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ORIGINAL ARTICLE

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A phase I trial of perillyl alcohol in patients with advanced solid tumors

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Abstract *Purpose*: Perillyl alcohol is a plant-derived lipid with preclinical antitumor activity. Its proposed mechanism of action involves inhibition of post-translational isoprenylation of small G proteins, including the proto-oncogene p21-*ras*, thereby blocking signal transduction. This phase I trial was conducted to determine the optimal dose of perillyl alcohol. *Methods*: The study group comprised 21 adults with advanced solid tumors who were treated with perillyl alcohol, delivered orally, four times daily, without interruption. Doses ranged from 4,800 to 11,200 mg/m^2 per day. *Results*: The maximum tolerated dose (MTD) for this schedule was determined to be 8400 mg/m^2 per day. The dose-limiting toxicities in this trial were nausea and vomiting, encountered in all patients at the highest dose level. No antitumor activity was observed. Pharmacokinetic data suggest dose-dependent increases in C_{max} of perillic acid, a metabolite of perillyl alcohol, but with high inter- and intrapatient variability. *Conclusions*: The MTD of perillyl alcohol for this schedule was determined to be 8400 mg/m^2 per day. This is higher than the MTDs determined in other similar phase I trials. This may have been due to the fact that the gastrointestinal symptoms caused by perillyl alcohol are highly subjective, with high interpatient variability. Phase II trials of perillyl alcohol in hormone-refractory prostate, breast, ovarian and colorectal cancer using doses in the range 4800–6400 mg/m^2 per day are underway.

Keywords Limonene · Perillyl alcohol · Monoterpenes · Isoprenylation · G proteins · p21-*ras*

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Introduction

Monoterpenes are plant-derived lipids which constitute a major component of many citrus oils. Perillyl alcohol [4-(1-methylethenyl)-1-cyclohexene-1-methanol; NSC 641066] is a naturally occurring hydroxylated monocyclic monoterpene which has demonstrated preclinical activity against pancreatic, stomach, lung, skin and liver tumors. It is a hydroxylated analog of limonene, which was the first monoterpene to be studied as an anticancer agent [5, 8, 10]. Phase I clinical trials of limonene demonstrated a partial response in a breast cancer patient and stable disease for ≥6 months in three patients with colon cancer [22]. Perillyl alcohol was identified in an in vitro screening program to evaluate the relative activities of monoterpene derivatives on proliferation and protein isoprenylation inhibition in HT-29 colon carcinoma cells. Perillyl alcohol was five times more potent than limonene in preclinical models at inducing regression of rat mammary tumors [7]. In addition, perillyl alcohol demonstrated antitumor effects in vivo against pancre-

atic and liver tumors and in vitro against neuroblastoma and colon carcinoma.

The mechanism of action of the monoterpenes is not established. Perillyl alcohol may act directly, or indirectly through its metabolites perillic acid (PA) and dihydroperillic acid (DHPA). It is not known whether the metabolites of perillyl alcohol have independent biologic activity. In vitro, perillyl alcohol selectively inhibits small G proteins, including the proto-oncogene p21-*ras*, by blocking post-translational isoprenylation [6, 15, 21]. Unprenylated *ras* proteins do not associate with the plasma membrane and are incapable of cellular transformation. Perillyl alcohol also reduces levels of antigenic *ras* protein as assessed by Western blotting and immunoprecipitation assays, and therefore may modulate *ras* by a mechanism independent of its inhibitory effects on protein prenylation [9]. Thus, perillyl alcohol may act by decreasing *ras* transcription/translation, or by increasing *ras* degradation. Other researchers have suggested that the mechanism of action of the monoterpenes is not dependent on *ras*, and have observed a variety of biochemical activities of these compounds including inhibition of ubiquinone synthesis, inhibition of conversion of lathesterol into cholesterol, increased expression of receptors for mannose-6-phosphate/insulin growth factor II (IGF-II) and transforming growth factor β (TGF-β), and modulation of expression and activity of AP-1-associated genes downstream from *ras* [1, 2, 3, 4, 12, 13, 18, 19, 21].

Pharmacology studies in dogs have shown that, after oral administration, perillyl alcohol is rapidly metabolized to PA and DHPA with elimination half-lives of both of these metabolites being approximately 2 h. In preclinical studies in dogs and rats, nausea, vomiting, and loose stool were identified as common toxicities with rare leukocytosis, thrombocytosis, lethargy, renal tubular degeneration with elevated serum creatinine, and gastritis. Elevated alanine aminotransferase (ALT) was noted in animals treated at the highest dose level. In dogs the maximum tolerated dose (MTD) of perillyl alcohol delivered orally is 600 mg/kg per day in three divided doses. In rats the MTD is 600 mg/kg per day in two divided doses.

In initial phase I trials of perillyl alcohol in patients with advanced malignancies, a continuous three-times-daily oral dosing schedule was employed, with doses as high as 7200 mg/m^2/day achieved, with variable drug tolerance [16]. The predominant toxicities were grade 1–2 nausea, vomiting, early satiety and belching. Pharmacokinetic studies revealed a short plasma half-life of PA and DHPA, with a $t_{1/2}$ of 2 h. Escalation of the dosage above 1600 mg/m^2 per dose did not increase peak plasma levels of the metabolites, suggesting a ceiling effect with large individual doses, perhaps due to saturation of absorption mechanisms. Therefore, Ripple et al. initiated an additional phase I trial with the drug administered four times daily to increase exposure [17]. Similarly, this phase I trial was designed to determine the MTD of perillyl alcohol given orally on a four-times-daily schedule, without interruption.

Materials and methods

Patient selection

Eligible patients had pathologic confirmation of a solid tumor by the Pathology Department at Memorial Sloan-Kettering Cancer Center, life expectancy ≥8 weeks, age ≥18 years, Karnofsky performance status (KPS) ≥70%, white blood cell count ≥3000/μl, absolute neutrophil count ≥1500/μl, platelet count ≥100,000/μl, hemoglobin ≥8.0 g/dl, bilirubin ≤ 2.0 mg/dl, SGOT not more than twice the upper limit of normal (ULN), alkaline phosphatase not more than twice the ULN, and serum creatinine ≤ 1.6 mg/dl or creatinine clearance ≥50 ml/min per 1.7 m^2, stable heart rhythm, no unstable angina, no clinical evidence of congestive heart failure, no radiation therapy or chemotherapy within 4 weeks of initiation of therapy, and no mitomycin or nitrosoureas within 6 weeks. Pregnant women, patients with hematologic malignancy, and patients taking antiseizure medications known to be metabolized by the cytochrome P-450 system were excluded. Patients were not allowed to take cholesterol-lowering agents during the study. The protocol and consent were reviewed and approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center.

Pretreatment evaluation

A complete medical history was obtained from each patient and each underwent a physical examination within 7 days of treatment initiation. Laboratory testing, including complete blood count (CBC), screening chemistry profile including liver function tests, and serum electrolytes were obtained within 14 days of treatment initiation. Electrocardiogram and chest roentgenogram were obtained within 4 weeks.

Treatment plan

Perillyl alcohol was distributed to patients as oral gelatin capsules containing 250 mg of perillyl alcohol per capsule with 250 mg of soybean oil. The drug was supplied by the National Cancer Institute, Division of Cancer Treatment, and stored at room temperature. Perillyl alcohol was prescribed four times daily, at a fixed dose, for 28 consecutive days followed by a reassessment. The study used a modified Fibonacci design for dose escalation. Dose levels were planned as a series of approximate 33% increments: 4800, 6400, 8400, 11,200, and 14,800 mg/m^2 per day, respectively. While on study, patients were seen weekly for the first month, and every 2 weeks thereafter. Patients were evaluated with weekly CBC, electrolyte and screening chemistry profile for 6 weeks, and every 2 weeks thereafter. Patients who suffered nausea and vomiting were offered therapeutic antiemetics. No prophylactic antiemetics were used.

At least three patients were to be evaluable for toxicity at any given dose level before patients were enrolled at the next dose level. Toxicity was measured using the Common Toxicity Criteria of the National Cancer Institute Cancer Therapy Evaluation Program, version 1.0. At any dose level in which grade 3 drug-related toxicity developed, at least six patients were to be enrolled before moving to a higher dose level. The MTD was defined as the dose level immediately below that dose which produced dose-limiting toxicity (DLT) in two or more of the three to six patients treated. DLT was defined as grade 4 hematologic toxicity, or grade 3 non-hematologic toxicity. Patients were removed from study if they demonstrated progressive disease, or if they refused to continue on study.

Pharmacokinetic studies

A minimum of three patients at each dose level underwent pharmacokinetic studies on days 1 and 15. Patients were instructed not to eat after midnight the evening prior to the pharmacokinetic studies. In order to explore the effect of food on drug absorption, alternate patients took their first morning dose on an empty stomach, or with a standardized meal consisting of 237 ml of Ensure. On day 15, patients who had fasted on day 1 were asked to drink Ensure, and patients who had drunk Ensure on day 1 were asked to fast. Blood and urine were analyzed for the content of perillyl alcohol and the metabolite PA. Blood samples were drawn at 0, 15 and 30 min, and at 1, 2, 4, 6 and 8 h. Urine samples were collected at time 0, and during the period 4–8 h as available.

Evaluation of response

Although indicator lesions were not required for entry into this study, whenever measurable or evaluable disease was present, tumor assessments were recorded every 4 weeks using the most appropriate imaging modality. Standard response criteria were used [14].

Additional studies

Patients completed the SF-36 Health Status Survey and the Memorial Symptom Assessment Scale (MSAS) questionnaires designed to assess quality of life at baseline, and on days 14 and 28. In addition, data on treatment-related expenses were collected and compared to projected charges for the appropriate "alternative standard treatment" in a pilot study to evaluate new methods of measuring cost effectiveness [20].

Statistics

Nonparametric tests were used to look for differences in C_{max} among dose levels and also differences in each patient's C_{max} values and time to C_{max} after fasting or taking Ensure. An exact version of McNemar's test was used to look for differences in patient's baseline and day-14 MSAS responses.

Results

A total of 22 patients were enrolled. One patient died before initiation of therapy. The median age of the evaluable patients was 55 years, and their median KPS was 80%. There were 11 males and 10 females. Diagnoses included non-small-cell lung cancer ($n=12$), melanoma ($n=3$), leiomyosarcoma of the uterus ($n=2$), and one each of renal cell carcinoma, mesothelioma, Ewing's sarcoma, and colon cancer. All patients enrolled in the trial had received prior chemotherapy.

Four patients were treated at a dose of 4800, five at 6400, nine at 8400, and three at 11,200 mg/m^2 per day. The chief toxicities were nausea and vomiting. All three patients treated at 11,200 mg/m^2 per day experienced at least grade 2 nausea, with two experiencing grade 3 nausea and one grade 3 vomiting. Of the nine patients treated at 8400 mg/m^2/day, one experienced grade 2 nausea, and two grade 2 vomiting. Antiemetic therapy was offered to all patients at the discretion of the treating physician. Of 15 patients who suffered any amount of nausea or vomiting, 6 received therapy with a phenothiazine antiemetic (prochlorperazine and/or metoclopramide), and 1 patient received ondansetron. Metoclopramide was documented to have alleviated nausea in four patients. One patient had grade 2 diarrhea at 4800 mg/m^2 per day but continued on treatment. One patient experienced grade 2 hypomagnesemia at a dose of 8400 mg/m^2 per day, but also continued on treatment.

The median time on study was 4 weeks, with 13 patients (62%) removed for progression of disease, 6 (28%) for drug intolerance due to nausea or abdominal symptoms, and 2 (9%) for adverse events, including an allergic skin reaction and an unrelated pulmonary embolus. One patient suffered right upper quadrant abdominal pains after 4 days of therapy at 6400 mg/m^2 per day and was taken off study. The urticarial skin reaction occurred on the first day of treatment at 8400 mg/m^2 per day. The pulmonary embolus occurred after 19 days of therapy at 4800 mg/m^2 per day. This patient was also found to have progression of disease on a coincident radiologic assessment. Overall, there were no objective antitumor responses. Five patients continued on study for 2 months or more with stable disease, including one patient with stage IV non-small-cell lung cancer metastatic to lung and lymph nodes who remained on study for 13 months.

Three successive patients could not tolerate the 11,200 mg/m^2 per day dose due to nausea, making the final MTD 8400 mg/m^2 per day. One of the patients at the highest dose level was unable to tolerate the drug despite treatment with prochlorperazine, metoclopramide, ondansetron and lorazepam antiemetics given sequentially. The other two patients at the highest dose level were removed from study without a trial of antiemetics. For patients at lower dose levels who experienced nausea, the nausea occurred within the first week. Continuous dosing did not result in cumulative nausea or fatigue, and it did not appear that a scheduled break in therapy would have improved tolerance.

Similar to the results of other investigators, we could not detect perillyl alcohol in the plasma presumably due to rapid metabolism of the drug. The metabolite PA was detectable in plasma, with high inter- and intrapatient variability. The data suggest a dose-dependent increase in C_{max} of PA. For fasting patients, the median C_{max} values were 36 μg/ml for the 1200 mg/m^2 dose level, 111 μg/ml for the 1600 mg/m^2 level, 185 μg/ml for the 2100 mg/m^2 level, and 147 μg/ml for the 2800 mg/m^2 dose level ($P=0.09$). For Ensure-fed patients, the median C_{max} values were 84 μg/ml for the 1200 mg/m^2 dose level, 112 μg/ml for the 1600 mg/m^2 dose level, 108 μg/ml for the 2100 mg/m^2 dose level, and 166 μg/ml for the 2800 mg/m^2 dose level ($P=0.06$). Variability of the data made quantitative and qualitative determinations of other pharmacokinetic parameters (induction, inhibition, AUC and $t_{1/2}$) unreliable. Consumption of Ensure prior to dosing had no clear effect on AUC, but

appeared to delay detection of the metabolite in the serum (Fig. 1). The median time to C_{max} for both fasting and Ensure-fed patients was 6 h, but a larger proportion of fasting patients reached C_{max} in under 6 h ($P = 0.06$). PA was also detectable in the urine at 8 h after dosing, and prior to dosing on day 15 (data not shown).

Quality of life assessments, including the MSAS and SF-36 instruments, showed trends towards increased frequency of nausea, and increased frequency and severity of vomiting and loss of appetite on treatment, but these trends did not reach statistical significance (Table 1). There was also a suggestion of deterioration in ability to perform activities of daily life of the SF-36 questionnaire while on treatment. These symptoms were more pronounced at the higher dose levels (data not shown). Of note, 30–50% of patients reported nausea and lack of appetite, and up to 70% of patients reported limitations in physical ability as baseline symptoms prior to starting perillyl alcohol.

Table 1 Quality of life data

	Baseline	Day 14[a]	Day 28
MSAS questionnaire[b]			
Nausea	9 (47%)	10 (71%)	6 (67%)
Vomiting	6 (32%)	7 (50%)	4 (44%)
Lack of appetite	6 (32%)	7 (50%)	5 (56%)
SF36 questionnaire[c]			
Cut down on activity time	6 (40%)	8 (57%)	5 (63%)
Accomplished less	8 (53%)	9 (64%)	5 (63%)
Limited in kind of work/activity	7 (47%)	10(71%)	6 (75%)
Difficulty performing work/activity	10 (67%)	7 (50%)	5 (63%)

[a]Individual comparisons of patients with nausea, vomiting, or lack of appetite at baseline versus day 14 showed no statistically significant differences ($P = 0.38$, $P = 0.45$, $P = 0.50$, respectively)
[b]Baseline $n = 19$, day 14 $n = 14$, day 28 $n = 9$
[c]Baseline $n = 15$, day 14 $n = 14$, day 28 $n = 8$

Discussion

This phase I trial was designed to determine the MTD of perillyl alcohol given orally on a four-times-daily schedule, without interruption. The MTD was determined to be 8400 mg/m^2 per day, or 2100 mg/m^2 per dose. The DLTs in this trial were nausea and vomiting, encountered in all patients at the highest dose level. In four patients treated at the MTD, the addition of an antiemetic (metoclopramide) alleviated nausea and/or vomiting somewhat. Antiemetics were offered once nausea and vomiting occurred, but were not administered prophylactically.

No antitumor activity was observed, but five patients continued on study for 2 months or more with stable disease, including one patient with advanced non-small-cell lung cancer who remained on study for 13 months. Pharmacokinetic data exhibited dose-dependent increases in C_{max} of PA, a metabolite of perillyl alcohol, but with high inter- and intrapatient variability.

Additional phase I trials of perillyl alcohol are summarized in Table 2. This trial employed a four-times-daily dosing regimen without a scheduled break in therapy. In a similar trial by Ripple et al., the MTD was identified as 4800 mg/m^2 per day on the four-times-daily dosing schedule [17]. Similar to their prior phase I trial using a three-times-daily schedule, the predominant toxicities were nausea, vomiting, satiety and belching, with significant interpatient variability in tolerance. Although gastrointestinal toxicity was mild (84% grade 1), the chronic nature of the toxicities made the treatment intolerable for many individuals. Several patients refused to continue on the trial despite only grade 1 toxicity, forcing the authors to include "patient intolerance" as a criterion for DLT. Evidence of antitumor activity was observed in one patient with meta-

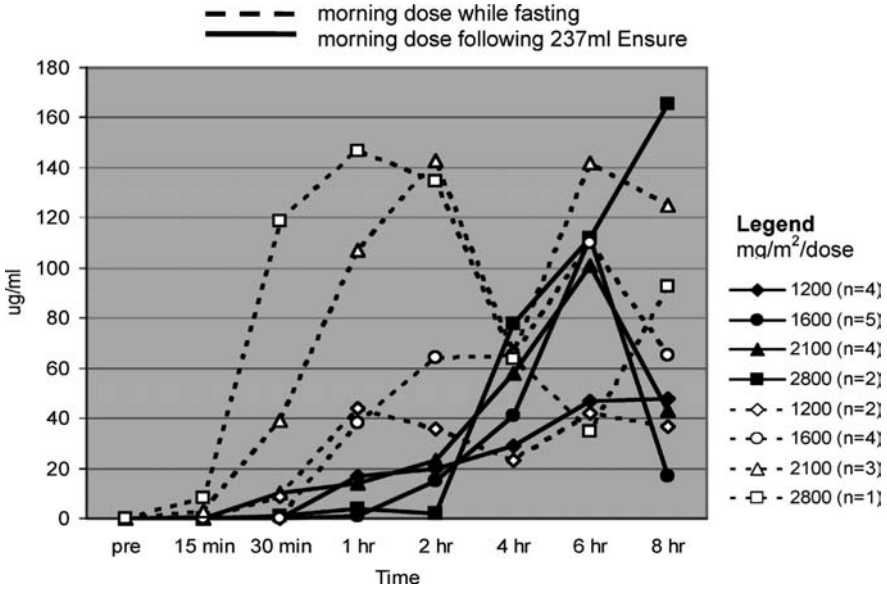

Fig. 1 Median plasma perillic acid levels. Note: error bars are not shown. High inter- and intrapatient variability made determinations of AUC and $t_{1/2}$ unreliable

Table 2 Summary of phase I trials of perillyl alcohol, delivered orally

Reference	Schedule	MTD (mg/m^2/day)	Toxicity
Current trial	Continuous treatment Four times daily	8400	Nausea, vomiting
[17]	Continuous treatment Four times daily	4800	Nausea, vomiting, early satiety, belching
[11]	14 days on, 14 days off Three times a day	6300	Nausea, fatigue
[16]	Continuous treatment Three times daily	Not determined (maximum dose delivered was 7200 mg/m^2/day)	Nausea, vomiting, early satiety, belching

static colorectal cancer with near complete resolution of pulmonary nodules persisting for more than 2 years. In addition, two patients with hormone-refractory prostate cancer, and one patient with adenoid-cystic carcinoma of the salivary gland demonstrated prolonged stable disease on perillyl alcohol for 8–13 months [17].

In a more recent phase I trial performed by Hudes et al., 17 patients were treated on a three-times-daily dosing schedule for 14 consecutive days in a 28-day cycle. On this regimen, the MTD was 6300 mg/m^2 per day with chronic nausea and fatigue limiting administration at 8400 mg/m^2 per day. Grade 1–2 hypokalemia was reported as a common side effect, and one patient developed grade 3 mucositis at the 8400 mg/m^2 per day level. Correlative studies failed to identify alterations in expression of various oncogenes (p21-*ras*, *rap1*, *rhoA*) in peripheral blood mononuclear cells [11].

Pharmacokinetic studies of perillyl alcohol have been challenging due to high inter- and intrapatient variability. Similar to the published results of other investigators, we could not detect perillyl alcohol in the plasma using standard gas chromatographic-mass spectrometry (GC-MS), presumably due to rapid metabolism of the drug [11, 17]. Perillyl alcohol levels have been successfully measured in plasma at levels as low as 2 ng/ml using ion-trap GC-MS with NH_3 chemical ionization and isotope-labeled internal standards [23].

We were able to measure the metabolite PA in serum and urine using standard GC-MS. However, reproducible, time-dependent changes were not observed. Toxicity and patient tolerance due to nausea did not correlate with observed C_{max} or estimated AUC. Both Ripple et al. and Hudes et al. measured levels of PA and DHPA after fixed doses of perillyl alcohol [11, 17]. Similar to this trial, peak plasma levels of PA occurred 2–3 h following ingestion, and there was little evidence to suggest that taking the drug on an empty stomach, versus with food, affected AUC. PA levels were consistently higher than DHPA levels, with similar trends in C_{max} and AUC. High inter- and intrapatient variability in all trials published to date has allowed few conclusions regarding the relationship of AUC and toxicity. The $t_{1/2}$ of PA has been calculated to be between 1 and 2 h, with no evidence of drug accumulation in the blood with time [11, 17].

Given that the oral bioavailability of perillyl alcohol is unknown, and given the observed variability in this and prior trials, it may be difficult to describe the pharmacokinetics of perillyl alcohol without resorting to an intravenous formulation of the drug. Our quality of life data suggest that oral consumption of perillyl alcohol is an unpleasant experience for most patients due to nausea and loss of appetite.

The variable MTDs calculated in the phase I trials of perillyl alcohol are attributable to the nonspecific and subjective gastrointestinal side effects of the drug. In the recent phase I trial by Ripple et al., some patients suffered only low-grade nausea, vomiting, and loss of appetite but withdrew from treatment due to overall gastrointestinal intolerance. Given the significant interpatient variability found in prior trials, it is not surprising that a higher MTD could be achieved in this trial. Additional toxicities, including myelosuppression and mucositis, which were found in previous phase I trials, were not encountered in this trial. Phase II trials of perillyl alcohol are currently underway in hormone-refractory prostate, breast, ovarian and colorectal cancer at doses in the range 4800–6400 mg/m^2 per day delivered in four divided doses [17].

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