Heart Association (NYHA) class III or class IV, active ischemia within 12 months, or cardiac arrhythmias; or were pregnant or breast feeding. Medications known to interact with CYP3A4 or CYP2C19 were prohibited. GM-CSF was not allowed, but antiemetics, antidiarrheals, G-CSF, and erythropoietin were permitted at the discretion of the treating physician.

Pharmacokinetics

Blood samples were collected on days 1 and 8 after administration of either formulation at the following times: predose, 30 min intrainfusion, just before the end of infusion, and 0.08-, 0.25-, 0.5-, 1-, 2-, 4-, 6-, 8-, and 24-h postinfusion. Plasma concentrations of tanespimycin and its major metabolite 17-AG were quantified by liquid

chromatography/mass spectrometry/mass spectrometry (LC–MS/MS). The lower limit of quantification was 10.0 ng/mL for tanespimycin and 5.0 ng/mL for 17-AG.

Safety and efficacy

AEs were graded by the investigator using CTCAE v3.0, and tumor responses and disease progression were determined using the Response Evaluation Criteria in Solid Tumors (RECIST) [29].

Statistical analyses

The safety population consisted of all patients who received at least 1 infusion of either formulation and completed 24-h postinfusion pharmacokinetic sampling. Descriptive statistics and frequency distributions were used to summarize patient characteristics, pharmacokinetic variables, and toxicity patterns.

Non-compartmental analyses were performed for estimation of pharmacokinetic parameters using the Kinetica® software package (Thermo Fisher Scientific Inc., Waltham, MA) The following pharmacokinetic parameters were calculated for tanespimycin and 17-AG: maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the concentration/time curve extrapolated to infinity (AUC[INF]), sum of exposure in terms of AUC(INF) for tanespimycin and 17-AG (AUC[SUM]), ratio of AUC(INF) of 17-AG to tanespimycin (AUC Ratio), total body clearance (CLT, for tanespimycin only), volume of distribution (Vz, for tanespimycin only), and half-life (t1/2).

Pharmacokinetic parameters were summarized descriptively by treatment and formulation. Comparison of the 2 formulations for the 340 mg/m^2 treatment was made based on log-transformed data for individual patients acting as their own control. The mixed effects ANOVA model contains fixed effects for sequence, period, and formulation, and a random effect for patients nested in sequence. The geometric mean ratios and 90% confidence intervals (CIs) of tanespimycin Cmax, and AUC(INF) comparing the 2 formulations were calculated.

Results

Patients

A total of 17 patients were enrolled in the study; 5 in cohort 1 and 12 in cohort 2 (Table 1). In the crossover phase, all patients received the suspension, whereas 1 patient in cohort 1 did not receive the Cremophor-based formulation. Fourteen patients entered the continuation phase, 3 in cohort 1 and 11 in cohort 2. The main reasons for study discontinuation were disease progression ($n = 7$, 41%), development of unacceptable toxicity all unrelated to study drug ($n = 4$, 24%), and death ($n = 3$, 18%).

The median age of patients was 63.0 years (range, 36–80), 77% were women, and all were white (Table 2). The most common primary diagnoses were breast cancer ($n = 5$) and non-small cell lung cancer ($n = 2$). All patients had received previous systemic therapy, and a majority had also had surgery or received radiotherapy.

Pharmacokinetics

Plasma concentration/time profiles of tanespimycin and 17-AG after administration of the suspension formulation and the Cremophor-based formulation at doses of 275 mg/m^2 and 340 mg/m^2 are shown in Fig. 2a and b. Profiles for the 2 formulations were similar. For both tanespimycin and 17-AG, the plasma concentration/time curves showed biexponential decay with rapid distribution followed by a slower elimination phase. The concentration/time profile for the metabolite 17-AG was more prolonged compared with the parent drug. Plasma concentrations of tanespimycin peaked at the end of infusion, with 17-AG peaking 60 to 90 min later.

Pharmacokinetic parameters for both formulations of tanespimycin are shown in Table 3. Systemic exposure in terms of Cmax and AUC(INF) increased at the 340 mg/m^2 dose. Peak concentrations of tanespimycin occurred primarily at the end of infusion with Tmax of 1 h. In cohort 1, the geometric mean estimates of CLT in the suspension and Cremophor-based formulations were 15.95 and 17.28 L/h/m^2, and in cohort 2, 16.39 and 16.05, respectively. The

Table 1 Patient enrollment

	Cohort 1 275 mg/m^2 $n = 5$	Cohort 2 340 mg/m^2 $n = 12$	Total $n = 17$
Safety population, *n* (%)			
Received suspension	5 (100)	12 (100)	17 (100)
Received Cremophor-based formulation	4 (80)	12 (100)	16 (94)
Enrolled in continuation phase, *n* (%)	3 (60)	11 (92)	14 (82)

Table 2 Patient demographics and baseline characteristics

	Cohort 1 275 mg/m^2 $n = 5$	Cohort 2 340 mg/m^2 $n = 12$	Total $n = 17$
Median age (range), y	62.0 (37–69)	64.5 (36–80)	63.0 (36–80)
Gender, *n* (%)			
Women	3 (60.0)	10 (83.3)	13 (76.5)
Race, *n* (%)			
White	5 (100.0)	12 (100.0)	17 (100.0)
Ethnicity, *n* (%)			
Hispanic or Latino	1 (20.0)	0 (0.0)	1 (5.9)
Not Hispanic or Latino	4 (80.0)	12 (100.0)	16 (94.1)
Primary diagnosis, *n* (%)			
Breast cancer	2 (40)	3 (25)	5 (29)
Non-small cell lung cancer	0 (0)	2 (17)	2 (12)
Larynx	0 (0)	1 (8)	1 (6)
Unknown primary	0 (0)	4 (33)	4 (24)
Other[a]	3 (60)	2 (17)	5 (29)
Previous therapy[b], *n* (%)			
Radiotherapy	3 (60.0)	7 (58.3)	10 (58.8)
Surgery	4 (80.0)	8 (66.7)	12 (70.6)
Systemic therapy	5 (100.0)	12 (100.0)	17 (100.0)

[a] Ampulla of vater, nasopharanx, urothelial, endometrial, neuroendocrine

[b] Patients could have more than 1 previous therapy

geometric mean estimates for Vz in the suspension and Cremophor-based formulations were 84.23 and 69.54 L/m2 in cohort 1 and 74.22 and 66.81 L/m^2 in cohort 2, respectively. Clearance (CLT) and Vz were comparable for the injection and suspension formulations within both cohorts. Terminal elimination t1/2 ranged from approximately 3 to 4 h.

Table 4 shows the pharmacokinetic parameters for 17-AG. Systemic exposure in terms of Cmax and AUC(INF) increased with the 340 mg/m^2 tanespimycin dose. Peak concentrations of 17-AG occurred after the end of the tanespimycin infusion with a median Tmax ranging from 1 to 2 h. The elimination t1/2 for 17-AG (approximately 5 h) was slightly longer than that of tanespimycin. The AUC ratio of 17-AG to tanespimycin was approximately 61 to 70% following administration of the 275 mg/m^2 treatment and increased to approximately 93–117% following administration of the 340 mg/m^2 treatment.

The geometric mean ratios and their associated 90% CIs comparing the pharmacokinetic parameters of tanespimycin and 17-AG following administration of the 340 mg/m^2 dose are summarized in Table 5. Following administration of the 340 mg/m^2 dose, tanespimycin AUC(INF) appears to be comparable, since the point estimates for the geometric mean ratios are 0.97 and the 90% CIs for the geometric mean ratios are within the 0.80 and 1.25 range. Tanespimycin Cmax for the suspension appears to be 17% lower than the injection.

Safety

During the crossover phase, the numbers and types of AEs overall and AEs Grade ≥3 were similar after administration of both formulations (Table 6). In the 340 mg/m^2 dose group, the most frequently reported treatment-emergent AEs (defined as any event not present before treatment or any event already present that worsens after exposure to the treatment) were diarrhea, nausea, vomiting, dizziness, headache, and elevated AST. Three patients in cohort 1 experienced ≥Grade 3 AEs while receiving the suspension formulation, and 8 patients in cohort 2 experienced ≥Grade 3 AEs (4 while receiving the suspension formulation and 4 while receiving the Cremophor-based formulation). One patient in cohort 1 experienced Grade 2 anemia during the crossover phase while receiving the Cremophor-based formulation. Another patient experienced Grade 5 disseminated intravascular coagulation (DIC) in the crossover phase while receiving the suspension formulation. The DIC AE was deemed unrelated to study medication. The patient also experienced septic shock with an eventual outcome of death.

In the continuation phase, three patients in cohort 1 received a median of 1 cycle of treatment (2 patients received 1 cycle and 1 patient received 11 cycles) and 11 patients in cohort 2 received a median of 2 cycles of treatment (range, 1–5 cycles). Diarrhea, vomiting, nausea, pneumonia, bacteremia/sepsis, fatigue, and elevated AST were the most common treatment-emergent AEs during the continuation phase. The most frequent treatment-emergent AEs Grade ≥3 were pneumonia, bacteremia/sepsis, and diarrhea. In all instances, the infections were deemed unrelated to study medication. No meaningful change in hematologic values, including ANCs, platelet counts, and hemoglobin, was observed during treatment. No hematologic toxicity Grade ≥3 was reported in any patient during the continuation phase.

Efficacy

Among 11 patients in whom antitumor responses could be evaluated, 7 patients had stable disease (duration, 4.1–35.6 weeks), and 4 patients experienced disease progression.

Discussion

This is the first clinical study to examine the pharmacokinetics and safety of the suspension formulation of

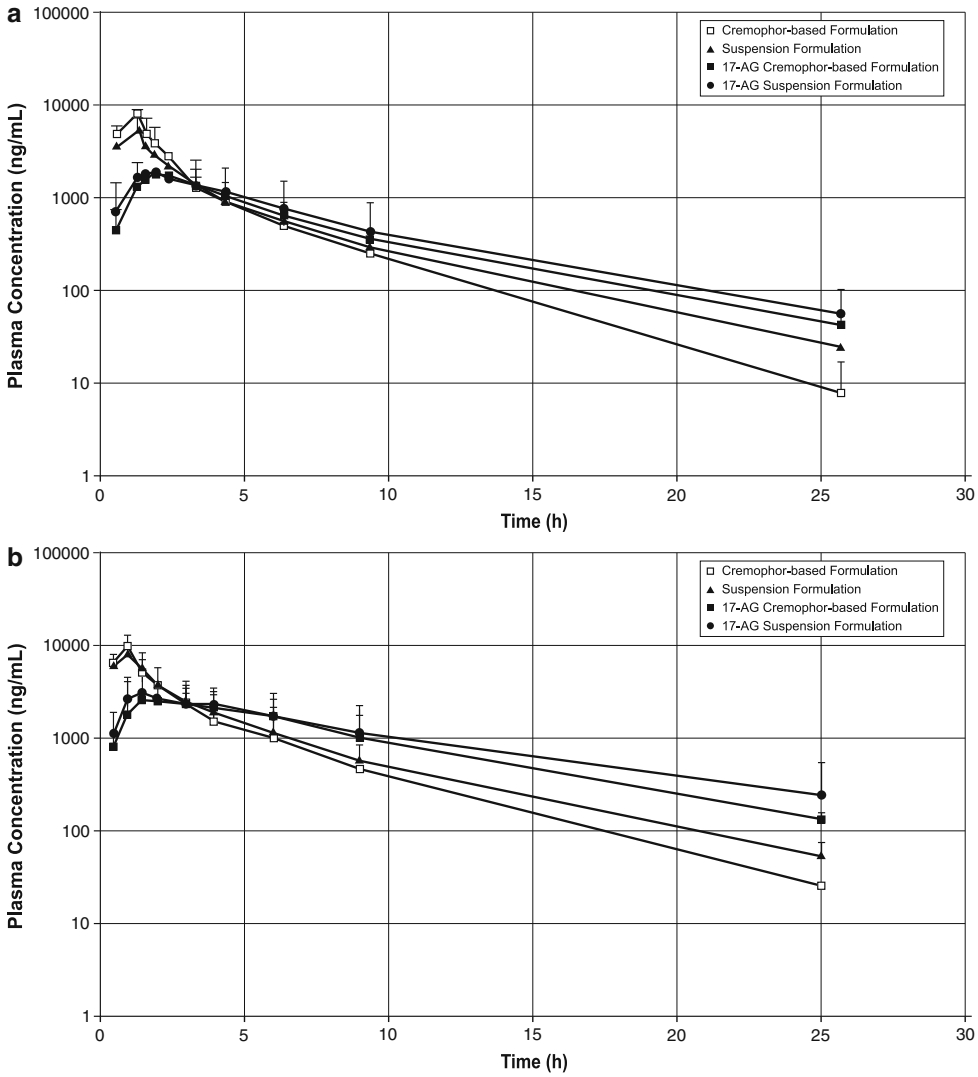

Fig. 2 **a** Plasma concentration: time profiles of tanespimycin and 17-AG after administration of tanespimycin 275 mg/m^2. **b** Plasma concentration/time profiles of tanespimycin and 17-AG after administration of tanespimycin 340 mg/m^2

Table 3 Geometric mean (% CV) tanespimycin pharmacokinetic parameters

Parameter	Cohort 1 275 mg/m^2		Cohort 2 340 mg/m^2	
	Suspension formulation $n = 5$	Cremophor-based formulation $n = 4$	Suspension formulation $n = 12$	Cremophor-based formulation $n = 12$
Mean t1/2 (SD), h	3.88 (1.40)	2.91 (0.94)	3.40 (1.48)	3.07 (1.10)
Cmax, ng/mL	5691.2 (43.6)	8030.5 (7.8)	8532.2 (31.2)	10263.1 (26.2)
Median Tmax (range), h	1 (1, 2)	1 (1, 2)	1 (0.5, 1.1)	1 (1.0, 1.1)
AUC(INF), ng h/mL	17184.8 (71.0)	15922.0 (29.9)	20768 (65.1)	21216 (47.6)
CLT, L/h/m^2	15.95 (63.48)	17.28 (23.2)	16.39 (44.3)	16.05 (44.8)
Vz, L/m^2	84.23 (46.52)	69.54 (29.8)	74.22 (28.2)	66.81 (34.6)

In cohort 1, 1 patient received only the suspension formulation

AUC(INF) area under the concentration/time curve from time zero extrapolated to infinity, *CLT* total body clearance, *Cmax* maximum observed concentration, *CV* coefficient of variation, *SD* standard deviation, *t1/2* terminal elimination half-life, *Tmax* time to reach Cmax, *Vz* volume of distribution

Table 4 Geometric mean (% CV) 17-AG pharmacokinetic parameters

Parameter	Cohort 1 275 mg/m^2		Cohort 2 340 mg/m^2	
	Suspension formulation $n = 5$	Cremophor-based formulation $n = 4$	Suspension formulation $n = 12$	Cremophor-based formulation $n = 12$
Mean t1/2 (SD), h	5.5 (1.6)	5.0 (0.5)	5.37 (1.73)	4.96 (1.24)
Cmax, ng/mL	1613.4 (70.4)	1515.1 (66.5)	3501.0 (44.5)	2478.6 (37.6)
Median Tmax (range), h	2 (1, 3)	2 (2, 2)	1.4 (1.1, 6)	2 (1.3, 6.1)
AUC(INF), ng h/mL	11372 (112)	9761 (44.5)	24304 (70.3)	19664 (57.9)
AUC ratio	0.70 (62.6)	0.61 (59)	1.17 (41.0)	0.93 (39.8)
AUC(SUM)	29343 (82.0)	26400 (21.8)	45951 (62.3)	41687 (46.3)

In Cohort 1, 1 patient received only the suspension formulation

AUC(INF) area under the concentration/time curve from time zero extrapolated to infinity, *AUC ratio* ratio of AUC(INF) of 17-AG to tanespimycin, *Cmax* maximum observed concentration, *CV* coefficient of variation, *SD* standard deviation, *t1/2* terminal elimination half-life, *Tmax* time to reach Cmax

Table 5 Comparison of the Pharmacokinetic parameters for tanespimycin and 17-AG between the suspension and injection formulations

Analyte	Parameter	Geometric mean ratio (suspension/injection)	90% Confidence interval
Tanespimycin	Cmax, ng/mL	0.83	0.71, 0.96
	AUC(INF), ng h/mL	0.97	0.85, 1.11
17-AG	Cmax, ng/mL	1.41	1.27, 1.58
	AUC(INF), ng h/mL	1.23	1.08, 1.40
Tanespimycin + 17-AG	AUC(INF), ng h/mL	1.09	0.96, 1.24

Pharmacokinetic analyses are based on 12 patients that received the 340 mg/m^2 dose

AUC(INF) area under the concentration/time curve from time zero extrapolated to infinity, *Cmax* maximum observed concentration

tanespimycin. The study shows that the pharmacokinetics of tanespimycin following administration of the suspension formulation is comparable to those of the Cremophor-based formulation. At the recommended 340 mg/m^2 phase 2 dose, both formulations were similar with respect to maximum plasma levels, total exposure, and elimination t1/2 of tanespimycin (3–4 h) and its major metabolite (5 h). Total exposure to active drug, reflecting combined exposure to both parent compound and metabolite, did not differ appreciably between the 2 formulations in 10 of 12 patients, although 2 patients showed increased exposure with the suspension formulation. The volume of distribution and total systemic clearance of tanespimycin were also comparable with both formulations. The large volume of distribution suggests that tanespimycin distributes into deep compartments such as fat or bone or is bound to a specific biological material.

The findings from this phase 1 clinical study corroborate the results from a similar preclinical comparison of the Cremophor-based and suspension formulations in dogs (Kosan Biosciences, data on file). The canine study demonstrated that pharmacokinetic parameters for both parent compound and active metabolite were similar for the 2 formulations.

The pharmacokinetic findings in this study for the 2 formulations are similar to results observed in patients with breast cancer treated with the Cremophor-based formulation (275–450 mg/m^2) in combination with trastuzumab [13]. A number of published NCI-sponsored phase 1 studies have used a formulation of tanespimycin containing DMSO with phospholipids. The pharmacokinetics in the current study appear to be comparable to those observed for doses between 300 mg/m^2 and 450 mg/m^2 in the phase 1 trials of the DMSO formulation. The t1/2, clearance, and distributive volumes were similar to those obtained from other phase 1 studies and were not related to dose [3, 26]. Values for Cmax, AUC, and t1/2 for tanespimycin and 17-AG were also comparable to those observed in earlier studies [16, 18, 26]. The considerable interpatient variability of Cmax and AUC that was noted in this study with the Cremophor-based and suspension formulations was also noted with the DMSO formulation [18].

AEs in the current study consisted primarily of gastrointestinal events and elevated hepatic enzyme levels. The

Table 6 Treatment-emergent adverse events in the crossover and continuation phases

Crossover phase	275 mg/m^2				340 mg/m^2			
	Cremophor-based formulation $n = 4$		Suspension formulation $n = 5$		Cremophor-based formulation $n = 12$		Suspension formulation $n = 12$	
Adverse event, *n*	All	Grades 3/4	All	Grades 3/4	All	Grades 3/4	All	Grades 3/4
Diarrhea	1	0	0	0	5	0	4	1
Nausea	1	0	1	0	4	0	2	0
Vomiting	0	0	2	0	2	0	1	0
Dizziness	0	0	0	0	1	0	2	0
Headache	0	0	0	0	2	0	1	0
Elevated AST	0	0	0	0	2	1	2	1
Elevated alkaline phosphatase	0	0	0	0	2	1	0	0

Continuation phase	Suspension formulation 275 mg/m^2 $n = 3$		Suspension formulation 340 mg/m^2 $n = 11$	
Adverse event, *n*	All	Grades ≥ 3	All	Grades ≥ 3
Diarrhea	0	0	8	2
Vomiting	2	0	6	0
Nausea	2	0	4	0
Abdominal distension	0	0	2	0
Pneumonia	0	0	3	3
Nasopharyngitis	0	0	2	0
Bacteremia/sepsis	0	0	3	3
Fatigue	1	0	3	1
Anorexia	0	0	2	0
Elevated AST	0	0	3	1
Elevated ALT	0	0	2	0
Anemia	0	0	2	0
Headache	1	0	2	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase

types of AEs noted during the crossover phase do not differ between the 2 formulations, although the frequency of AEs was higher with the higher dose of both formulations. Most toxicities were Grade 1 or 2. All 6 cases of Grade $\geq$3 pneumonia or bacteremia were deemed unrelated to treatment with tanespimycin. Neither formulation appears to be myelosupressive, consistent with the clinical toxicology. No meaningful changes in ANC, platelets, or hemoglobin were noted across the different formulations. Neutropenia and thrombocytopenia were both recorded as an AE in 1 patient each, with both cases being Grade 2.

These toxicity results and the types of AEs observed compare favorably with those noted in previous phase 1 studies in which tanespimycin was administered twice weekly using the DMSO formulation. In these studies, the primary toxicities were nausea, vomiting, diarrhea, anorexia, fatigue, and transient elevations in liver enzymes; hematologic toxicity was minimal [16, 17]. Grade 3/4 gastrointestinal AEs (i.e., nausea, vomiting, and diarrhea) and hepatic enzyme elevations were reported in several studies with the DMSO formulation [3, 8, 16–18].

Although this study was not designed to assess efficacy, stable disease was achieved in 7 of 11 patients. The antitumor response to tanespimycin monotherapy is consistent with findings from other studies that evaluated varying tanespimycin monotherapy regimens in patients with advanced cancers [3, 8, 9, 17, 18, 26]. The synergistic antitumor activity of tanespimycin and traditional or targeted antitumor agents suggests that tanespimycin may be effective as a sensitizer to other anticancer agents. This hypothesis has been substantiated in early clinical studies in patients with advanced multiple myeloma. Treatment with single-agent tanespimycin provided antitumor benefit [21], whereas a combination of bortezomib

and tanespimycin produced durable responses in both bortezomib-naive and bortezomib-refractory patients [20]. A combination of trastuzumab and tanespimycin also achieved objective tumor regressions in trastuzumab-resistant breast cancer patients [13].

The suspension formulation of tanespimycin provides several advantages over the Cremophor-based formulation. Because it is not associated with hypersensitivity reactions, the suspension formulation is easier and safer to use, and pretreatment with antihistamines and corticosteroids is not required. The osmolality of the diluted drug product is more physiological (approximately 260 mmol/kg), compared with 550 mmol/kg to 600 mmol/kg for the Cremophor-based formulation, and the suspension is more stable in the vial and after dilution. At a comparable dose, the infusion volume for the suspension is 3.5-fold smaller, which shortens the infusion time. The similarity in pharmacokinetics and active drug exposure of the Cremophor-based and suspension formulations supports the use of the suspension formulation in future clinical studies.

Conclusions

The pharmacokinetics of tanespimycin and its major metabolite are similar and independent of formulation when administered either as the suspension formulation or as the Cremophor-based formulation. Tanespimycin suspension is well tolerated and is not associated with any new safety concerns.

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