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ORIGINAL ARTICLE

**Sherry Morgan-Meadows · Sarita Dubey
Michael Gould · Kendra Tutsch · Rebecca Marnocha
Rhoda Arzoomanin · Dona Alberti · Kimberly Binger
Chris Feierabend · Jennifer Volkman · Shawna Ellingen
Sandra Black · Marcia Pomplun · George Wilding
Howard Bailey**

Phase I trial of perillyl alcohol administered four times daily continuously

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Abstract *Purpose*: Previous experience with perillyl alcohol (POH) was with a formulation of 500-mg capsules each containing 250 mg POH and soybean oil. This formulation resulted in the ingestion of large amounts of soybean oil (> 10 g/day). Dose-limiting toxicities (DLT) were primarily gastrointestinal. Prior studies also showed no further increase in POH metabolite concentrations with doses of > 1600 mg/m^2. Therefore, a new formulation of POH was developed (700 mg containing 675 mg POH) in an effort to improve dose and metabolite concentrations delivered and toxicity encountered with chronic dosing. *Experimental design*: Eligible patients had refractory solid malignancies. Dose escalation occurred in cohorts of three at the dose levels/dose of 1350 mg, 2025 mg, 2700 mg, 3375 mg and 4050 mg, administered orally four times a day in a 28-day cycle. *Results*: A group of 19 patients were enrolled. One DLT occurred at dose level 5. This cohort was expanded to six patients, and no further DLT occurred. The maximum tolerated dose was not reached. The predominant toxicity was gastrointestinal. Nausea and vomiting occurred in 63% of patients (12/19, grade 1 in 10). The same proportion of patients (12/19) experienced heartburn and indigestion, primarily grade 1. Although the side effects were mild in nature, three patients withdrew from treatment, citing intolerable gastrointestinal toxicity. The AUCs of POH metabolites did not appear to increase from level 1 to level 2 or change significantly from day 1 to day 29. Inter- and intrapatient variability in metabolite levels was observed. *Conclusions*: This reformulation of POH appears to be an improvement upon the prior formulation, by reducing the number of capsules ingested and the degree of gastrointestinal toxicity per dose. It does not appear to offer any metabolite pharmacokinetic advantage. A dose of 2050 mg administered four times daily was easily tolerated. Higher doses can be administered but with increasing gastrointestinal toxicity that limits compliance.

Keywords Apoptosis · Monoterpene
Pharmacokinetics · Reformulation

Abbreviations *AUC* Area under the curve · *DHPA* Dihydroperillic acid · *DLT* Dose-limiting toxicity · *IGF* Insulin-like growth factor · *M6P* Mannose-6-phosphate · *MTD* Maximum tolerated dose · *PA* Perillic acid · *POH* Perillyl alcohol · *TGF* Transforming growth factor · *ULN* Upper limit of normal

Introduction

As the understanding of the molecular events surrounding carcinogenesis has advanced, emphasis has shifted to developing new agents with novel mechanisms of action. An example is the family of monoterpenes. Monoterpenoids occur naturally in plant products such as fruits and vegetables. Monoterpenes have monocyclic, bicyclic and acyclic forms, as well as simple or modified hydrocarbon forms. Preclinical models have explored limonene, the simplest monocyclic monoterpene, as an anticancer agent. In 1971, Homburger at al. [10] showed

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S. Morgan-Meadows (✉) · S. Dubey · M. Gould · K. Tutsch
R. Marnocha · R. Arzoomanin · D. Alberti · K. Binger
C. Feierabend · J. Volkman · S. Ellingen · S. Black
M. Pomplun · G. Wilding · H. Bailey
University of Wisconsin Comprehensive
Cancer Center, 600 Highland Ave K4/601,
Madison, Wisconsin 53792, USA
E-mail: slm@medicine.wisc.edu
Tel.: +1-608-265-8131
Fax: +1-608-265-8133

that coadministration of limonene with the carcinogen benzo(rst)pentaphene results in inhibition of tumor development. Elegbede et al. [6] demonstrated the potential of limonene in the treatment of tumors. They reported that limonene can cause regression of chemically induced rat mammary tumors. Haag et al. [9] extended these findings further by demonstrating the regression of advanced rat mammary carcinomas following treatment with limonene. An additional study by Chander et al. [2] revealed the synergy between limonene and aromatase inhibitors in the treatment of advanced rat mammary carcinoma. The above findings have led to the clinical testing of limonene in the UK [14].

The therapeutic potential of limonene prompted screening of other monoterpenes. As a result of in vitro screening [5], perillyl alcohol (POH), the naturally occurring hydroxylated noncyclic monoterpene, was selected for in vivo testing. Dietary POH can induce tumor regression with a potency five times that of limonene. Equivalent doses of POH and limonene produce the same circulating metabolites, but rats fed with POH have much higher levels of these metabolites than those fed limonene [8].

The mechanisms of action of terpenes continue to undergo study. Proposed actions include:

- G_1 block [21] and induction of apoptosis [16].
- Inhibition of isoprenylation of a class of proteins of 21–26 kDa, including $p21^{RAS}$ and other GTP-binding proteins, at a point in the mevalonic acid pathway distal to 3-hydroxy-3-methylglutaryl-CoA reductase [4].
- Differential gene regulation including overexpression of M6P/IGF-II and TGF-β II receptor genes. Tumors responding to POH have increased M6P/IGF-II receptor levels compared to treated nonresponding tumors [12]. Liver tumors from POH-treated animals show increased levels of mRNA for M6P/IGF-II and TGF-β I, II and III receptors compared to untreated animals [12].
- Modulation of Ap-1 through induction of c-jun and c-fos and phosphorylation of c-jun [22].

In previous phase I studies [11, 19, 20], a formulation of 500-mg capsules each containing 250 mg POH and soybean oil was used. In the study by Ripple et al. [20], 4 of 19 patients showed disease stabilization for at least 8 months. One patient with metastatic colon cancer showed almost complete resolution of disease after 10 months of therapy and no progression of disease for more than 2 years. In the trial by Hudes et al. [11], 8 of 15 patients had stable disease for at least 2 months. In both trials, toxicity occurred in a dose-related manner and consisted mainly of gastrointestinal toxicity and fatigue. One postulate proposes that much of the gastrointestinal toxicities are related to the large amounts of soybean oil ingested. Hence, we designed a phase I trial using reformulated drug (700-mg capsules containing 675 mg POH) to study the maximum tolerated dose (MTD), toxicities and pharmacokinetics of POH.

Patients and methods

Patient selection

Eligible patients fulfilled the following criteria: (1) histological or cytological confirmation of solid tumor malignancy who had failed standard therapy or for whom no standard therapy existed; (2) measurable or evaluable disease; (3) Zubrod performance status of 0, 1, or 2; (3) age greater than 18 years; and (4) adequate organ function as evidenced by WBC $\geq 4000/mm^3$, platelets $\geq 100{,}000/mm^3$, AGC $\geq 1500/mm^3$, bilirubin ≤ 1.5 mg/dl, SGOT not more than twice the ULN, BUN ≤ 30 mg%, and creatinine ≤ 1.5 mg%. Ineligible patients were pregnant or nursing patients, patients with primary or metastatic brain tumors, or patients receiving cholesterol-lowering agents. In addition, 4 weeks had to have elapsed since completion of prior chemotherapy or radiotherapy and patients had to have recovered fully from toxicity. The Institutional Review Board approved this phase I study and informed consent was obtained from the participants.

Clinical evaluations

Pretreatment evaluations included complete history and physical examination, weight, performance status, hematological laboratory evaluation, serum electrolytes, and hepatic and renal function. Patients underwent tumor assessment up to 2 weeks prestudy and prior to each course. Disappearance of all clinical evidence of active tumor and symptoms for at least 1 month, with stable performance status constituted a complete response. Partial response consisted of greater than 50% decrease in the sum of the products of the perpendicular tumor diameters of all measurable lesions for at least 4 weeks without simultaneous increase in the size of any lesions or any new lesions. Progressive disease was defined as an unequivocal increase of at least 25% in the size of any measurable lesion or the appearance of any significant new lesion. Stable disease did not meet the criteria for complete response, partial response or disease progression.

Pharmacokinetic methods

Methods for pharmacokinetic sampling are the same as those described by Ripple et al. [20]. During course 1, patients took a single dose of POH on day 1. Heparinized blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after the oral dose. On day 29 (course 2, day 1) samples were collected over the period 0–6 h from the first dose. Plasma was separated by centrifugation and frozen at −70°C until assay. On day 1, urine was collected over the periods 0–8 and 8–24 h. The total volume of each collection was measured and aliquots frozen at −70°C until assay. All patients had pharmacokinetic sampling on day 1. Six patients did not undergo pharmacokinetic sampling on day 29 due to toxicity or progressive disease.

Plasma and urine samples were assayed for POH and the metabolites perillic acid (PA) and dihydroperillic acid (DHPA) by the method of Phillips et al. [17]. Briefly, plasma or diluted urine samples were extracted with *t*-butyl methyl ether after addition of the internal standard perillaldehyde. Samples were separated using a Supelco SPB-5 column (Supelco, Bellefonte, Pa.) and quantitated using flame ionization detection. POH was detected in urine but not plasma. The POH and PA standard curves were linear in the range 5–1200 μM (mean $r^2 = 0.998$), and the DHPA standard curve was linear in the range 5–300 μM (mean $r^2 = 0.995$) for 12 standard

Table 1 Dose escalation scheme

Level	Dose (mg, four times a day)	Patients enrolled
1	1350	3
2	2025	4
3	2700	3
4	3375	3
5	4050	6

Table 2 Patient characteristics

Male	11
Female	8
Age (years)	
Median	59
Range	37–76
Performance status	
0	6
1	11
2	0
Unknown	2
Prior therapy	
0	1
1	3
2	8
3 or more	7

curves run over 6 months. The intraday coefficient of variation (CV) for the standards was less than 6% over the concentration range for triplicate determinations. The interday variability was less than 8% over the concentration range for triplicate determinations of the standards. A control plasma sample was run seven times over 10 months. The CV was 8.1% for PA and 5.0% for DHPA.

Pharmacokinetic parameters were determined by noncompartmental methods [7]. For each single-dose data set, the area under the concentration-time curve (AUC) was determined using the linear trapezoidal rule. Cmax and tmax were determined by inspection of the data. The half-life was calculated by log-linear regression of the terminal portion of the concentration-time curve.

Administration and dose escalation

POH 700-mg soft red gelatin capsules (containing 675 mg POH) were administered four times a day for 28 days, which constituted one cycle. Fasting before and after drug administration was not required.

Patients enrolled in cohorts of three. Dose escalation proceeded according to the scheme outlined in Table 1. The initial cohort received 1350 mg four times a day. If no patient in a cohort experienced dose-limiting toxicity (DLT), escalation proceeded to the next dose level. If one of three had a DLT, an additional three patients received that dose. If none of the additional three patients experienced a DLT, the escalation continued. However, if one additional patient experienced a DLT, then the MTD had been exceeded. The MTD was defined as the dose level prior to the level at which two or more of six patients experienced a DLT. Grading of toxicity used the Common Toxicity Criteria version 2.0. DLT consisted of: (1) greater than grade 2 vomiting lasting three or more days despite optimal antiemetic therapy; (2) greater than grade 2 diarrhea lasting three or more days despite optimal antidiarrheal therapy; or (3) greater than grade 2 increase in creatinine.

Results

Patient demographics

Enrolled in this trial were 19 patients, 11 males and 8 females. Their median age was 59 years. The patient characteristics are given in Table 2. The trial encompassed a wide variety of tumor types, including renal cell carcinoma (four patients), soft tissue sarcoma (four patients), melanoma (two patients), salivary gland tumor (two patients), and gastric cancer, ovarian adenocarcinoma, cervical cancer, non-small-cell lung cancer, rectal cancer, adenocarcinoma of unknown primary and pancreatic adenocarcinoma (one patient each). Most patients had received prior treatments and had a performance status of 1. Patients received an average of 3.8 courses (range 1–12).

Toxicity

Dose escalation proceeded according to the scheme outlined in Table 1. Within the first four levels, no DLT occurred. One patient at dose level 2 (2025 mg) did not complete course 1 and an additional patient was added to this level. At dose level 5 (4050 mg), the first patient enrolled experienced grade 3 vomiting, a DLT. An additional five patients accrued were to this level, without additional DLT. Further dose escalation did not occur due to lack of clinical benefit with this compound.

Toxicities are summarized in Table 3. Gastrointestinal toxicity predominated. Nausea and vomiting occurred in 63% of patients (12/19). Ten of these patients had grade 1 nausea and vomiting. One patient had grade 2 and one patient had grade 3. Nausea developed within 2 weeks of initiating therapy in ten patients. The remaining two patients developed nausea in course 6 and course 8. Antiemetic therapy consisted of scheduled metoclopramide and prochlorperazine as needed. One patient required granisetron. Heartburn and indigestion occurred in 63% of patients (12/19). Again, grade 1 occurred in all but one patient, who had grade 2. Patients experiencing this toxicity received an H_2 blocker. Fatigue occurred in 32% (6/19). Similar to the gastrointestinal toxicity, fatigue appeared as early as course 1 and persisted while on therapy. These toxicities did not appear to worsen with further courses. Despite the chronic, low-grade toxicities (nausea in two, indigestion in one) observed, only three patients discontinued for drug intolerance (one each at dose levels 2, 3 and 5).

Pharmacokinetics

Tables 4 and 5 summarize plasma pharmacokinetic data for the five dose levels studied. The method employed does not detect POH in plasma. Peak plasma

Table 3 Toxicity

Dose level (mg)	Worst toxicity experienced by patients											
	Nausea/vomiting (grade)				Heartburn/indigestion (grade)				Fatigue (grade)			
	1	2	3	4	1	2	3	4	1	2	3	4
1350	3	0	0	0	1	0	0	0	2	0	0	0
2025	2	1	0	0	1	0	0	0	1	0	0	0
2700	0	0	0	0	3	0	0	0	1	0	0	0
3375	1	0	0	0	3	0	0	0	0	0	0	0
4050	4	0	1	0	3	1	0	0	1	1	0	0
Total number of patients experiencing toxicity (%)	12 (63)				12 (63)				6 (31)			

Table 4 Pharmacokinetic parameters for PA (values are means ± SD)

Dose level (mg/dose)	Course	Cmax (μ*M*)	tmax (h)	6-h AUC (μ*M*·h)	$t_{1/2}$ (h)
1 (1350)	1	161.3 ± 137.7	1.2 ± 0.8	277.1 ± 171.1	2.40 ± 2.72
	2	175.9 ± 93.3	0.8 ± 0.4	586.3 ± 157.0	1.55 ± 0.93
2 (2025)	1	491.5 ± 385.9	1.5 ± 0.4	853.4 ± 695.8	0.95 ± 0.22
	2	244.8 ± 149.0	1.2 ± 0.8	307.6 ± 134.4	0.84 ± 0.45
3 (2700)	1	535.2 ± 332.2	1.7 ± 1.3	975.2 ± 558.5	0.87 ± 0.14
	2	277.2 ± 155.7	2.0 ± 1.8	457.7 ± 233.9	0.68 ± 0.24
4 (3375)	1	338.8 ± 167.3	2.7 ± 0.6	860.0 ± 384.7	0.74 ± 0.37
	2	191.4 ± 155.5	3.7 ± 2.1	590.6 ± 65.5	0.61 ± 0.29
5 (4050)	1	539.0 ± 247.9	1.8 ± 0.4	1171.4 ± 594.3	0.83 ± 0.30
	2	539.3 ± 188.9	1.2 ± 0.3	1120.3 ± 107.9	0.40

Table 5 Pharmacokinetic parameters for DHPA (values are means ± SD)

Dose level (mg/dose)	Course	Cmax (μ*M*)	tmax (h)	6-h AUC (μ*M*·h)	$t_{1/2}$ (h)
1 (1350)	1	9.9 ± 2.6	2.2 ± 1.4	21.3 ± 9.3	4.4 ± 2.7
	2	12.6 ± 1.9	1.3 ± 0.4	45.7 ± 6.9	1.1 ± 0.4
2 (2025)	1	28.9 ± 23.9	2.8 ± 0.5	109.5 ± 90.9	7.0 ± 8.1
	2	18.7 ± 6.6	2.0 ± 0.9	62.1 ± 31.3	2.9 ± 0.1
3 (2700)	1	32.8 ± 9.1	3.0 ± 1.0	101.8 ± 47.3	1.4 ± 0.2
	2	28.0 ± 17.0	2.5 ± 1.3	59.4 ± 39.8	1.8 ± 2.0
4 (3375)	1	41.8 ± 35.3	4.0 ± 0.0	136.6 ± 119.0	0.9 ± 0.1
	2	33.9 ± 10.3	3.5 ± 0.7	100.9 ± 45.4	1.1 ± 0.4
5 (4050)	1	30.3 ± 16.3	3.0 ± 0.9	94.0 ± 63.3	1.9 ± 1.5
	2	44.4 ± 29.5	2.5 ± 0.7	77.2 ± 70.3	1.2 ± 0.3

concentrations of PA occurred at 0.5–3.0 h after ingestion (mean 1.7 h), and of DHPA, at 0.5–4.0 h (mean 3.0 h). The mean half-life of PA was 1.1 h (range 0.7–2.4 h), and of DHPA 3.4 h (range (0.9–7.0 h). Half-life and time to peak concentration (tmax) were not dose-dependent. The 6-h AUC and metabolite peak plasma concentrations (Cmax) for both metabolites increased from dose level 1 to 2. No apparent increase from dose level 2 through 5 occurred. Marked interpatient and intrapatient variability in Cmax and AUC did occur. Of 18 patients, 12 had 6-h pharmacokinetic sampling repeated on day 29. The differences in metabolite peak concentrations or AUC did not reach statistical significance when compared with day-1 levels.

At levels 1 to 4, urinary excretion was determined from 0 to 24 h. An average of 15.9 ± 7.9% of the dose was excreted in 24 h, primarily as PA. This recovery was slightly higher than in our previous studies, which averaged about 10% recovery.

Clinical activity

Of the 19 patients, 5 had stable disease for 6 months or more. In addition, one patient with liposarcoma and one patient with salivary gland tumor (adenocystic carcinoma) had disease stabilization for 11 and 12 months, respectively. No objective responses were observed. No dose response relationship to stable disease occurred.

Table 6 Comparison of gastrointestinal toxicity across four phase I trials (nausea, vomiting, diarrhea, indigestion and heartburn) (*NR* not reported)

Reference	Dosing		Courses	Gastrointestinal toxicity				Withdrawals
				1	2	3	4	
19	Three times daily mg/m^2)	800	11	1	0	0	0	22% (4/18)
		1600	22	19	1	0	0	
		2400	26	13	2	2	0	
20	Four times daily (mg/m^2)	800	26	1	0	0	0	5% (1/19)
		1200	17	11	1	0	0	
		1600	33	4	1	1	0	
11	Three times daily (mg/m^2)	1600	NR	0	0	0	0	18% (3/17)
		2100	NR	0	3	0	0	
		2800	NR	0	8	0	0	
Current study	Four times daily (mg)	1350	21	3	9	0	0	16% (3/19)
		2025	26	8	1	0	0	
		2700	12	7	0	0	0	
		3375	9	5	0	0	0	
		4050	8	6	0	1	0	

Discussion

In previous phase I studies of POH [11, 19, 20], a formulation of 500-mg capsules each containing 250 mg POH and soybean oil was used. In the study by Ripple et al. [20], the MTD was 1200 mg/m^2 per dose administered four times a day. In the study by Hudes et al. [11], DLT was seen at 2800 mg/m^2 per dose administered three times a day. DLTs were predominantly gastrointestinal consisting of nausea, vomiting, indigestion and eructation. Most of these toxicities were attributed to this particular formulation of POH. The prior formulation contained a significant proportion of soybean oil and a smaller amount of POH, thus requiring large numbers of capsules to be ingested per dose. Hence, we launched a study with reformulated POH capsules (700 mg containing 675 mg POH) in an effort to improve the toxicity profile of POH and to see if higher POH metabolite concentrations could be achieved. Similar to the original formulation, the new formulation also produced gastrointestinal toxicity. These toxicities were mild, but occurred with high frequency.

The observed gastrointestinal toxicities in all four phase I trials are compared in Table 6. With the exception of the study by Hudes et al., grade 1 toxicity predominated. Only four episodes of grade 3 toxicity occurred in the entire phase I experience and no grade 4 toxicity occurred. In the current study, almost all toxicities were grade 1 to 2. One patient had grade 3 toxicity (vomiting) at level 5. Although we encountered a toxicity profile similar to that seen in the prior phase I experience, no DLT occurred. Thus, a higher dose could be given with this formulation. Dose escalation was stopped at of 4050 mg/dose, where one out of five experienced a DLT, due to lack of pharmacokinetic advantage.

In pharmacokinetic sampling, POH was not detected in the blood. The relatively short half-lives of POH metabolites, PA and DHPA, necessitate frequent dosing of POH. The AUCs on day 29 were not significantly greater than on day 1, showing that toxicity was not cumulative. Preclinical dog data show linear pharmacokinetics and less variability. However, in our study, there was lack of linear correlation, and POH doses greater than level 2 (2025 mg) did not produce significantly higher levels of metabolites than lower doses. Similar to the findings of prior studies, there was marked inter- and intrapatient variability. In contrast to our earlier studies in which doses were calculated by body surface area, the current study employed unit dosing. This feature may be a contributing factor to some of the variability observed.

Unlike in our prior phase I experience with POH, we did not observe obvious signs of clinical benefit except for prolonged (more than 6 months) stable disease. Clinical development of POH has included three phase II trials conducted at the University of Wisconsin using the original formulation of POH: a metastatic colon cancer trial [15], a metastatic breast cancer trial (H.H. Bailey, personal communication) and an advanced ovarian cancer trial [1]. Although preclinical data support antitumor activity in these tumor types, no clinical benefit was observed. One reason for lack of benefit may be stage of disease. POH has been shown to prevent carcinogenesis in a mouse lung cancer model [13], a rat colon cancer model [18], and a rat breast cancer model [3]. Thus the appropriate position for this drug may be as a chemopreventative agent. To further explore the role of POH in prevention, the National Cancer Institute is currently conducting a study to assess disease recurrence in patients previously treated for stage I-IIIA breast cancer.

In conclusion, this formulation of POH produced a spectrum of gastrointestinal toxicity similar to that with the original formulation. However, the intensity of side effects observed with this formulation was lower. Based on our pharmacokinetic data alone, metabolite levels appeared similar from dose level 2 to 5. Therefore dose level 2 (2025 mg four times daily) would be

the recommended phase II dose. In comparison with the prior formulation, this formulation allows fewer capsules per dose and appears to allow a greater total dose with similar to less toxicity.

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