Cancer Therapy: Clinical

Voreloxin, a First-in-Class Anticancer Quinolone Derivative, in Relapsed/Refractory Solid Tumors: A Report on Two Dosing Schedules

Ranjana H. Advani1, Herbert I. Hurwitz2, Michael S. Gordon3, Scot W. Ebbinghaus4, David S. Mendelson3, Heather A. Wakelee1, Ute Hoch5, Jeffrey A. Silverman7, Nancy A. Havrilla8, Craig J. Berman8, Judith A. Fox8, Roberta S. Allen8, and Daniel C. Adelman8

Abstract

Purpose: Voreloxin, a novel replication-dependent DNA-damaging agent, intercalates DNA and inhibits topoisomerase II. Voreloxin induces site-selective DNA double-strand breaks and apoptosis. We report the phase 1 experience of voreloxin in patients with relapsed/refractory solid tumors, including dose-limiting toxicity (DLT), maximum-tolerated dose (MTD), pharmacokinetics, and clinical activity.

Experimental Design: Two dose-escalation studies evaluated voreloxin administered i.v. every 3 weeks (SPO-0001) or weekly for 3 weeks every 28 days (SPO-0002). In SPO-0001, patients were classified as heavily pretreated (HP) or minimally pretreated (MP) based on therapeutic history.

Results: In the SPO-0001 study, 41 patients (24 HP/17 MP) were treated in eight dose cohorts (3-75 mg/m²). At 60 mg/m², four HP patients experienced DLTs: grade 4 neutropenia (n = 3, one with fever) and grade 3 febrile neutropenia/pneumonia (n = 1). At 75 mg/m², two MP patients experienced DLTs: grade 4 neutropenia/thrombocytopenia (n = 1) or grade 2 oral thrush for >29 days (n = 1). Therefore, the MTD was 48 mg/m² (HP patients) and 60 mg/m² (MP patients). In the SPO-0002 study, 21 patients were treated in six dose cohorts (3-24 mg/m²). At 18 mg/m², two patients experienced DLTs: grade 3 neutropenia, one with pleural effusion (>14 days each). The MTD was 15 mg/m². Voreloxin exhibited low clearance (2 L/h/m²), a long terminal half-life (22 hours), and dose-proportional exposure. Overall, 31 of 62 patients had stable disease and 1 patient (ovarian cancer) had a partial response per Rustin criteria.

Conclusions: Voreloxin showed an acceptable safety profile with clinical activity in patients with relapsed/refractory solid tumors. The MTD was schedule-dependent. Voreloxin is currently in clinical studies of ovarian cancer and acute myeloid leukemia. Clin Cancer Res; 16(7); 2167–75. ©2010 AACR.

Voreloxin, a novel naphthyridine analogue, is structurally related to the quinolone class of compounds and is the first member of a new drug class of anticancer quinolone derivatives. Quinolone derivatives have been shown to mediate antitumor activity by targeting mammalian topoisomerases and have shown promising preclinical antitumor activity (1–4). Voreloxin is a replication-dependent DNA-damaging agent that intercalates DNA and inhibits topoisomerase II. Voreloxin induces site-selective DNA double-strand breaks, G2 arrest, and apoptosis (5).

Preclinical data have shown that voreloxin has potent, dose-dependent cytotoxic activity in multiple tumor models, including human xenografts and several multidrug-resistant and aggressive murine syngeneic tumor models (6). Studies with voreloxin in rodents and non-human primates have shown that the compound has favorable pharmacokinetic properties: dose-proportional exposure, low interindividual and intraindividual variability, and moderate clearance (7, 8). Voreloxin is not a substrate for the P-glycoprotein efflux pump and is not dependent on p53 family members for its activity (9), unlike other DNA intercalators and topoisomerase II inhibitors that are susceptible to these common drug resistance mechanisms (10–12).
We report the results of two phase 1 studies (SPO-0001 and SPO-0002) conducted in patients with a variety of relapsed/refractory solid tumors. The objectives were to determine the safety and tolerability of voreloxin administered by i.v. injection either once every 3 weeks or once weekly for 3 weeks every 28 days (six cycles in total), assess the pharmacokinetic profile after one i.v. dose, define the recommended dosing schedule for phase 2 studies, and obtain preliminary objective tumor response data. The primary end points were determination of dose-limiting toxicities (DLT) and the maximum-tolerated dose (MTD).

Materials and Methods

Study design. SPO-0001 and SPO-0002 were open-label, phase 1, dose-escalation studies conducted in four medical centers in compliance with local institutional review board approval. All patients provided informed consent in accordance with the principles of the Declaration of Helsinki. Eligibility criteria, safety and efficacy assessments, dose-escalation procedures, DLT definitions, pharmacokinetic sampling schedule, and methods were identical for both studies.

Patient selection. Eligible patients were required to be 18 y of age or older with advanced, measurable, histologically or cytologically confirmed, relapsed or refractory solid tumors. Required pretreatment laboratory values included hemoglobin, ≥9.0 g/dL; absolute neutrophil count (ANC), ≥1,500 cells/mm³; platelets, ≥100,000 plt/mm³; serum creatinine, ≤1.5 times the upper limit of normal; total bilirubin, ≤2 mg/dL; prothrombin time and international normalized ratio/activated partial thromboplastin time within the institutional normal limit; and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤ 3 times the upper limit of normal unless malignant hepatic involvement was present. Patients were required to have Eastern Cooperative Oncology Group performance status scores of 0-1, and prior to study initiation, must not have received any chemotherapy or immunotherapy within 4 wk or radiation therapy within 2 wk. Additionally, patients with active comorbid conditions or with a history of prior pelvic radiation or radiation to ≥ 25% of bone marrow reserve were excluded. Patients with brain metastases were excluded unless they had received adequate treatment for their central nervous system disease and had a minimum of 3 mo with no radiologic evidence of progressive central nervous system disease following treatment completion.

No limit was imposed on the number of therapies that patients could have received before enrollment. To characterize the dose-limiting effects of voreloxin in the context of prior therapy, in SPO-0001, patients were classified as heavily pretreated (HP) if they previously received more than six courses of an alkylator-containing chemotherapy regimen, had more than two courses of carboplatin or mitomycin-C, received any regimen containing a nitrosourea, had radiation to 25% of bone marrow areas, or had widespread bone metastases (13). Patients were classified as minimally pretreated (MP) if their therapeutic history did not meet the HP definition.

Treatment evaluation of two dosing schedules. Voreloxin was administered on day 1 of a 21-d cycle in SPO-0001 (dose levels 3, 6, 12, 24, 36, 48, 60, and 75 mg/m²) and on days 1, 8, and 15 of a 28-d cycle in SPO-0002 (dose levels 3, 6, 12, 15, 18, and 24 mg/m²), for up to six cycles. The initial dose for cohort 1 in both studies was 3 mg/m², which was doubled for subsequent cohorts until a protocol-defined DLT occurred. After the first DLT, dose escalation proceeded based on a modified Fibonacci sequence (13).

In both studies, voreloxin was administered undiluted at 10 mg/mL by i.v. injection over 10 min without antimetic premedication during cycle 1. Prophylactic antimetic therapy was allowed during subsequent cycles if the patient experienced vomiting. A DLT was defined as any of the following: ANC ≤ 500 cells/mm³ (grade 4 neutropenia) lasting more than 7 d or ANC ≤ 1,000 cells/mm³ (grade 3 neutropenia) accompanied by fever ≥ 38.5°C; platelet count < 25,000 plt/mm³ (grade 4 thrombocytopenia) or bleeding requiring transfusion; nonhematologic adverse events grade ≥ 3 by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0,9 or any adverse event requiring a voreloxin dose delay longer than 14 d. The MTD was

Translational Relevance

This original article describes the results of the initial clinical research studies with voreloxin, the first member of a new drug class of anticancer quinolones in clinical testing. Voreloxin, a first-in-class anticancer quinolone derivative, is a replication-dependent DNA-damaging agent that intercalates DNA and inhibits topoisomerase II. Voreloxin induces site-selective DNA double-strand breaks, G2 arrest, and apoptosis. Voreloxin has shown potent antitumor activity in a variety of nonclinical models. In these phase 1 dose-escalation studies in patients with relapsed or refractory solid tumors, the safety profile, pharmacokinetics, and preliminary clinical activity of voreloxin are described for two dosing schedules: every 3 weeks or weekly for 3 weeks. Based on these results, additional phase 1 and phase 2 clinical studies of voreloxin as a single agent were initiated in patients with ovarian cancer, lung cancer, and acute myeloid leukemia; and voreloxin in combination with cytarabine in patients with acute myeloid leukemia.

defined as the highest dose level that produced no more than a 33% incidence of DLT.

The target enrollment was three patients per dose cohort, with cohort expansion to six patients if a DLT was observed in one of the first three patients. Cohort expansion was discontinued after two patients experienced a DLT in a cohort, and the prior cohort dose was declared the MTD. After the MTD was determined, additional patients were enrolled at MTD to further assess safety and tolerability at the MTD.

**Assessment of response.** Objective tumor response was measured radiographically according to Response Evaluation Criteria in Solid Tumors (RECIST; ref. 14). In patients with ovarian cancer, response was also measured using the Rustin criteria, which defines response as either a 50% or 75% decrease in serum CA-125 levels (15).

**Assessments of safety and follow-up.** Patients had a physical examination, laboratory evaluation, vital signs assessment, and ECG at baseline. Laboratory values and vital signs were assessed at every visit for both studies. Adverse events were recorded beginning on the first day of treatment in cycle 1 through 28 d after the last treatment. Serious adverse events (SAE) were defined as events that resulted in death, were immediately life-threatening, resulted in or prolonged hospitalization, or caused significant disability/incapacity. The severity of adverse events was defined using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Adverse events assessed by the investigator as having a reasonable possibility of being causally related to voreloxin were followed until the condition returned to baseline grade, stabilized and was considered irreversible, or resulted in death. This assessment included patients who discontinued voreloxin treatment due to adverse events, but who did not withdraw consent for further follow-up. Safety data were collected for 28 d after the final dose of voreloxin was administered.

**Pharmacokinetic analysis.** The pharmacokinetic profile was determined for the first dose of voreloxin in SPO-0001 and for the first and third weekly doses in SPO-0002. Blood for pharmacokinetic evaluation was collected before the i.v. dose was administered, at the end of the infusion, and then at 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, 33, and 48 h postdose. Plasma samples were analyzed for voreloxin by Alta Analytical Laboratory, Inc., using a validated liquid chromatography-tandem mass spectrometry method that had a lower limit of quantitation of 1 ng/mL (401.45 ng was equivalent to 1 μmol/L of voreloxin). The analytic method for the determination of voreloxin concentrations in plasma has been described previously (16). Peak concentration (C_{max}), area under the concentration-time curve (AUC), time zero to infinity (AUC_{0-inf}), mean residence time when the drug concentration-time profile was extrapolated to infinity (MRT_{inf}), terminal half-life, total body clearance, and apparent volume of distribution at steady state (V_{ss}) were estimated by noncompartmental analysis assuming bolus administration, using WinNonlin software (version 4.1, Pharsight Corporation).

### Results

**SPO-0001**

**Patient characteristics.** Forty-three patients were enrolled and 41 were treated between June 2004 and December 2005. Two patients did not receive voreloxin due to active comorbid conditions. The treatment population consisted of 25 males and 16 females with a median age of 59 years (Table 1). The most common tumor type was ovarian (n = 9), followed by non–small cell lung (n = 6) and colon (n = 5) cancer. Seventeen patients (42%) classified as MP received a median of 2 prior anticancer treatments; 24 (59%) classified as HP received a median of 5.5 prior anticancer treatments.

**Determination of MTD.** No patients enrolled in the 3, 6, 12, 24, or 36 mg/m2 groups experienced a DLT. At
48 mg/m², one of three patients developed DLTs (grade 4 neutropenia); therefore, the cohort was expanded to six patients and no further events occurred. Eight patients were treated at the next cohort dose at 60 mg/m² (five HP, three MP). Although none of the MP patients experienced DLTs, four of the HP patients experienced DLTs: grade 4 neutropenia (n = 3, one with fever), and grade 3 febrile neutropenia with pneumonia (n = 1). Thereafter, dose escalation proceeded separately for HP and MP patients. For the HP group, 5 additional patients were treated at the previous dose level (48 mg/m²) for a total of 11 patients; 2 patients experienced DLTs with grade 4 neutropenia (1 with concomitant grade 4 thrombocytopenia and grade 3 nausea/vomiting), and this dose was considered the MTD. For the MP group, dose escalation continued as planned to the next dose level of 75 mg/m², the level at which two patients experienced DLTs (one patient with grade 4 neutropenia and grade 4 thrombocytopenia, and one patient with grade 2 oral thrush lasting 29 days and grade 3 neutropenia), and further dose escalation was stopped. Thus, according to the predefined DLT criteria, MTDs were determined to be 48 mg/m² for HP patients and 60 mg/m² for MP patients. A summary of protocol-defined DLTs is presented in Table 2.

Safety profile. The median number of completed cycles was three (range, one to six). Eleven (27%) patients (five HP and six MP) completed all six cycles. Overall, nausea was the most frequent adverse event of any relationship or grade (25 of 41 patients, 61%), followed by vomiting (42%), neutropenia (37%), fatigue (32%), and constipation (29%). Nonhematologic toxicity was mild, grades 1 to 2 in severity, and transient in most patients. Grades 3 or 4 nonhematologic toxicity was reported in 18 patients, all at voreloxin doses of ≥48 mg/m² as shown in Table 3.

Neutropenia was the most commonly reported grade 3 to 4 hematologic event in patients treated with 48 mg/m² or higher: grade 4 neutropenia (n = 12) and grade 3 neutropenia (n = 3, one with fever). The ANC nadir occurred between days 7 and 14 of cycle 1, and recovery was within 14 to 21 days for most patients. Other hematologic toxicities reported were grade 3 anemia (n = 4) and grade 4 thrombocytopenia (n = 2). No patient required a voreloxin dose delay longer than 14 days after cycle 1, or had bleeding requiring transfusion.

In 10 patients, toxicities were considered to be SAEs, and six of the events experienced by 5 patients were assessed as related to voreloxin as shown in Table 3. Six patients died during the study; all deaths were secondary to disease progression.

**Table 2. DLTs of voreloxin**

<table>
<thead>
<tr>
<th>Voreloxin dose (mg/m²)</th>
<th>SPO-0001 (n = 41)</th>
<th>SPO-0002 (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, 6, 12, 24, 36</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>75</td>
<td>3, 6, 12, 15, 18, 24</td>
<td></td>
</tr>
<tr>
<td>No. of patients with DLTs</td>
<td>HP 3 4 2 0 2 1</td>
<td>HP 3 4 2 0 2 1</td>
</tr>
<tr>
<td>Pretreatment status (HP/MP)</td>
<td>HP 3 4 2 0 2 1</td>
<td>HP 3 4 2 0 2 1</td>
</tr>
<tr>
<td>Protocol-defined DLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC ≤500/μL lasting &gt;7 d</td>
<td>0 3 3 1 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>ANC ≤1,000/μL with fever &gt;38.5°C</td>
<td>0 0 2 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Platelets &lt;25,000/μL</td>
<td>0 1 0 1 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>0 0 0 0 0 0 0</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Nonhematologic AE grade ≥3</td>
<td>0 2 1 0 1 0</td>
<td>0 1 0 0 0 0</td>
</tr>
<tr>
<td>Any AE grade requiring dose delay &gt;14 d</td>
<td>0 0 0 0 0 0</td>
<td>2 0 0 0 0 0</td>
</tr>
<tr>
<td>Inability to receive all three doses in cycle 1 due to any AEs related to voreloxin</td>
<td>0 0 0 1 0</td>
<td>2 0 1 0 0 0</td>
</tr>
</tbody>
</table>

NOTE: Dose group (number of patients) in SPO-0001: 3, 6, 12, and 24 mg/m² (3 each), 36 mg/m² (6), 48 mg/m² (11), 60 mg/m² (8), and 75 mg/m² (4); SPO-0002: 3 mg/m² (4), 6 mg/m² (3), 12 mg/m² (3), 15 mg/m² (6), 18 mg/m² (4), and 24 mg/m² (1). Voreloxin dosing was every 3 wk (SPO-0001) or weekly for 3 wk every 28 d (SPO-0002). Abbreviations: NE, not evaluated; AE, adverse event.
experienced DLTs (two with grade 3 neutropenia, one with a pleural effusion requiring voreloxin dose delay for recovery and causing inability to receive all three doses in cycle 1). Per study design, the next cohort dose was reduced further to 15 mg/m$^2$, and at this level, none of the six patients experienced a DLT. Therefore, the MTD for the weekly dosing schedule was determined to be 15 mg/m$^2$.

**Safety profile.** Two of the 21 patients completed all six cycles of treatment with a follow-up assessment at 28 days. For the remaining 19 patients, study discontinuation was due to disease progression ($n = 13$); adverse event (grade 3 neutropenia, hepatic steatosis), withdrawal of consent, or physician discretion ($n = 2$ each). Adverse events of any relationship or grade included nausea and constipation ($n = 8$), abdominal pain ($n = 6$), diarrhea, vomiting, pyrexia, and pain in extremity ($n = 5$ each). No grade 4 hematologic or nonhematologic events were reported. Four patients experienced grade 3 neutropenia: 15 mg/m$^2$ ($n = 1$), 18 mg/m$^2$ ($n = 2$), and 24 mg/m$^2$ ($n = 1$). All grade 3 non-hematologic adverse events at 18 mg/m$^2$ occurred in a single patient, and all but one event at 6 mg/m$^2$ occurred in a single patient. Five patients experienced six SAEs, including one each of gastrointestinal obstruction, bile duct obstruction, recurrent malignant pleural effusion, increased abdominal pain, pneumonia (exacerbation of), and congestive heart failure. None of the SAEs was assessed by the investigators as related to voreloxin.

One patient with a history of hypertension, hyperlipidemia, myocardial infarction, coronary artery disease, and

### Table 3. All grade 3/4 adverse events in SPO-0001 ($n = 41$)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Voreloxin dose (mg/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Small intestinal obstruction</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcal infection</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE: Additional SAEs included grade 2 right leg thrombosis (related), febrile neutropenia (related), and pancreatitis (not related), and grade 5 left hemiplegia/pleural effusion in the same patient (both not related). Dose group (number of patients): 3, 6, 12, and 24 mg/m$^2$ (3 each), 36 mg/m$^2$ (6), 48 mg/m$^2$ (11), 60 mg/m$^2$ (8), 75 mg/m$^2$ (4). Voreloxin dosing was every 3 wk (SPO-0001) or weekly for 3 wk every 28 d (SPO-0002).

*Related SAE.
†Unrelated SAE.
congestive heart failure died on study due to congestive heart failure and pneumonia considered unrelated to voreloxin.

**Pharmacokinetics**

Pharmacokinetic evaluation of the first dose of voreloxin on cycle 1 day 1 (both studies) and the third dose on day 15 (SPO-0002) showed that plasma voreloxin concentrations were highest immediately postdose, ranged from 0.07 to 14.4 \( \mu \text{g/mL} \), and declined in a biphasic fashion consisting of a short initial phase followed by a longer terminal phase (Fig. 1). Pharmacokinetic variables were similar for the two dosing schedules. As shown in Table 4, voreloxin exhibited low clearance (2 L/h/m\(^2\)) and a long terminal half-life (22 hours), and notably, clearance, \( V_{ss} \), and terminal half-life were unaffected by dose. Systemic exposure (AUC) increased linearly with dose (17). Differences in infusion times (1-11 minutes, median 5 minutes) precluded the assessment of proportionality based on \( C_{\text{max}} \). No change in pharmacokinetic variables was observed for the third weekly dose of voreloxin compared with the first dose on day 1.

**Tumor response**

Overall, half of patients (31 of 62) across both studies had the best overall response of stable disease (SD) as determined radiographically by RECIST guidelines. Of 10 patients with ovarian cancer, five also had a best overall response of SD and all completed at least four cycles of treatment with voreloxin.

In SPO-0001, 21 of 41 patients (51%) were considered to have SD as the best overall response. Of 11 patients treated at 48 mg/m\(^2\), five (four HP and one MP) had SD: ovarian cancer (\( n = 2 \)) and colon, unknown primary adenocarcinoma, and non–small cell lung cancer (\( n = 1 \) each). Of eight patients treated at 60 mg/m\(^2\), six (three HP and three MP) had SD: ovarian cancer (\( n = 2 \)) and melanoma, pancreatic cancer, neuroendocrine tumor, and metastatic myxoid liposarcoma (\( n = 1 \) each).

Of the nine patients with ovarian cancer in SPO-0001, six had CA-125 samples at both baseline and postbaseline. According to Rustin criteria, four of the six patients had a \( \geq 50\% \) decrease in CA-125, including a 75% decrease in one patient. Three of these four patients had SD and completed all six treatment cycles, and then subsequently continued voreloxin treatment in an extension study (SPO-0003). A summary of response data for patients with ovarian cancer is shown in Table 5.

In SPO-0002, 10 of 21 patients (48%) had the best overall response of SD across a wide range of histologies. Ten patients who completed the SPO-0001 or SPO-0002 studies continued to receive voreloxin treatment in SPO-0003, and eight (80%) completed at least four additional cycles (range, 2-29 months). The three patients with ovarian cancer entering from SPO-0001 completed an additional two, three, and four cycles in SPO-0003 before disease progressed.

**Discussion**

Our studies, evaluating two dosing schedules, reveal that voreloxin is well tolerated and shows clinical activity in patients with a variety of advanced solid tumors. The primary DLT was neutropenia, which was noncumulative. Other toxicities were infrequent, and mild nausea was the main nonhematologic adverse event. In the SPO-0001 study, as anticipated, MP patients tolerated treatment better than HP patients, as shown by the higher MTD (60 versus 48 mg/m\(^2\)). Based on these findings, the initial recommended phase 2 single-agent dose of voreloxin is 48 mg/m\(^2\) administered every 3 weeks in all patients with advanced solid tumors. In SPO-0002 (weekly administration), the MTD was defined as 15 mg/m\(^2\).
No differences were observed in the pharmacokinetic profiles for the two dosing schedules tested (once every 3 weeks or weekly for 3 weeks every 28 days). Voreloxin exhibited low clearance (2 L/h/m²) and a long terminal half-life (22 hours). Exposure to voreloxin increased linearly with dose, with no changes across doses in clearance, Vss, and terminal half-life. No drug accumulation or change in pharmacokinetic variables was seen after repeated weekly dosing. In SPO-0001, average plasma voreloxin concentrations of ≥1 μmol/L were maintained for up to 25 hours in patients treated with voreloxin doses of 48 mg/m² and higher. Voreloxin levels ≥1 μmol/L have been reported to correlate in vitro with IC₉₀ in multiple hematologic cancer cell lines (18, 19) and >80% inhibition of proliferation of breast (17 of 20) and ovarian (11 of 20) cancer biopsies (20). Our data suggest that clinically active plasma voreloxin concentrations of ≥1 μmol/L are achieved at tolerable doses (48 mg/m² and higher) in patients with relapsed/refractory solid tumors.

In addition to its favorable pharmacokinetic profile, the DNA damage that results from voreloxin treatment is highly selective (9). The interaction of voreloxin with DNA is saturable, suggesting a specificity of interaction with the DNA and topoisomerase II enzyme analogous to the saturation of bacterial DNA-topoisomerase II by antibacterial quinolones (21). A limitation of the SPO-0001 and SPO-0002 studies is that no provisions were made in the study protocols and patient-informed consent forms to collect patient samples (e.g., tumor biopsies or blood) to perform target-based analysis or investigate the pharmacodynamic profile of voreloxin. However, clinical proof of mechanism has been shown by pharmacodynamic profiling of DNA-damage responses in peripheral blood mononuclear cells from patients with acute myeloid leukemia treated with voreloxin and cytarabine (22).

The combined study population in our studies included 62 patients with a variety of advanced solid tumors that had progressed despite standard chemotherapy or for which no standard effective or curative therapy was available at the time of study. In this group of patients, best overall response of SD was achieved in 50%: 51% (21 of 41) in SPO-0001 and 48% (10 of 21) in SPO-0002.

The largest subgroup of patients in the two studies had platinum-resistant relapsed or refractory ovarian cancer (10 of 62, 16%). Encouraging preliminary clinical activity of voreloxin was observed in this population based on radiographic response (RECIST) and measurement of serum CA-125 (Rustin criteria). Although molecular profiling of patient tumor samples was not included in this study, the activity of voreloxin in ovarian cancer is intriguing because the DNA damage induced can be repaired by homologous recombination repair. Cells deficient in this BRCA-dependent repair mechanism, such as ovarian cancer with BRCA mutations, may have greater sensitivity to voreloxin (20).

In conclusion, voreloxin is a novel agent with evidence of tolerability and antitumor activity in patients with advanced tumors.
advanced solid tumors. Preliminary objective tumor response data from both dosing schedules warrant the evaluation of voreloxin efficacy in future studies. Two phase 2 studies of voreloxin have recently been completed in non–small cell and small cell lung cancers, and voreloxin is currently under investigation in a phase 2 study in platinum-resistant ovarian cancer. Early results from the ovarian cancer study suggest that doses of voreloxin above 48 mg/m² are well tolerated, and studies with 60 mg/m² and 75 mg/m² are ongoing (23, 24). Voreloxin is also being evaluated in a phase 2 clinical study (REVEAL-1) in patients ≥60 years of age with newly diagnosed acute myeloid leukemia (25), and in a phase 1b/2 clinical study in combination with cytarabine for the treatment of patients with relapsed/refractory acute myeloid leukemia (26). Results from these ongoing studies will provide additional data regarding the full potential of voreloxin as a new cancer treatment.

Disclosure of Potential Conflicts of Interest

R. Allen and J. Fox are current employees of Sunesis; D. Adelman, C. Berman, N. Havrilla, U. Hoch, and J. Silverman are former Sunesis employees.

Acknowledgments

Helix Medical Communications LLC edited early drafts of the manuscript. 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.

Received 08/18/2009; revised 01/01/2010; accepted 01/25/2010; published OnlineFirst 03/16/2010.

References

9. Hawrin RE, Stockett DE, Byl JA, et al. Voreloxin is an anticancer...
A quinolone derivative that intercalates DNA and poisons topoisomerase II. 2009, Located at: Public Library of Science [forthcoming].


Clinical Cancer Research

Voreloxin, a First-in-Class Anticancer Quinolone Derivative, in Relapsed/Refractory Solid Tumors: A Report on Two Dosing Schedules


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-09-2236

Cited articles
This article cites 18 articles, 8 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/16/7/2167.full#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/16/7/2167.full#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, use this link
http://clincancerres.aacrjournals.org/content/16/7/2167.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.