Phase I Clinical and Pharmacokinetic Study of Perillyl Alcohol Administered Four Times a Day

Gregory H. Ripple, Michael N. Gould, Rhoda Z. Arzooomanian, Dona Alberti, Chris Feierabend, Kris Simon, Kim Binger, Kendra D. Tutsch, Marcia Pomplun, Amy Wahamaki, Rebecca Marnocha, George Wilding, and Howard H. Bailey

University of Wisconsin Comprehensive Cancer Center, Developmental Therapeutics Program, Madison, Wisconsin 53792

ABSTRACT

We conducted a phase I dose-escalation trial of perillyl alcohol (POH; NSC 641066) given p.o. on a continuous four times a day basis to characterize the maximum tolerated dose, toxicities, pharmacokinetic profile, and antitumor activity. Sixteen evaluable patients with advanced refractory malignancies were treated at the following doses: level 1 (L1), 800 mg/m²/dose; L2, 1200 mg/m²/dose; L3, 1600 mg/m²/dose. POH was formulated in soft gelatin capsules containing 250 mg of POH and 250 mg of soybean oil. The predominant toxicities seen were gastrointestinal (nausea, vomiting, satiety, and eructation), which were dose limiting. There appeared to be a dose-dependent increase in levels of the two main metabolites, perillic acid and dihydroperillic acid. No significant differences were seen whether the drug was taken with or without food. There was a trend toward decreasing metabolite levels on day 29 compared with days 1 and 2. Peak metabolite levels were seen 1–3 h post ingestion. Metabolite half-lives were ~2 h. Approximately 9% of the total dose was recovered in the urine in the first 24 h, the majority as perillic acid. Evidence of antitumor activity was seen in a patient with metastatic colorectal cancer who has been conducted in Great Britain (4, 5). Evidence of clinical activity consisted of a partial response in a patient with breast cancer and stable disease for ≥6 months in three patients with colorectal cancer.

POH3 (see Fig. 1), a naturally occurring hydroxylated monomeric monoterpene, has been shown to be markedly more potent (>5-fold) than limonene at inducing tumor regression in rats (6). Preclinical studies have shown antitumor and/or preventative effects in mammary, pancreatic, colon, stomach, lung, skin, and liver cancers in rodent models (7–14). The mechanism of the antitumor activity of the terpenes has not been established, but several potentially important drug-related activities have been observed, including G1 cell cycle arrest and induction of apoptosis (15), inhibition of isoprenylation of a class of 21- to 26-kDa proteins involved in signal transduction, and differential gene regulation, including overexpression of the M6P/IGF II and TGF-β type II receptor genes (14, 16). Ariazi et al. demonstrated a temporal correlation between POH-mediated rat mammary carcinoma regression and activation of the TGF-β signaling pathway. Induction of the TGF-β-related genes, TGF-β1, the M6P/IGF II receptor, TGF-β type I and II receptors, and Smad3 was noted. In situ protein expression studies confirmed up-regulation and showed colocalization of TGF-β1, the M6P/IGF II receptor, TGF-β type I and II receptors, and Smad2/Smad3 in epithelial cells. RNA expression studies demonstrated differential expression of cell cycle- and apoptosis-related genes: p21Cip1/WAF1, bax, bad, and annexin I were induced; cyclin E and cyclin-dependent kinase 2 were repressed; and bcl-2 and p53 were unchanged. None of the POH-mediated activities were observed in normal mammary tissues (17).

As a result of the above preclinical work, a phase I dose-escalation trial was undertaken to assess the pharmacokinetics and toxicity of POH. The results with POH administered p.o. on a continuous tid schedule have been reported previously (18).

INTRODUCTION

Monoterpenes are formed by the condensation of two isoprene molecules. The compounds are produced primarily by plants and are found in many commonly consumed fruits and vegetables. Limonene, the first monoterpene to be studied as an anticancer agent, has been shown in preclinical studies to prevent tumor development and to cause regression of primary rat mammary carcinomas (1–3). A phase I trial of limonene has been conducted in Great Britain (4, 5). Evidence of clinical activity consisted of a partial response in a patient with breast cancer and stable disease for ≥6 months in three patients with colorectal cancer.

Received 7/19/99; revised 10/18/99; accepted 10/19/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported by Grants NIH-U01CA62591, RR03186, CaP CURE, and R37CA38128.

2 To whom requests for reprints should be addressed, at University of Wisconsin Comprehensive Cancer Center, 600 Highland Avenue, Madison, WI 53792. Phone: (608) 263-8600; Fax: (608) 263-8613.

3 The abbreviations used are: POH, perillyl alcohol; M6P/IGF II, mannose-6-phosphate/insulin-like growth factor II; TGF-β, transforming growth factor-β; tid, three times a day; GI, gastrointestinal; AUC, area under the curve; qid, four times a day; PA, perillic acid; DHPA, dihydroperillic acid; t1/2, half-life; NCI, National Cancer Institute; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; cmax, peak plasma concentration; tmax, time to peak concentration; L1, L2, and L3, levels 1, 2, and 3.
The predominant toxicity, which appeared to be dose related, was GI, consisting of nausea and vomiting, early satiety, and eructation. The toxicity was generally mild (grade 1–2) by traditional grading criteria but was occasionally considered intolerable due to the chronic nature of the toxicity. Dose escalations >1600 mg/m²/dose did not increase the peak plasma levels or AUCs of the metabolites, PA and DHPA, and the observed $t_{1/2}$ of the metabolites were relatively short (~2 h). Doses >1600 mg/m² did appear to be associated with greater toxicity. Preclinical data have implied that the optimum delivery of POH would result in relatively high, sustained concentrations of the metabolites. Given this and the apparent ceiling effect in metabolite levels with larger individual doses, a more frequent dosing schedule was chosen to achieve more constant metabolite exposure or greater AUC. Here, we report results with the drug given on a continuous qid basis.

**PATIENTS AND METHODS**

**Patient Selection.** Individuals with advanced malignancy for whom no effective standard therapy was available and who gave informed written consent according to Food and Drug Administration and institutional guidelines were eligible. Patients were required to have adequate bone marrow function (WBC count ≥4,000/mm³; absolute neutrophil count ≥1,500/ mm³, and platelet count ≥100,000/mm³), renal function (blood urea nitrogen ≤30 mg/dl; creatinine ≤1.5 mg/dl), and hepatic function (bilirubin ≤1.5 mg/dl; aspartate aminotransferase ≤2.0 times upper limit of normal). Patients with an Eastern Cooperative Oncology Group performance status >2, life expectancy <12 weeks, or brain metastases were ineligible. Patients must not have received any hormonal or immunological therapy within 2 weeks or cytotoxic chemotherapy or radiation therapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of receiving the drug. Patients were required to have radiographically measurable or evaluable disease. Patients were not permitted to take cholesterol-lowering agents, vitamins, or other antihypertensive agents while on study.

**Drug Formulation.** POH was formulated in soft gelatin capsules containing 250 mg of POH and 250 mg of soybean oil. Capsules were supplied by the Investigational Drug Branch, Division of Cancer Treatment, Diagnosis and Centers, NCI (Bethesda, MD).

**Drug Administration and Dose Escalation.** POH was administered p.o. on a continuous qid basis. Patients remained on the drug until evidence of disease progression, the development of irreversible or life-threatening toxicity, patient refusal to continue therapy, or changes in a patient’s condition rendering him or her unacceptable for further therapy in the judgement of the investigator.

Dose escalation was carried out according to a standard phase I design. The starting dose was based on experience obtained with POH given on a continuous tid schedule. A minimum of three patients were treated and evaluated for ≥4 weeks at each dose level prior to dose escalation. If one of the initial three patients experienced a DLT, three additional patients were to be added at the same dose level. DLT was defined as any toxicity of grade 3 or higher according to NCI common toxicity criteria that occurred within the first 4 weeks on study with the following additions: grade 2 or higher vomiting of ≥3 days duration, grade 2 or higher diarrhea of ≥3 days duration, grade 2 or higher creatinine, and patient refusal to continue on therapy because of drug intolerance regardless of the grade of toxicity. The MTD was defined as the dose level prior to that at which two or more of six patients experienced DLT. Hematological and nonhematological parameters were monitored weekly during courses 1, 2, and 3 and every 2 weeks thereafter.

During course 1, patients took only one dose of drug on days 1 and 2. Patients were randomized to take their day 1 dose in a fasting versus fed state. Their day 2 dose was taken in the opposite manner. Patients were hospitalized on the General Clinical Research Center unit for these 2 days and received standardized meals and snack controlled for intake of fat and total calories. The day on which drug was taken with food, patients received three meals and a snack at bedtime. The day on which drug was taken without food, patients received two meals (lunch and dinner) and a snack. Men received a total of 2400 kcal (2200 on fasting days), and women received 1800 kcal (1600 on fasting days) divided into 15% protein, 40% fat, and 45% carbohydrate.

**Pharmacokinetic Sampling.** During course 1, heparinized blood samples were collected to measure POH and its metabolites at baseline (assay blank) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 23, and 25 h on days 1 and 2. On day 15 of course 1 and day 1 of course 2 or later courses, samples were drawn before the drug was administered and at 0.5, 1, 1.5, 2, 3, 4, and 6 h after ingestion of the first dose. Urine samples were collected for patients at all three dose levels but were complete only for patients at L2 and L3. A 24-h collection was performed on day 1, and 6-h collections were performed on days 15 and 29.

**Analytical Methods.** POH, PA, and DHPA were measured in plasma and urine, using the gas chromatographic method of Phillips et al. (19). Standards for the assay were provided by the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, NCI. For each single-dose concentration-time data set, pharmacokinetic parameters for PA and DHPA were determined by noncompartmental methods (20). The AUC for 0–6 h was determined using the linear trapezoidal rule. The $c_{\text{max}}$ and $t_{\text{max}}$ were determined by direct inspection of the data. The single-dose $t_{1/2}$ was determined by log-linear regression on the terminal portion of the concentration-time curve. PKAnalyst (MicroMath Scientific Software, Salt Lake City, UT) and Sigma Stat (Jandel Scientific, San Rafael, CA) were used to determine the AUC and to perform the linear regression.
Phase I Trial of Perillyl Alcohol

RESULTS

were treated for a total of 76 courses. One patient (L3) remains completing 1 month of therapy. Therefore, 16 evaluable patients removed with symptomatic disease progression prior to noncompliance unrelated to drug toxicity, and a third (L3) was (one at L2 and one at L3) were removed from study because of dosing schedule. The dose escalation scheme is shown in Table 1. Three patients were not evaluable for toxicity. Two patients removed with symptomatic disease progression prior to completing 1 month of therapy. Therefore, 16 evaluable patients were treated for a total of 76 courses. One patient (L3) remains on study at >24 months. Patient characteristics are shown in Table 2. All patients except one (with hormone-refractory prostate cancer) had received prior chemotherapy or radiation therapy.

Toxicity. Table 3 summarizes the toxicity data. The predominant toxicity seen was GI. This was generally mild (grade 1). Three patients developed GI toxicity more severe than grade 1. At L3, one patient experienced grade 2 nausea and vomiting, and another experienced grade 3 nausea and vomiting. One patient at L2 experienced grade 2 nausea and vomiting. Two of these patients had ovarian cancer, and one had metastatic rectal cancer. An additional patient at L3 requested removal from study after 4 days because of drug intolerance consisting of grade 1 nausea and vomiting. Other GI symptoms included early satiety, anorexia, eructation, and unpleasant taste. The episode of grade 3 nausea and vomiting and the removal of the patient from study at their request because of drug intolerance constituted DLTs by the definitions set out in this protocol.

No significant problems with myelosuppression were seen. Grade 1 leukopenia and neutropenia were observed in several patients, but this did not appear to be drug related. Grade 1 anemia and thrombocytopenia were seen in one patient (L1). Three patients (seven courses) at L2 experienced grade 1 fatigue that was thought to be drug related. No hepatic, renal, or neurological toxicity thought to be related to the drug was seen. Overall, the drug appeared to be better tolerated when taken in a fed state as opposed to fasting.

Pharmacokinetics. Tables 4 and 5 summarize the pharmacokinetic data. Peak plasma levels of the two main metabolites occurred 1–2.5 h post ingestion for PA and 2–3.5 h post ingestion for DHPA. The t1/2 for the metabolites were ~1–2 h for PA and 1.5–2.5 h for DHPA. Plasma metabolite levels (cmax and 6-h AUC) were considerably higher for PA than for DHPA. These results are similar to those seen with POH given on a continuous tid schedule.

Statistical analysis was done by paired t test. No significant differences were seen in metabolite levels at any given dose level when comparing drug taken in a fasting versus fed state. When analyzed by combining data from all three doses and comparing metabolite levels in a fed versus fasting state, the 6-h AUC for PA was significantly higher when POH was taken without food (P = 0.032). No other statistically significant differences were seen.

In general, metabolite levels (cmax and AUC) appeared to increase from L1 to L3, although this increase was significant.
only at L3 (c_{max} and AUC for both metabolites were significantly greater at L3 than at either L1 or L2 on days 1 and 2). There was no evidence of drug accumulation. There was a trend toward decreasing metabolite levels on day 29 compared with days 1 and 2, although this was not statistically significant. Metabolite levels were rechecked at 7 months in two patients treated at L1 (who were on study for 13 and 10 months, respectively). In the first patient, metabolite levels were unchanged compared with the day 29 values. However, the second patient showed lower peak levels and AUCs for both metabolites: PA, c_{max} on day 29 and month 7 of 212 and 90 μM, respectively; PA, 6-h AUCs on day 29 and at month 7 were 324 and 151 μM × h, respectively. Levels of DHPA were >70% lower at month 7 compared with day 29. One patient at L3 had metabolite levels rechecked at month 13 and also showed substantially lower levels compared with day 29 (40–50% reduction in c_{max} and AUCs for both PA and DHPA).

Urinary drug and metabolite levels are summarized for patients at L2 and L3 in Table 6. Approximatively 8–9% of the total dose was recovered in the urine in the first 24 h following drug administration on days 1 and 2, and no difference was seen whether the dose was taken with or without food. A similar proportion of drug was recovered in the first 6 h post drug administration on days 15 and 29. This is consistent with results

---

**Table 4** Single-dose pharmacokinetic parameters for PA

At each dose level, the peak plasma concentration (c_{max}), time to peak plasma concentration (t_{max}), area under the concentration-time curve for the first 6 h (6-h AUC), and plasma half-life (t_{1/2}) are shown for PA on days 1 and 2 (in both the fed and fasting state), day 15, and day 29. Values represent means ± SD.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>c_{max} (μM)</th>
<th>t_{max} (h)</th>
<th>6-h AUC (μM × h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>215 ± 89</td>
<td>1.2 ± 1.8</td>
<td>399 ± 143</td>
<td>0.85 ± 0.44</td>
</tr>
<tr>
<td>Fasting</td>
<td>297 ± 197</td>
<td>2.0 ± 1.7</td>
<td>553 ± 308</td>
<td>0.46 ± 0.16</td>
</tr>
<tr>
<td>Day 15</td>
<td>167 ± 129</td>
<td>1.3 ± 1.4</td>
<td>183 ± 117</td>
<td>NA^a</td>
</tr>
<tr>
<td>Day 29</td>
<td>138 ± 96</td>
<td>1.2 ± 0.6</td>
<td>187 ± 138</td>
<td>NA</td>
</tr>
<tr>
<td>L2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>232 ± 59</td>
<td>1.4 ± 0.9</td>
<td>483 ± 215</td>
<td>2.0 ± 1.7</td>
</tr>
<tr>
<td>Fasting</td>
<td>339 ± 161</td>
<td>1.6 ± 0.6</td>
<td>797 ± 366</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>Day 15</td>
<td>302 ± 137</td>
<td>1.8 ± 1.2</td>
<td>442 ± 101</td>
<td>NA</td>
</tr>
<tr>
<td>Day 29</td>
<td>189 ± 96</td>
<td>2.5 ± 1.5</td>
<td>352 ± 178</td>
<td>NA</td>
</tr>
<tr>
<td>L3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>493 ± 216</td>
<td>1.8 ± 0.9</td>
<td>1241 ± 559</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Fasting</td>
<td>415 ± 187</td>
<td>1.9 ± 0.8</td>
<td>1351 ± 733</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>Day 15</td>
<td>422 ± 201</td>
<td>1.6 ± 1.1</td>
<td>710 ± 733</td>
<td>NA</td>
</tr>
<tr>
<td>Day 29</td>
<td>416 ± 295</td>
<td>2.0 ± 1.2</td>
<td>699 ± 366</td>
<td>NA</td>
</tr>
</tbody>
</table>

^a NA, not applicable.

**Table 5** Single-dose pharmacokinetic parameters for DHPA

At each dose level, the peak plasma concentration (c_{max}), time to peak plasma concentration (t_{max}), area under the concentration-time curve for the first 6 h (6-hour AUC), and plasma half-life (t_{1/2}) are shown for DHPA on days 1 and 2 (in both the fed and fasting state), day 15, and day 29. Values represent means ± SD.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>c_{max} (μM)</th>
<th>t_{max} (h)</th>
<th>6-h AUC (μM × h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>12.8 ± 4.4</td>
<td>2.3 ± 0.6</td>
<td>45.1 ± 19.6</td>
<td>1.8 ± 0.7</td>
</tr>
<tr>
<td>Fasting</td>
<td>13.9 ± 9.3</td>
<td>2.7 ± 1.2</td>
<td>47.7 ± 31.0</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Day 15</td>
<td>10.2 ± 6.0</td>
<td>1.7 ± 1.3</td>
<td>27.6 ± 15.8</td>
<td>NA^a</td>
</tr>
<tr>
<td>Day 29</td>
<td>12.3 ± 8.2</td>
<td>1.8 ± 1.3</td>
<td>40.9 ± 31.8</td>
<td>NA</td>
</tr>
<tr>
<td>L2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>15.1 ± 6.2</td>
<td>1.8 ± 0.6</td>
<td>61.8 ± 39.5</td>
<td>2.3 ± 1.8</td>
</tr>
<tr>
<td>Fasting</td>
<td>18.1 ± 7.6</td>
<td>2.5 ± 0.6</td>
<td>68.7 ± 40.3</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>Day 15</td>
<td>23.5 ± 7.1</td>
<td>2.0 ± 1.3</td>
<td>59.8 ± 24.9</td>
<td>NA</td>
</tr>
<tr>
<td>Day 29</td>
<td>16.8 ± 12.4</td>
<td>2.7 ± 1.4</td>
<td>35.2 ± 29.9</td>
<td>NA</td>
</tr>
<tr>
<td>L3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 1 and 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food</td>
<td>38.6 ± 21.8</td>
<td>3.2 ± 0.9</td>
<td>162 ± 84</td>
<td>1.8 ± 0.8</td>
</tr>
<tr>
<td>Fasting</td>
<td>35.1 ± 19.7</td>
<td>3.6 ± 0.5</td>
<td>154 ± 93</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>Day 15</td>
<td>31.9 ± 13.9</td>
<td>2.0 ± 0.8</td>
<td>90.3 ± 48.1</td>
<td>NA</td>
</tr>
<tr>
<td>Day 29</td>
<td>41.3 ± 20.8</td>
<td>2.6 ± 0.9</td>
<td>101 ± 54</td>
<td>NA</td>
</tr>
</tbody>
</table>

^a NA, not applicable.
seen on the tid schedule in which ~9% of the total dose was recovered in the urine in 24 h, most of it in the first 8 h. No differences were seen between L2 and L3. The vast majority of drug was recovered as PA, with ~1% recovered as parent drug.

**TGF-β1 Levels.** Plasma TGF-β1 levels were characterized by marked interpatient variability and no clear correlation with response to therapy or toxicity. Mean levels at L2 and L3 were 3.8 ± 2.4 and 3.4 ± 2.2 ng/ml on day 1, and 2.6 ± 1.4 and 2.1 ± 0.6 ng/ml on day 29, respectively.

**Activity.** Evidence of objective tumor response was observed in a patient with metastatic colorectal cancer. The patient had a history of resected liver metastases and prior 5-fluorouracil and radiation therapy for metastatic colon cancer. In January 1997, new bilateral pulmonary nodules up to 2 cm in size were noted. The patient was started on POH (L3), and disease evaluation by computed tomography scanning was interpreted as stable for the first 8 months of therapy. Disease evaluation at month 10 revealed complete resolution of all lesions except one, which showed near-complete resolution. The patient remains on study at ≥2 years with no evidence of disease progression.

Several other patients showed evidence of prolonged disease stabilization. Two patients with hormone-refractory prostate cancer were treated at L1 with stable disease for 13 and 10 months, respectively. In addition, one patient with adenoidcystic carcinoma of the salivary gland was treated at L2 for 8 months before showing evidence of progressive disease.

**DISCUSSION**

The ability to treat most advanced malignancies with classic cytotoxic DNA-damaging agents is limited, with little curative potential and rare durable remissions. This has led to emphasis on the development of new therapeutic agents with novel mechanisms of action. POH is a monoterpene that has shown preclinical activity in a number of different tumor types, including mammary, pancreatic, stomach, lung, skin, and liver cancers. Although the mechanism of action is not yet clear, a number of potentially important drug-related activities have been observed in preclinical studies, including cellular effects such as an early G1 arrest and the induction of apoptosis, biochemical effects such as the inhibition of post-translational modification of proteins involved in signal transduction, and differential gene regulation with overexpression of the M6P/IGF-II and TGF-β type II receptor genes (15, 17, 18, 21).

Preclinical data suggested that these monoterpenes may have a tumorstatic effect and that the optimal schedule of administration would result in continuous drug exposure. The plasma t1/2 of POH is relatively short, suggesting that multiple daily doses would be required to achieve this effect. On the basis of this work, a phase I dose-escalation study was begun, with the drug initially given on a continuous tid basis (19). The most common toxicities observed in this study were GI, consisting of nausea, early satiety, eructation, and unpleasant taste as well as fatigue. The chronic nature of the toxicities led to problems with patient tolerance and compliance. In addition, pharmacokinetic studies did not show a significant difference in metabolite levels between the two highest doses (1600 and 2400 mg/m2), suggesting the possibility of saturation of the mechanism governing absorption or metabolism. On the basis of these results, the schedule was amended to a more frequent (qid) dosing schedule in hopes of achieving a greater (higher AUC) and more prolonged exposure to POH and/or its metabolites.

As on the tid schedule, the predominant toxicity seen with the drug administered continuously qid was GI. Three patients experienced GI toxicity more severe than grade 1, one at L2 (grade 2 nausea and vomiting), and two at L3 (one each with grade 2 and grade 3 nausea and vomiting). In addition, one patient treated at L3 was removed from study at the patient’s request after 4 days because of drug intolerance, consisting of grade 1 nausea and vomiting. Although this represents mild toxicity by traditional criteria, it was felt that chronic low-grade toxicities are more significant and have the potential to affect patient compliance in the setting of continuously administered agents.

Therefore, patient refusal to continue on study because of drug intolerance, regardless of grade of toxicity, was included in the criteria for DLT. By the study’s definition, two DLTs occurred at L3 and therefore, the L2 dose (1200 mg/m2/dose) was determined to be the MTD and the recommended phase II dose. However, there is considerable individual variability in drug tolerance. For example, one patient at L3 has been on study for ≥2 years with no significant toxicity. Two of the patients with GI toxicity greater than grade 1 had advanced ovarian cancer, a patient group in which GI symptoms are relatively
common, indicating the potential importance of patient selection. Mild (grade 1) fatigue also occurred, but was less frequent than on the tid schedule. No significant myelosuppression was seen, in contrast to the tid schedule, on which two heavily pretreated ovarian cancer patients developed neutropenia of grade 3 or higher. No significant hepatic, renal, or neurological toxicities thought to be related to the drug were seen. In general, patients seemed to feel they tolerated the drug better when taken with food than without.

The two main metabolites of POH seen in humans are PA and DHPA. Taking the drug in a fed versus fasting state did not have a significant impact on metabolite levels within any given dose level. Metabolite levels at L3 were higher than those seen at L2, although there was substantial interpatient variability. There was a trend toward higher levels at L2 than L1, but this did not reach statistical significance. Urinary metabolite levels showed a consistent proportion of total drug recovered in the first 24 h, indicating consistent absorption kinetics across the range of doses examined in this study.

The single-dose AUC0–6 h values for both PA and DHPA were similar to those seen on the tid schedule at comparable doses, suggesting more consistent exposure to higher circulating metabolite levels on the more frequent dosing schedule. Metabolite levels seen in random samples from rats at dietary levels of POH shown to be effective at inducing tumor regression were 390–480 µM for PA and 110–230 µM for DHPA. The peak levels of both metabolites were somewhat lower than this for patients treated at L2 on this study. At L3, the cmax for PA was similar to that seen in the rat studies, whereas the cmax for DHPA was below this range, possibly because of known species differences in metabolism. Pharmacodynamic analysis did not reveal any clear relationship between metabolite levels and either toxicity or response.

There was no evidence of drug accumulation. There was a trend toward decreasing metabolite levels on day 29 compared with days 1 and 2, although this was not statistically significant. Three patients had metabolite levels rechecked at >6 months on drug. In two of these patients, the levels were considerably lower than those seen on day 29, whereas in the third patient, they were unchanged. The reason for a decrease in metabolite levels with time on drug is not known. One possible explanation is that monoterpenes have been shown to up-regulate phase 1 enzyme activity and DHPA. Taking the drug in a fed state did not reveal any clear relationship between metabolite levels and either toxicity or response.

Objective evidence of antitumor activity has been seen in a patient with metastatic rectal cancer treated at L3. The patient had a significant and durable response with near complete resolution (>95%) of pulmonary nodules and remains on study at >2 years. Three other patients had prolonged stable disease. Two patients with hormone-refractory prostate cancer, both treated at L1, had stable disease for 10 and 13 months, respectively. The third patient, with adenocystic carcinoma of the salivary gland, was treated at L2 for 8 months before the disease progressed. The possible mechanism(s) of action POH imply that a clinically beneficial effect may be manifested only as disease stabilization in some patients.

Monoterpenes, including POH, have been shown to modify levels of growth factors and their receptors. In particular, increased levels of the M6P/IGF-II receptor and TGF-β1 have been seen in POH-treated, regressing tumors. The M6P/IGF-II receptor degrades IGF-II, a potent mitogen, and facilitates the activation of TGF-β1, which has been shown to inhibit both malignant and normal cell growth (24, 25). Plasma levels of TGF-β1 were measured in all patients at specified time points to investigate its potential role in the actions of POH. These results were characterized by marked inter- and intrapatient variability and no clear correlation with response to treatment. There are several possible reasons for this. The study sample was small and included only one patient with an objective response to treatment. Agitation of patient samples can increase levels via release of platelet TGF-β, and it is possible that the results, particularly of earlier samples, were affected by this. In addition, the preclinical work demonstrating an increase in TGF-β1 levels in regressing tumors was done by immunohistochemical analysis of tumor tissue, and it is possible that plasma levels do not correlate with levels within the tumor itself.

On the basis of the results of this study, the recommended starting phase II dose for POH given on a continuous qid basis is 1200 mg/m²/dose, with dose escalation to 1600 mg/m²/dose for those who can tolerate an increased dose. Phase II studies of POH given on this schedule have started with hormone-refractory prostate cancer, breast cancer, ovarian cancer, and colorectal cancer.

REFERENCES

Phase I Clinical and Pharmacokinetic Study of Perillyl Alcohol Administered Four Times a Day


**Updated version**
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/6/2/390

**Cited articles**
This article cites 22 articles, 13 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/6/2/390.full.html#ref-list-1

**Citing articles**
This article has been cited by 8 HighWire-hosted articles. Access the articles at:
/content/6/2/390.full.html#related-urls

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.