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ORIGINAL ARTICLE

Pharmacokinetics and antitumor activity of patupilone combined with midazolam or omeprazole in patients with advanced cancer

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Abstract
Purpose Patupilone is a novel microtubule-targeting cytotoxic agent with potential interaction with CYP3A4/CYP2C19 enzymes. Midazolam and omeprazole are primarily metabolized by CYP3A4 and CYP2C19, respectively. We evaluated the inhibitory effects of patupilone on the CYP3A4/CYP2C19 pathways.
Methods This study had 2 parts: in an initial core phase, patients were randomly assigned to receive midazolam 4 mg or omeprazole 40 mg PO (days 1 and 29) and patupilone 10 mg/m^2 IV (days 8 and 29). Patients without progression continued patupilone every 3 weeks until disease progression or unacceptable toxicity (extension phase).
Results Forty-six patients were treated. The areas under the concentration–time curves (AUC)s of midazolam with or without patupilone co-administration were similar. The C_{max} of midazolam when co-administered with patupilone was highly variable and was lower compared with midazolam alone; however, the oral clearance and terminal half-lives were similar. Both the C_{max} and AUC of omeprazole when co-administered with patupilone were highly variable and lower than with omeprazole alone. However, the oral clearance and terminal half-lives were similar. The latter data suggest that patupilone decreased the absorption of omeprazole (by $\sim$20%). The overall safety profile was consistent with that of previous single-agent patupilone studies; 2 partial responses (ovarian and pancreatic cancer) and 1 complete response (serous ovarian adenocarcinoma) were observed.
Conclusions Patupilone was not a potent CYP3A4 or CYP2C19 inhibitor. No dose adjustment is required when omeprazole or midazolam is used in patients treated with patupilone. Patupilone exhibited promising antitumor activity in heavily pretreated patients with ovarian and pancreatic cancer.

Keywords Patupilone · Solid tumors · Phase 1 · Pharmacokinetics · Midazolam · Omeprazole · Drug interaction

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Introduction

Patupilone is a novel microtubule-targeting cytotoxic agent that exerts its antitumor effect through microtubule stabilization, which eventually leads to apoptosis and cell death in

a manner similar to the effects of taxanes [5, 16]. However, patupilone is several times more potent than taxanes in vitro and appears to have a different β-tubulin-binding site than taxanes. Patupilone is not affected by common tumor-resistance mechanisms, including β-tubulin mutation and over-expression of drug efflux pumps such as P-glycoprotein [3, 11, 12]. Its antitumor activity has been demonstrated in several clinical trials with various tumor types, including ovarian, prostate, lung, and colon cancers [2, 4, 6, 9, 14, 18].

The metabolism of patupilone is characterized by hydrolytic and oxidative steps, and carboxyl esterase—catalyzed hydrolysis appears to be the major metabolic pathway in humans. However, based on in vitro data, patupilone is a moderate inhibitor of the human cytochrome P-450 isoenzymes CYP2C19 and CYP3A4 (both IC_{50} values are $\sim$5 μM) (Novartis Pharmaceuticals, unpublished data). Thus, patupilone may potentially alter the metabolism of drugs processed through these enzymes, but it is very unlikely that drugs metabolized through CYP3A4 and CYP2C19 would have an effect on patupilone metabolism because patupilone is mainly eliminated by carboxylesterases.

Midazolam and omeprazole are commonly used drugs that are metabolized through specific cytochrome P-450 pathways. Therefore, those drugs are used as prototypes (probe substrates) to study drug–drug interactions. Midazolam, a central nervous system depressant in the benzodiazepine class, is rapidly absorbed after oral administration and primarily metabolized by CYP3A4 to its major pharmacologically active metabolite, alpha-hydroxy-midazolam (1-hydroxy-midazolam) [10, 13]. Midazolam is used as a probe substrate for CYP3A4. Omeprazole, a proton-pump inhibitor indicated for the treatment of gastric or duodenal ulcer and gastroesophageal reflux disease, is metabolized by CYP2C19 to one of its major metabolites, 5-hydroxy-omeprazole [1]. Omeprazole is used as a probe substrate for CYP2C19.

The primary objective of this study was to evaluate the effects of patupilone on the pharmacokinetics (PK) of midazolam or omeprazole in patients with advanced malignancies. The secondary objectives of this study were to evaluate the safety and tolerability of patupilone when administered concomitantly with midazolam or omeprazole. The objectives of the extension phase were to determine the safety, tolerability, and potential activity of patupilone administered intravenously once every 21 days at a dose of 10 mg/m^2 in patients with advanced cancer.

Patients and methods

Patient eligibility

Eligibility criteria included a documented advanced solid tumor that failed prior standard therapy or for which no standard therapy existed; age $\geq$18 years; World Health Organization (WHO) performance status 0–2; adequate bone marrow (absolute neutrophil count $\geq 1.5 \times 10^9$/l, hemoglobin $\geq$10.0 g/dl, and platelet count $\geq 100 \times 10^9$/l); alkaline phosphatase $\leq 1.0 \times$ the upper limit of normal (ULN); adequate liver function (alanine transaminase (ALT) and aspartate transaminase (AST) $\leq 1 \times$ ULN); total bilirubin $\leq$ ULN; adequate renal function (serum creatinine level $< 2 \times$ ULN); and albumin level $\geq$2.5 g/dl. Patients with bone metastases who had an ALP $\geq 4 \times$ ULN were eligible if their ALT, AST, and total bilirubin levels were within the normal range. Patients were excluded if they were pregnant or breast-feeding; had hypersensitivity to midazolam, omeprazole, or related compounds; were using central nervous system depressants or opiate drugs; had severe and/or uncontrolled medical disease; were previously treated with epothilone; had a diagnosis of HIV infection; had undergone a colostomy procedure; had symptomatic brain metastases or leptomeningeal disease; had peripheral neuropathy > grade 1; had received anticancer therapy or radiation therapy or undergone major surgery within 28 days prior to study entry; had unresolved diarrhea 7 days prior to treatment; or were on hematopoietic growth factors, except erythropoietin.

Patients were recruited at The University of Texas MD Anderson Cancer Center (MD Anderson), Houston, TX; Fox Chase Cancer Center, Philadelphia, PA; University of California San Diego, Moores Cancer Center, San Diego, CA; and Sarah Cannon Cancer Center, Nashville, TN. Signed informed consent was obtained from all participants in accordance with institutional policies. The study was approved by the respective institutional review boards and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines on Good Clinical Practice.

Treatment plan

This was a multi-center, open-label, drug–drug interaction study. In the core phase of the study, patients were randomly assigned (using an automated randomization system—created list) to receive midazolam or omeprazole at a ratio of 1:2, respectively, concomitantly with patupilone. Patupilone (10 mg/m^2 intravenously over 20 min) was administered on days 8 and 29 and subsequently (extension phase) every 3 weeks. Omeprazole (40 mg orally) or midazolam (4 mg orally) alone was administered on day 1 and concomitantly with patupilone on day 29. Patients who may have been benefiting from patupilone treatment (as reflected by stable disease or tumor regression) were allowed to continue to receive additional cycles of patupilone every 3 weeks until progression of disease, death, or unacceptable toxicity occurred (extension phase). All

patients were evaluable for safety and pharmacokinetic analysis.

Blood sample collection and analytical assays

Blood samples

Plasma concentrations of midazolam and its metabolite 1-hydroxy-midazolam and of omeprazole and its metabolite 5-hydroxy-omeprazole were measured when midazolam or omeprazole was administered alone or concomitantly with patupilone. Blood samples were collected immediately prior to the administration of each agent. After the administration of midazolam, serial blood samples (3 ml each) were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h post-midazolam dose on days 1 and 29. After the administration of omeprazole, serial blood samples (5 mL each) were collected at 20 min, 40 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h post-omeprazole dose on days 1 and 29.

Blood samples were also collected to determine patupilone pharmacokinetics. Blood samples (4 ml each) were collected at 504 h post-patupilone dose on days 29 (prior to cycle 2 of patupilone administration) and 50 (prior to patupilone administration in cycle 3).

Analytical assays

Blood concentrations of patupilone were determined using a liquid chromatography–mass spectrometry (LC/MS/MS) method described previously [14]. Plasma concentrations of midazolam and its metabolite 1-hydroxy-midazolam were also determined using the LC/MS/MS method (SGS Cephac Europe, France). The lower limit of quantitation was 0.10 ng/ml, and the linearity of the analytical methods in blood was validated (range from 0.10 to 100 ng/ml). The internal standard for midazolam and 1-hydroxy-midazolam in these assays was alprazolam. Within-study assay validation at nominal midazolam and 1-hydroxy-midazolam concentrations of 0.3, 30, and 80 ng/ml showed an assay precision (coefficient of variation) of 4.5–8.7% for midazolam and 5.7–9.1% for 1-hydroxy-midazolam. The bias was −1.7 to 1.7% for midazolam and −3.3 to −1.8% for 1-hydroxy-midazolam.

Plasma concentrations of omeprazole and its metabolite 5-hydroxy-omeprazole were also determined using the LC/MS/MS method. The lower limit of quantitation was 2.0 ng/ml, and the linearity of the analytical methods in blood was validated (range from 2.0 to 2,000 ng/ml). The internal standard for omeprazole and 5-hydroxy-omeprazole in these assays was omeprazole-D_3. Within-study assay validation at nominal omeprazole and 5-hydroxy-omeprazole concentrations of 5, 800, and 1,600 ng/ml showed an assay precision (coefficient of variation) of 5.3–7.3% for omeprazole and 5.6–11% for 5-hydroxy-omeprazole. The bias was 4.4–9.2% for omeprazole and 2.6–6.3% for 5-hydroxy-omeprazole.

Pharmacokinetic parameters

Pharmacokinetic parameters determined for midazolam, 1-hydroxy-midazolam, omeprazole, and 5-hydroxy-omeprazole were area under the concentration–time curve (AUC) from 0 to 48 h for midazolam and 1-hydroxy-midazolam and from 0 to 12 h for omeprazole and 5-hydroxy-omeprazole, time (T_{max}) to reach the maximum plasma concentration (C_{max}), apparent total plasma clearance for midazolam or omeprazole (CL/F), and the terminal half-life ($T_{1/2}$). These pharmacokinetic parameters were calculated by standard non-compartmental analysis and a linear trapezoidal method using WinNonlin® 5.2 (Pharsight, Mountain View, CA). The pharmacokinetic parameter determined for patupilone was the blood concentration at 504 h post-dose (C_{min}) on days 29 and 50.

Statistical analysis

Statistical comparisons of log-transformed AUC and C_{max} were performed via a linear mixed effects model using the SAS® procedure PROC MIXED (SAS Institute Inc., Cary, NC). The geometric mean ratios for AUC and C_{max} with associated 90% confidence intervals (CIs) for co-administration of midazolam plus patupilone compared with midazolam alone and co-administration of omeprazole plus patupilone compared with omeprazole alone were determined using the above model.

Safety and efficacy assessments

Patients were assessed at screening, prior to each administration of treatment (patupilone and midazolam or omeprazole) and at the end of study. Safety assessments consisted of monitoring and recording all adverse events, including serious adverse events; regular monitoring of hematology, coagulation profile, blood chemistry and urine, vital signs, and performance status; and physical and neurological examinations. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used to grade toxicity. Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. Tumor assessments were performed at baseline, at the end of the core study (day 50), and subsequently, every 2 cycles (1 cycle = 3 weeks).

Results

Patient demographics

From November 2006 to August 2008, 46 patients with advanced cancer were enrolled (25 from MD Anderson, 8 from Fox Chase Cancer Center, 8 from the University of California San Diego, and 5 from Sarah Cannon Cancer Center), of whom 18 were randomized to the midazolam arm and 28 to the omeprazole arm.

Patient characteristics are summarized in Table 1. The median ages were 59.5 and 62.5 years for the midazolam and omeprazole arms, respectively. Most patients (95.7%) had a WHO performance status of 0 or 1 at study entry. The median time from initial diagnosis was 36.1 months, and 28 (60.9%) patients had received ≥4 prior systemic antineoplastic therapies.

Treatment

Thirty of the 46 patients completed the core study; eight of 18 (44.4%) patients in the midazolam arm and 8 of 28 (28.6%) patients in the omeprazole arm discontinued treatment prematurely. Sixteen of the 30 patients who completed the core phase entered the extension phase. The major reasons for discontinuation in both the core and the extension phases were adverse events and disease progression. The reasons for discontinuation are shown in Table 2.

Pharmacokinetics of patupilone

This study determined only the trough (504 h post-dose) concentrations of patupilone following a 20-min intravenous infusion administered at 10 mg/m^2 every 3 weeks. The mean trough blood concentrations of patupilone in the midazolam and omeprazole arms were 0.82 ± 0.78 and 1.28 ± 2.19 ng/ml, respectively.

Pharmacokinetics of midazolam and its metabolite 1-hydroxy-midazolam

The mean plasma concentration versus time profiles of midazolam following oral administration of 4 mg midazolam in the presence or absence of 10 mg/m^2 patupilone are presented in Fig. 1a. Plasma concentrations of midazolam were unchanged by co-administration with patupilone on day 29. The pharmacokinetic parameters of midazolam are summarized in Table 3. The AUC of midazolam (70 ± 41 ng h/ml) when co-administered with patupilone was similar to that of midazolam alone (86 ± 76 ng h/ml). The geometric mean ratio of midazolam plus patupilone to midazolam alone for AUC was 1.0. The 90% CI for this geometric mean ratio was not within the equivalence limits of 0.80 and 1.25 owing to the large variability (coefficient of variance ranged from 78 to 97%). The C_{max} of midazolam (17 ± 9 ng/ml) when co-administered with patupilone was highly variable and slightly lower than that of midazolam alone (24 ± 10 ng/ml), and the 90% CI for the geometric mean ratio for C_{max} was not within the equivalence limits of 0.80 and 1.25 (Table 3). The oral clearance (83 ± 59 l/h) and terminal half-life (5.6 ± 2.1 h) of midazolam following co-administration with patupilone were similar to those of midazolam alone (82 ± 71 l/h and 6.5 ± 3.7 h, respectively).

The mean plasma concentration versus time profiles of 1-hydroxy-midazolam following oral administration of 4 mg midazolam in the presence or absence of 10 mg/m^2 patupilone are presented in Fig. 1b. Plasma concentrations of 1-hydroxy-midazolam were unchanged by co-administration with patupilone. The pharmacokinetic parameters of 1-hydroxy-midazolam are summarized in Table 3. The AUC (24 ± 25 ng h/ml) and C_{max} (6.9 ± 5.5 ng/ml) of 1-hydroxy-midazolam after co-administration of midazolam and patupilone were highly variable and slightly lower than those of midazolam alone (26 ± 22 ng h/ml and 9.9 ± 6.4 ng/ml, respectively), and the 90% CI for the geometric mean ratio of co-administration versus midazolam alone for AUC and C_{max} of 1-hydroxy-midazolam were not within the equivalence limits of 0.80 and 1.25 owing to the large variability (coefficient of variance ranged from 67 to 116%). The terminal half-life (5.3 ± 2.3 h) of 1-hydroxy-midazolam following co-administration of midazolam and patupilone was similar to that following treatment with midazolam alone (5.7 ± 2.9 h).

Pharmacokinetics of omeprazole and its metabolite 5-hydroxy-omeprazole

The mean blood concentration versus time profiles of omeprazole following oral administration of 40 mg omeprazole in the presence or absence of 10 mg/m^2 patupilone are presented in Fig. 1c. Blood concentrations of omeprazole when administered with patupilone were slightly lower than those of omeprazole alone. The pharmacokinetic parameters of omeprazole are summarized in Table 4. Both the C_{max} (1,029 ± 449 ng/ml) and AUC (3,781 ± 2,239 ng h/ml) of omeprazole co-administered with patupilone were highly variable and slightly lower than those of the omeprazole control (1,139 ± 613 and 4,227 ± 2,932 ng h/ml, respectively), and the 90% CI for the geometric mean ratios of co-administration to omeprazole alone for C_{max} and AUC was not within the equivalence limits of 0.80 and 1.25 (Table 4). However, the oral clearance (16 ± 17 l/h) and terminal half-life

Table 1 Pretreatment patient characteristics

Characteristics	Midazolam + patupilone $N = 18$ (%)	Omeprazole + patupilone $N = 28$ (%)	All patients $N = 46$ (%)
Median age, years	59.5	62.5	62.0
Gender			
Male	7 (38.9)	15 (53.6)	22 (47.8)
Female	11 (61.1)	13 (46.4)	24 (52.2)
Race			
Caucasian	14 (77.8)	26 (92.9)	40 (87.0)
Black	1 (5.6)	1 (3.6)	2 (4.3)
Asian	1 (5.6)	0 (0.0)	1 (2.2)
Other	2 (11.1)	1 (3.6)	3 (6.5)
Performance status (WHO)			
0	5 (27.8)	12 (42.9)	17 (37.0)
1	11 (61.1)	16 (57.1)	27 (58.7)
2	2 (11.1)	0 (0.0)	2 (4.3)
Primary site of cancer			
Ovary	4 (22.2)	6 (21.4)	10 (21.7)
Pancreas	3 (16.7)	6 (21.4)	9 (19.6)
Colon	4 (22.2)	4 (14.3)	8 (17.4)
Head and neck	0 (0.0)	3 (10.7)	3 (6.5)
Prostate	1 (5.6)	1 (3.6)	2 (4.3)
Thyroid	1 (5.6)	1 (3.6)	2 (4.3)
Lung	0 (0.0)	2 (7.1)	2 (4.3)
Bone sarcoma	0 (0.0)	1 (3.6)	1 (2.2)
Breast	0 (0.0)	1 (3.6)	1 (2.2)
Rectum	0 (0.0)	1 (3.6)	1 (2.2)
Renal	0 (0.0)	1 (3.6)	1 (2.2)
Pleura	1 (5.6)	0 (0.0)	1 (2.2)
Testis	1 (5.6)	0 (0.0)	1 (2.2)
Skin melanoma	0 (0.0)	1 (3.6)	1 (2.2)
Other[a]	3 (16.7)	0 (0.0)	3 (6.5)
Median time from initial diagnosis, months[b]	32.7	36.5	36.1
Median time from first recurrence, months[c]	18.0	16.3	16.9
No. of prior systemic therapies			
0	0 (0.0)	1 (3.6)	1 (2.2)
1	1 (5.6)	4 (14.3)	5 (10.9)
2	3 (16.7)	2 (7.1)	5 (10.9)
3	3 (16.7)	4 (14.3)	7 (15.2)
≥4	11 (61.1)	17 (60.7)	28 (60.9)
Prior radiotherapy			
Yes	10 (55.6)	19 (67.9)	29 (63.0)
No	8 (44.4)	9 (32.1)	17 (37.0)
Prior surgery			
Yes	17 (94.4)	28 (100.0)	45 (97.8)
No	1 (5.6)	0 (0.0)	1 (2.2)

[a] The 3 patients with "other" primary site of cancer reported a poorly differentiated adenocarcinoma of unknown origin ($n = 1$), an adenocarcinoma of the anterior mediastinum ($n = 1$), and a poorly differentiated thymus cancer ($n = 1$)

[b] Time since initial diagnosis of primary site (months) = (First dose date − initial diagnosis date + 1)/30.4375

[c] Time since first recurrence/relapse (months) = (First dose date − first recurrence date + 1)/30.4375

(2.2 ± 0.8 h) of omeprazole co-administered with patupilone were similar to those of omeprazole alone (17 ± 15 l/h and 2.1 ± 1.2 h, respectively).

The mean blood concentration versus time profiles of 5-hydroxy-omeprazole following oral administration of 40 mg omeprazole in the presence or absence of 10 mg/m^2

Table 2 Patient disposition

Disposition	Midazolam + patupilone $N = 18$ (%)	Omeprazole + patupilone $N = 28$ (%)	All patients $N = 46$ (%)
Core phase			
Randomized	18 (100.0)	28 (100.0)	46 (100.0)
Completed therapy	10 (55.6)	20 (71.4)	30 (65.2)
Discontinued therapy	8 (44.4)	8 (28.6)	16 (34.8)
Adverse event(s)	4 (22.2)	1 (3.6)	5 (10.9)
Disease progression	3 (16.7)	5 (17.9)	8 (17.4)
Consent withdrawal	1 (5.6)	1 (3.6)	2 (4.3)
Death	0 (0.0)	1 (3.6)	1 (2.2)
Extension phase			
Entered extension	16 (100.0)		
Discontinued therapy	16 (100.0)		
Adverse event(s)	7 (43.8)		
Disease progression	6 (37.5)		
Consent withdrawal	1 (6.3)		
Satisfactory response	1 (6.3)		
Death	1 (6.3)		

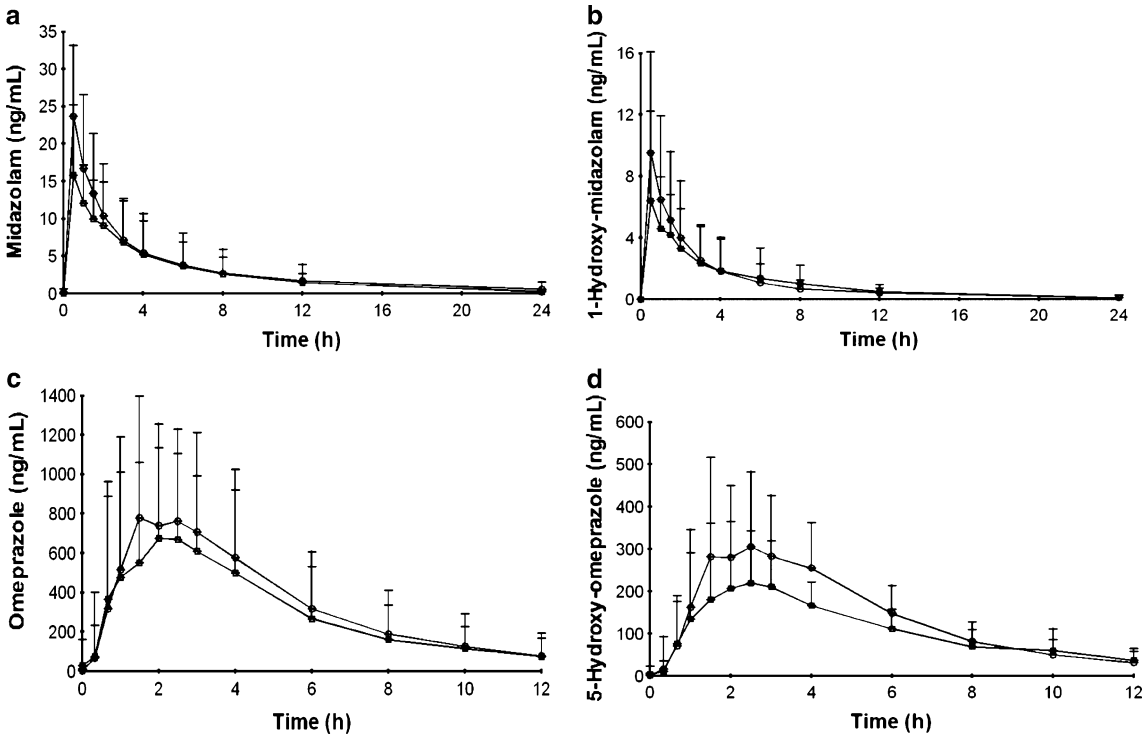

Fig. 1 **a** Mean midazolam plasma concentration–time profiles following oral administration of a single oral dose of 4 mg midazolam alone (*circle* + SD) or in combination with patupilone at 10 mg/m^2 (*square* + SD). **b** Mean 1-hydroxy-midazolam plasma concentration–time profiles following oral administration of a single oral dose of 4 mg midazolam alone (*circle* + SD) or in combination with patupilone at 10 mg/m^2 (*square* + SD). **c** Mean omeprazole plasma concentration–time profiles following oral administration of a single oral dose of 40 mg omeprazole alone (*circle* + SD) or in combination with patupilone at 10 mg/m^2 (*square* + SD). **d** Mean 5-hydroxy-omeprazole plasma concentration–time profiles following oral administration of a single oral dose of 40 mg omeprazole alone (*circle* + SD) or in combination with patupilone at 10 mg/m^2 (*square* + SD)

patupilone are presented in Fig. 1d. Blood concentrations of 5-hydroxy-omeprazole after co-administration of omeprazole and patupilone were highly variable and slightly lower than those of omeprazole alone. The pharmacokinetic parameters of 5-hydroxy-omeprazole are summarized in Table 4. Both the C_{max} (305 ± 147 ng/ml) and

Table 3 PK parameters of midazolam and 1-hydroxy-midazolam in the absence or presence of patupilone

Parameters	Midazolam		1-Hydroxy-midazolam	
	Midazolam alone	Midazolam + patupilone	Midazolam alone	Midazolam + patupilone
C_{max}, ng/ml	24 ± 10	17 ± 9	9.9 ± 6.4	6.9 ± 5.5
T_{max}, h	0.5 (0.5–2)[a]	0.7 (0.5–2)[a]	0.5 (0.5–1.5)[a]	0.7 (0.5–3)[a]
AUC[b], ng h/ml	86 ± 76	70 ± 41	26 ± 22	24 ± 25
CL/F, l/h	82 ± 71	83 ± 59	NA	NA
$T_{1/2}$, h	6.5 ± 3.7	5.6 ± 2.1	5.7 ± 2.9	5.3 ± 2.3
Ratio (co-medication/monotherapy) of geometric means[c]:				
C_{max}	0.67 (0.54–0.83)		0.51 (0.36–0.72)	
AUC	1.01 (0.77–1.34)		0.77 (0.60–1.00)	

NA Not available

Arithmetic mean ± standard of deviation

[a] Median T_{max} (range)

[b] AUC from 0 to 48 h post-midazolam dose

[c] Mean (90% confidence intervals)

Table 4 PK parameters of omeprazole and 5-hydroxy-omeprazole in the absence or presence of patupilone

Parameters	Omeprazole		5-Hydroxy-omeprazole	
	Omeprazole alone	Omeprazole + patupilone	Omeprazole alone	Omeprazole + patupilone
C_{max}, ng/ml	1,139 ± 613	1,029 ± 449	399 ± 205	305 ± 147
T_{max}, h	1.6 (0.4–6)[a]	2.0 (0.7–4)[a]	2.5 (0.4–4)[a]	2.3 (1.0–10)[a]
AUC[b], ng h/ml	4,227 ± 2,932	3,781 ± 2,239	1,720 ± 514	1,371 ± 342
CL/F, l/h	17 ± 15	16 ± 17	NA	NA
$T_{1/2}$, h	2.1 ± 1.2	2.2 ± 0.8	2.5 ± 1.1	2.9 ± 1.2
Ratio (co-medication/monotherapy) of geometric means[c]:				
C_{max}	0.79 (0.67–0.94)		0.78 (0.67–0.90)	
AUC	0.81 (0.72–0.91)		0.81 (0.74–0.88)	

NA Not available

Arithmetic mean ± standard of deviation

[a] Median T_{max} (range)

[b] AUC from 0 to 12 h post-omeprazole dose

[c] Mean (90% confidence intervals)

$AUC_{0\text{-tlast}}$ (1,371 ± 342 ng h/ml) of 5-hydroxy-omeprazole after co-administration of omeprazole and patupilone were highly variable and slightly lower than those of omeprazole alone (399 ± 205 ng/ml and 1,720 ± 514 ng h/ml, respectively), and the 90% CI for the geometric mean ratios of co-administration to omeprazole control for C_{max} and AUC for 5-hydroxy-omeprazole were not within the equivalence limits of 0.80 and 1.25 (Table 4). However, the terminal half-life of 5-hydroxy-omeprazole after co-administration of omeprazole and patupilone (2.9 ± 1.2 h) was similar to that of omeprazole alone (2.5 ± 1.1 h).

Safety and tolerability

The most common adverse events related to study drug administration were diarrhea, nausea, vomiting, and fatigue, and these occurred with similar frequency in both the midazolam and omeprazole arms. In addition, several patients reported peripheral neuropathy, mainly in the extension phase (Table 5).

Nine (50%) patients in the midazolam arm and 18 (64.3%) patients in the omeprazole arm experienced grade 3 adverse events regardless of study drug relationship, with

Table 5 Most common study drug-related adverse events

Adverse Events	Midazolam core $N = 18$ n (%)	G3/4	Midazolam extension $N = 6$ n (%)	G3/4	Midazolam All patients $N = 18$ n (%)	G3/4	Omeprazole core $N = 28$ n (%)	G3/4	Omeprazole extension $N = 10$ n (%)	G3/4	Omeprazole All patients $N = 28$ n (%)	G3/4
Any adverse event	16 (88.9)	7 (38.9)	6 (100.0)	1 (16.7)	16 (88.9)	8 (44.5)	26 (92.9)	8 (28.6)	10 (100.0)	2 (20.0)	27 (96.4)	10 (35.7)
Diarrhea	13 (72.2)	4 (22.2)	5 (83.3)	–	14 (77.8)	4 (22.2)	23 (82.1)	6 (21.4)	8 (80.0)	–	24 (85.7)	6 (21.4)
Nausea	9 (50.0)	1 (5.6)	1 (16.7)	–	10 (55.6)	1 (5.6)	12 (42.9)	–	2 (20.0)	–	12 (42.9)	–
Vomiting	4 (22.2)	2 (11.1)	2 (33.3)	–	5 (27.8)	2 (11.1)	11 (39.3)	–	2 (20.0)	–	11 (39.3)	–
Fatigue	7 (38.9)	1 (5.6)	2 (33.3)	1 (16.7)	7 (38.9)	2 (11.1)	9 (32.1)	1 (3.6)	–	–	9 (32.1)	–
Anorexia	6 (33.3)	1 (5.6)	–	–	6 (33.3)	1 (5.6)	6 (21.4)	–	–	–	6 (21.4)	–
Peripheral neuropathy	1 (5.6)	–	4 (66.7)	–	4 (22.2)	–	2 (7.1)	–	6 (60.0)	2 (20.0)	6 (21.4)	2 (7.1)
Anemia	2 (11.1)	–	–	–	2 (11.1)	–	3 (10.7)	–	–	–	3 (10.7)	–
Dehydration	2 (11.1)	1 (5.6)	–	–	2 (11.1)	1 (5.6)	2 (7.1)	2 (7.1)	1 (10.0)	–	3 (10.7)	2 (7.1)
Abdominal pain	4 (22.2)	–	–	–	4 (22.2)	–	1 (3.6)	–	1 (10.0)	–	1 (3.6)	–

Adverse events are reported if they occurred in >10% of patients in any of the listed groups

Midazolam: Midazolam + Patupilone; Omeprazole: Omeprazole + Patupilone

Adverse events are sorted in descending order of frequency, as reported in the Omeprazole All Patients column

A patient with multiple occurrences of an adverse event is counted only once in the adverse event category for that treatment

Table 6 Best overall response

Best overall response	Patupilone ($N = 40$) n (%)
Complete response (CR)	1 (2.5)
Partial response (PR)	2 (5.0)
Stable disease (SD)	15 (37.5)
Progressive disease (PD)	13 (32.5)
Unknown[a]	9 (22.5)
Overall response rate (ORR): CR or PR	3 (7.5)
Response rate for ovarian cancer	2/10 (20%)
Response rate for pancreatic cancer	1/9 (11%)

Response is based on investigator's evaluation (RECIST)

[a] Missing baseline and/or post-baseline tumor evaluation

diarrhea being the most common grade 3 adverse event (three patients [16.7%] in the midazolam arm and six patients [21.4%] in the omeprazole arm). One patient in the midazolam arm developed drug-related grade 4 diarrhea, and two patients in the omeprazole arm developed grade 4 pulmonary embolism/arrhythmia (drug related, $n = 1$) and aspiration pneumonia (non-drug related, $n = 1$).

Preliminary activity

Best overall response according to RECIST is summarized in Table 6. The overall response rate was 7.5%, with one patient achieving a complete response (CR) and two patients a partial response (PR). Fifteen (37.5%) patients reported stable disease (≥6 weeks) and 13 (32.5%) had disease progression as their best overall response. Best overall response was unknown in nine (22.5%) patients owing to missing baseline and/or post-baseline tumor evaluation.

The patient who achieved a CR was a 56-year-old woman with a serous adenocarcinoma of the ovary. She was initially diagnosed in 2001 and received five prior lines of chemotherapy, including high-dose chemotherapy with autologous stem cell transplantation and mobilization with ifosfamide and etoposide, followed by high-dose topotecan, melphalan, and cyclophosphamide and post-transplant consolidation radiotherapy in 2002. In 2007, she had progressive disease, as evidenced by an enlarging midline mesenteric mass, a mass in the sigmoid colon, enlarging multi-compartmental mediastinal right hilar lymphadenopathy, and enlarging left diaphragmatic implant. The patient received eight cycles of patupilone, which was then discontinued owing to peripheral neuropathy. She remains in CR approximately 3 years after completion of chemotherapy, as evidenced by PET/CT imaging studies; her tumor markers (CA125) decreased from 153.6 u/ml, at baseline, to normal.

The first patient who had a PR was a 59-year-old man with an adenocarcinoma of the pancreas (60% reduction in tumor size). He was initially diagnosed in 2005, and he was treated with perioperative gemcitabine, cisplatin, and chemoradiation followed by a Whipple procedure; gemcitabine and erlotinib; and gemcitabine, docetaxel, and capecitabine. In 2007, he started patupilone therapy; he completed eight cycles, but treatment was discontinued owing to peripheral neuropathy. Two months later, he was started on another phase I clinical trial for treatment of residual disease.

The second patient with a PR (53% decrease in tumor measurements by RECIST) was a 72-year-old woman with a mixed Mullerian stromal sarcoma of the ovary initially diagnosed in 2004 who had previously been treated with one line of prior chemotherapy (cisplatin and ifosfamide). She was enrolled in this study in 2007 and received six cycles of patupilone that was subsequently discontinued due to satisfactory response (PR on the last CT scan; the investigator felt that the patient had received the maximum benefit from the treatment). The PR lasted for at least 3 months.

Discussion

Our results show that patupilone is not a potent CYP3A4 or CYP2C19 inhibitor; therefore, no dose adjustments for drugs metabolized through these pathways are required when the drugs are used in patients treated with patupilone.

The mean trough concentrations of patupilone in the midazolam and omeprazole arms were similar to those of patupilone alone in previous studies [14], supporting adequate exposure to patupilone in this study. The AUCs of midazolam with and without co-administration of patupilone were similar, with a geometric mean ratio close to unity, suggesting that patupilone does not affect the AUC of midazolam. In addition, the oral clearance and terminal half-life of midazolam following co-administration with patupilone were similar to those of midazolam alone, which further supports evidence that patupilone does not affect the exposure to midazolam. The C_{max} of midazolam following co-administration with patupilone was lower than that of midazolam alone, with the geometric mean ratio less than unity, suggesting that patupilone delayed the absorption of midazolam into the systemic circulation. This delayed absorption of midazolam following co-administration of midazolam and patupilone resulted in a slightly lower AUC and C_{max} of 1-hydroxy-midazolam than those of the midazolam control. Theoretically, a potent CYP3A4 inhibitor would inhibit the elimination of midazolam, resulting in increased midazolam concentration, C_{max}, AUC, and terminal half-life [17]. No increase in the exposure, C_{max}, AUC, or terminal half-life of midazolam following co-administration of midazolam and patupilone was observed in the current study, suggesting that patupilone is not a clinically potent CYP3A4 inhibitor. Thus, no dose adjustment of midazolam is required when it is co-administered with patupilone.

The AUC and C_{max} of omeprazole following co-administration with patupilone were not equivalent to those of omeprazole alone, and their geometric mean ratios were less than unity, suggesting that patupilone decreased the oral absorption of omeprazole in these patients. It is known that irritation of the gastrointestinal tract decreases the absorption of omeprazole [8]. Since patupilone caused diarrhea in a significant number of these patients, it may have resulted in a decrease in the oral absorption of omeprazole. However, the oral clearance and terminal half-life of omeprazole in patients with co-administered omeprazole and patupilone were similar to those of patients given omeprazole alone.

Omeprazole is metabolized by CYP2C19 to 5-hydroxy-omeprazole. The decreased exposure of omeprazole following co-administration with patupilone resulted in slightly lower AUC and C_{max} of 5-hydroxy-omeprazole than for omeprazole alone. Theoretically, a potent CYP2C19 inhibitor would inhibit the elimination of omeprazole, resulting in increased omeprazole concentrations, C_{max}, AUC, and terminal half-life [7]. No increase in the exposure, C_{max}, AUC, or terminal half-life of omeprazole was observed in the current study, suggesting that patupilone is not a clinically potent CYP2C19 inhibitor. However, the current data showed that patupilone decreased the exposure of omeprazole by $\sim$20%, suggesting that patupilone may decrease the oral absorption of omeprazole into the systemic circulation. Omeprazole is marketed at 20 and 40 mg (Prilosec®) over the counter in the USA and has adequate clinical safety and efficacy profiles. Thus, no dosage adjustment of 40 mg omeprazole is required when it is co-administered with patupilone.

The safety profile of patupilone in this study was consistent with that of previous studies as well as with the investigator brochure and was characterized predominantly by gastrointestinal events such as diarrhea, nausea, and vomiting, as well as fatigue. In addition, several patients developed peripheral neuropathy, particularly in the extension phase, suggesting a potential cumulative effect. Of note, the patient who achieved a CR and one of the two patients who had a PR discontinued therapy because of cumulative peripheral neuropathy. Keeping in mind that both of these responders had prior platinum and/or taxane therapy, it is likely that prior therapies may have contributed to these complications. However, since these patients responded, similar patients should not be excluded from future trials of patupilone. There were no new or

unexpected findings when patupilone was co-administered with omeprazole or midazolam, and the events were fairly balanced between the two arms.

Promising antitumor activity was observed with patupilone in this study, with one CR and two PRs according to RECIST. Despite the small number of patients, which is typical for this type of study, the antitumor activity is encouraging.

Conclusions

In conclusion, even though bioequivalance could not be established for midazolam and omeprazole owing to the large pharmacokinetic variability, and potentially decreased oral absorption of omeprazole, the exposure and oral clearance of both drugs were not increased by co-administration of patupilone. This suggests that patupilone is not a potent CYP3A4 and CYP2C19 inhibitor. Thus, no dose adjustment is required when drugs metabolized through these two pathways are co-administered with patupilone at 10 mg/m^2 every 3 weeks. Of note, patupilone was well tolerated overall and showed promising antitumor activity in heavily pretreated patients with epithelial ovarian and pancreatic cancer and a mixed Mullerian stromal sarcoma of the ovary.

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