Clinical Trial Brief Report

Clinical Cancer Research

Phase I Study of Fenretinide Delivered Intravenously in Patients with Relapsed or Refractory Hematologic Malignancies: A California Cancer Consortium Trial

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Abstract

Purpose: A phase I study was conducted to determine the MTD, dose-limiting toxicities (DLT), and pharmacokinetics of fenretinide delivered as an intravenous emulsion in relapsed/refractory hematologic malignancies.

Experimental Design: Fenretinide (80–1,810 mg/m^2/day) was administered by continuous infusion on days 1 to 5, in 21-day cycles, using an accelerated titration design.

Results: Twenty-nine patients, treated with a median of three prior regimens (range, 1–7), were enrolled and received the test drug. Ninety-seven courses were completed. An MTD was reached at 1,280 mg/m^2/day for 5 days. Course 1 DLTs included 6 patients with hypertriglyceridemia, 4 of whom were asymptomatic; 2 patients experienced DLT thrombocytopenia (asymptomatic). Of 11 patients with response-evaluable peripheral T-cell lymphomas, two had complete responses [CR, progression-free survival (PFS) 68+ months; unconfirmed CR, PFS 14+ months], two had unconfirmed partial responses (unconfirmed PR, PFS 5 months; unconfirmed PR, PFS 6 months), and five had stable disease (2–12 cycles). One patient with mature B-cell lymphoma had an unconfirmed PR sustained for two cycles. Steady-state plasma levels were approximately 10 mcg/mL (mid-20s μmol/L) at 640 mg/m^2/day, approximately 14 mcg/mL (mid-30s μmol/L) at 905 mg/m^2/day, and approximately 22 mcg/mL (mid-50s μmol/L) at 1,280 mg/m^2/day.

Conclusions: Intravenous fenretinide obtained significantly higher plasma levels than a previous capsule formulation, had acceptable toxicities, and evidenced antitumor activity in peripheral T-cell lymphomas. A recommended phase II dosing is 600 mg/m^2 on day 1, followed by 1,200 mg/m^2 on days 2 to 5, every 21 days. A registration-enabling phase II study in relapsed/refractory PTCL (ClinicalTrials.gov identifier: NCT02495415) is ongoing. *Clin Cancer Res; 23(16); 4550–5. ©2017 AACR.*

Introduction

The activity of synthetic retinoid, N-(4-hydroxyphenyl)retinamide (fenretinide, 4-HPR), has been widely studied in cell lines of multiple cancer types *in vitro*. Fenretinide is reported to induce cytotoxicity by multiple mechanisms, including p53- and caspase-independent apoptosis and/or nonapoptotic mechanisms independent of classic retinoid receptors (1, 2); reactive oxygen species (ROS) contributed to cytotoxicity in some leukemia and solid cancer cell lines (3); levels of potentially cytotoxic dihydroceramides (4) were increased in a dose- and time-dependent manner through concurrent stimulation of *de novo* synthesis and inhibition of dihydroceramide desaturase 1 (5–8). Significantly, fenretinide was cytotoxic to lymphoblastic leukemia cell lines *in vitro* (4, 9), but minimally toxic to fibroblasts, peripheral blood mononuclear cells, and marrow myeloid progenitors (6), suggesting a potential for use in hematologic malignancies. However, fenretinide is sparingly soluble in water, challenging clinical testing.

Previously, a capsule formulation was tested at 200 to 900 mg/day in multiple cancer types, obtaining 1 to 3 μmol/L plasma levels with minimal toxicity but limited evidence of activity (10, 11). Phase I and II high-dose capsule trials (500–4,800 mg/m^2/day) demonstrated minimal toxicities and some suggestions of activity, but still obtained plasma levels of only 7.5 to 12.5 μmol/L (12, 13).

We hypothesized that intravenous delivery would obtain higher plasma drug levels, increase tumor drug exposures, and possibly increase responses. The goals of this study were to determine the MTD of an oil-in-water fenretinide emulsion

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Translational Relevance

Fenretinide is a cytotoxic retinoid possessing potentially novel mechanisms of antitumor action, including increase of tumor cell dihydroceramide levels, but being sparingly soluble in water has limited its clinical advancement. To overcome this limitation, we conducted a phase I trial of a novel oil-in-water intravenous emulsion formulation in hematologic malignancies. The emulsion was well tolerated and obtained multifold higher plasma levels than a previously reported capsule formulation. Promising sustained complete and partial responses were observed in heavily pretreated patients with T-cell lymphomas.

administered as a continuous intravenous infusion (c.i.v.) for 5 days, once every 3 weeks, describe toxicities, evaluate pharmacokinetics, and within the confines of a phase I trial, determine preliminary estimates of hematologic disease response.

Materials and Methods

Drug sources and formulation

N-(4-hydroxyphenyl)retinamide (fenretinide, 4-HPR; NSC 374551) formulated as a 20% soy oil-in-water emulsion was provided by the Rapid Access to Intervention Development (RAID) Program, Developmental Therapeutics Program (DTP), NCI (Rockville, MD). Fenretinide, N-(4-methoxyphenyl)retinamide (4-MPR), and N-(4-ethoxyphenyl)retinamide (4-EPR) were obtained from the NCI/DTP Open Chemicals Repository.

Patients

Patients were $\geq$18 years of age with documented, previously treated leukemias, lymphomas, or multiple myeloma, with measurable or evaluable disease, excluding preexisting central nervous system (CNS) disease, for whom standard therapies did not exist or were not effective, and who had absolute granulocytes $\geq$1,500/μL, platelets $\geq$75,000/μL, creatinine $\leq$1.5$\times$ upper limit of normal (ULN), bilirubin $\leq$1.5$\times$ ULN, serum transaminases $\leq$2.5$\times$ ULN, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, and estimated survival of $\geq$3 months. The study, registered as ClinicalTrials.gov Identifier: NCT00104923, was approved by local Investigational Review Boards in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services and the precepts of the Helsinki Declaration. ICH-GCP guidelines were followed. Written informed consent was obtained from each patient. Patient diagnoses were captured by assigned NCI Cancer Therapy Evaluation Program Clinical Data Update System (CDUS) codes supplemented by MedDRA code version 9.0 (patients 1–10) or version 10.0 (patients 11–29); for patients #1 to 22, the diagnoses and responses of responding patients were confirmed by chart and scan review by an independent reviewer.

Clinical trial design and treatment

Fenretinide was given as a c.i.v. for 5 consecutive days (day 1 through day 5) on 21-day cycles. The starting dose was 80 mg/m^2/day, and escalation proceeded through a modified accelerated titration design (Supplementary Table S1; ref. 14). Escalation was based on assessment of dose-limiting toxicity (DLT) in the first cycle as scored according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, if toxicity was possibly, probably, or definitely attributed to fenretinide. For DLT assessment, patients had to receive $\geq$90% of the planned first course dose and be observed for $\geq$21 days from day 1, or experience toxicity that met the definition of DLT at any time. Patients not evaluable for DLT assessment were replaced. Initially, one patient was treated per level, and dosing advanced in every-other level increments; when 2 patients experienced $\geq$grade 2, or one patient experienced a DLT, standard 3 + 3 rules applied. The MTD was the highest level with at least 6 patients treated at which <33% of patients experienced DLT. Treatment was held for grade 3 or 4 toxicity until resolved to grade $\leq$1. After non-DLT toxicity resolution, treatment was restarted without dose reduction. For DLT, treatment was held until resolution and resumed at a one-dose level reduction. Patients were removed from treatment if a scheduled cycle was delayed >3 weeks due to toxicity or for recurrence of a same DLT. Patients with stable disease (SD) or better response were treated for six or more cycles or until evidence of disease progression. Once the original MTD was determined, the protocol was amended to exclude "minimally symptomatic intralipid intolerance" (defined below) as a DLT for dose escalation purposes, and escalation resumed using standard 3 + 3 rules to "backfill" levels to determine an MTD in "lipid-tolerant" patients. As an overly frequent occurrence of "intralipid intolerance" could have impacted the practicality of treatment, the following stopping rule concerning "minimally symptomatic intralipid intolerance" was adopted but never invoked: for each dose level, 3 of the first 5 patients, or 4 of the first 8 patients, or 5 of the first 10 patients, or 6 of the first 12 patients. If the true probability of minimally symptomatic intralipid intolerance was about 0.30, then there was a 34% chance that the flag would be exceeded; if the true probability was 0.50, then there was an 83% chance that the flag would be exceeded.

Toxicity management and definition of DLT

DLT was defined as (i) grade 4 thrombocytopenia; (ii) grade 4 neutropenia lasting more than 7 days, or febrile neutropenia, (iii) any toxicity resulting in treatment delays of >3 weeks; or (iv) any $\geq$grade 3 nonhematologic toxicity excluding nyctalopia; $\geq$grade 3 headache with history of migraines or grade 3 headache not due to pseudotumor cerebri treatable by medical management; grade 3 nausea, vomiting, or diarrhea controllable with medical management; grade 3 ALT or AST increase, or grade 3 or 4 alkaline phosphatase increase, that recovered to $\leq$grade 2, or baseline, by day 21; grade 3 fever or infection with $\leq$grade 2 neutropenia; grade 4 fever or infection associated with a central venous catheter or other known cause; and CNS toxicity attributable to disease that developed after enrollment. All patients who received any drug are included in toxicity summaries.

Definition of minimally symptomatic intralipid intolerance

Because of decreased plasma clearance of the soy oil vehicle in some patients (i.e., hypertriglyceridemia), but to not limit dosing in the majority of patients who did not experience hypertriglyceridemia, "minimally symptomatic intralipid intolerance" was defined as asymptomatic grade 3 or 4 hypertriglyceridemia that returned to baseline within 96 hours after stopping infusion, with $\leq$grade 1 lipase elevation that returned to baseline within 72 hours, and absent signs/symptoms of pancreatitis. Triglycerides were monitored every 12 hours during the first course. Patients

with hypertriglyceridemia had their infusion stopped and were re-treated at a 25% dose reduction if resolved within 48 hours during the same course, or at a 50% dose reduction in the subsequent course; triglycerides were monitored for one further course after a dose reduction.

Evaluation of response

Response was evaluated every two cycles. Complete response (CR) was defined as the disappearance of target and nontarget lesions, no new lesions, and normalization of marrow, lasting >4 weeks; CR, unconfirmed (CRu) was defined as a response otherwise qualifying as a CR but lacking marrow response testing; partial response (PR) was defined by disease-specific criteria and no unequivocal progression of nontarget lesions, lasting >4 weeks; PR, unconfirmed (PRu) was defined as a response otherwise qualifying as a PR but lacking marrow response testing (15–17). Progressive disease was defined as ≥25% increase in a perpendicular dimension of target lesions, new lesions, >25% increase of leukemia in blood or marrow, or 25% increase in myeloma paraprotein within 8 weeks of entry. SD was any condition not meeting other criteria. Patients completing one course were evaluable for disease response. Most responses were reviewed by an independent reviewer.

Pharmacokinetics

Blood samples were drawn preinfusion, at hours +6, +12, +18, +24, +36, +48, +72, +96, and +120 during infusion, and at +2 and +48 hours after the end of infusion. Plasma levels of fenretinide, and inactive major metabolite, N-(4-methoxyphenyl)retinamide (4-MPR), were assayed by a validated high-performance liquid chromatography methodology (18).

Statistical analysis

Standard descriptive statistics were used to summarize results. Progression-free survival (PFS) was calculated from the start of treatment to documentation of disease progression or death; if death occurred prior to progression, survival was calculated as time from the start of treatment until death; alive patients were censored at the date of last contact. Kaplan–Meier plots summarized PFS and overall survival (OS); SEs were estimated using Greenwood formula; *P* values were based on the log-rank test. Analysis of covariance was used to evaluate AUC (based on natural logarithm of plasma levels) with dose and lipid intolerance.

Results

Participant and disease characteristics, dose escalation, and DLTs

Twenty-nine patients (median 59 years, range: 23–79) were enrolled and received drug; most had ECOG status of 0 or 1 (Table 1; Supplementary Table S2). A total of 101 courses were started, of which 97 were completed, with a median of two courses per patient (range: <1–25); 11 patients completed 2 or 3 courses, 7 completed ≥four courses (Supplementary Table S2). During accelerated escalation, one patient each was treated at dose levels 1, 3, 5, 7, and 9, without DLT; only 2 experienced grade 1 toxicity at least possibly attributed to fenretinide (Supplementary Table S3). At dose level 10 (1,810 mg/m^2/day), 2 of 3 patients experienced DLT; therefore, dose level 9 (1,280 mg/m^2/day) was expanded. Two of the next 4 patients experienced DLT, so dose level 8 (905 mg/m^2/day) was expanded. Two of the next 5 patients experienced DLT, so dose level 7 (640 mg/m^2) was expanded; 5 patients tolerated 640 mg/m^2/day without DLT, which was tentatively labeled the MTD (Supplementary Table S3). However, review revealed that four of six DLTs were "minimally symptomatic intralipid intolerance" that resolved once the infusion was stopped; 2 such patients went on to receive additional courses. To not limit dosing for the majority of patients who were lipid tolerant, the protocol was amended to consider "lipid-intolerant" patients as a separate cohort; dose levels were reopened, backfilled, and an MTD for "lipid-tolerant" patients was established at 1,280 mg/m^2/day (Supplementary Table S3). In an expansion cohort, a "ramped" dosing schedule was tested (day 1 dosing of 600 mg/m^2 and days 2–5 dosing of 1,200 mg/m^2/day), to determine whether allowing for a reactive increase in serum lipase capacity during the first 24 hours could reduce intralipid intolerance. Of the 4 patients accrued prior to the exhaustion of drug supply, none experienced hypertriglyceridemia.

Table 1. Patient characteristics

Characteristics	Patients (*N* = 29), *n* (%)
Age, years	
Median	59
Range	23–80
Gender	
Male	20 (69%)
Female	9 (31%)
ECOG performance status	
0	4 (14%)
1	23 (79%)
2	2 (7%)
Diagnosis	
Acute leukemia	3 (10%)
Mature B-cell lymphoma	11 (38%)
T-cell lymphoma	14 (48%)
Malignant myeloma	1 (3%)
Prior treatment	
Chemotherapy	29 (100%)
Radiotherapy	8 (28%)
Marrow transplant	6 (21%)
Number of prior chemotherapy regimens	
Median	3
1	2 (7%)
2	8 (28%)
3–4	11 (38%)
5–7	8 (28%)

Adverse events

Intravenous fenretinide was generally tolerated with minimal to modest toxicities and adverse events (AE). Across all courses, grade 3 or 4 hematologic toxicity (Table 2) was seen in 20 patients without clear dose–response relationships, likely reflecting varied prior therapies. Thirteen patients experienced hematologic grade 3 or 4 toxicities at ≥905 mg/m^2/day: grade 3 or 4 asymptomatic thrombocytopenia was seen in 8 patients, none of whom required platelet transfusion, all of whom recovered to baseline by day 28, and thrombocytopenia did not necessarily recur in subsequent cycles in the same patient; grade 3 or 4 neutropenia was seen in 5 patients who recovered to baseline without complications of infection and which did not necessarily recur in subsequent cycles; grade 3 anemia was seen in 3 patients. Other toxicities included metabolic abnormalities likely related to the load of the soy oil vehicle. These included 9 patients with grade 3 and 4 hypertriglyceridemia, only one of which was symptomatic (elevated

Table 2. Grade 3 and 4 AEs in 3 or more patients at least possibly related to study drug, all cycles

	80–640 mg/m^2/day ($n = 8$)		905 mg/m^2/day ($n = 6$)		1,280 mg/m^2/day ($n = 8$)		1,810 mg/m^2/day ($n = 3$)		Expanded cohort ($n = 4$)	
AE	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hypertriglyceridemia	1	0	0	4	0	2	0	2	0	0
Nonhematologic, any	2	0	1	4	3	4	0	3	1	3
Hemoglobin reduced	0	0	0	0	1	0	1	0	1	0
Leukocytes reduced	0	0	1	0	0	0	1	0	1	0
Lymphocytes reduced	0	0	0	0	1	1	0	0	1	0
Neutrophils reduced	0	0	1	1	1	1	1	0	0	0
Platelets reduced	0	0	0	0	3	1	0	1	0	3
Hematologic, any	0	0	1	1	3	3	0	1	1	3

lipase and rapidly resolved grade 2 pancreatitis), which occurred at 1,810 mg/m^2/day prior to the institution of triglyceride monitoring.

Pharmacokinetic analysis

End-of-infusion plasma samples were available for 20 patients (Fig. 1A). Analysis showed a dose-to-plasma level relationship with mean steady-state drug levels of approximately 10 mcg/mL (mid-20s μmol/L) at 640 mg/m^2/day, approximately 14 mcg/mL (mid-30s μmol/L) at 905 mg/m^2/day, and approximately 22 mcg/mL (mid-50s μmol/L) at 1,280 mg/m^2/day. The AUCs for fenretinide and its 4-MPR metabolite over the first 48 hours of the infusion were available for 22 patients (Supplementary Table S4); the presence of drug emulsion was visually noted in the pharmacokinetic blood samples from some lipid-intolerant patients.

Antitumor activity

A variety of hematologic cancer diagnoses were enrolled (Supplementary Table S2). Five of 26 response-evaluable patients demonstrated objective responses and 7 had stable disease for 2 to 12 courses. Nine of 11 response-evaluable peripheral T-cell lymphomas had object response or SD (Table 3; Supplementary Table S2); one of 11 B-cell malignancies achieved an unconfirmed PR sustained for two cycles at 320 mg/m^2/day; one hairy cell leukemia and one B-cell lymphoma treated at 1,280 mg/m^2/day had SD for two and three cycles, respectively.

Of response-evaluable peripheral T-cell lymphoma patients, 4 patients dosed at ≥905 mg/m^2/day had objective responses and 5 had SD for 2 to 12 courses (Supplementary Table S2). Of the four responders, two were complete responders; one, with systemic cutaneous T-cell lymphoma (Sézary syndrome), treated at 1,280 mg/m^2/day (initial dosing) for 25 courses, achieved complete remission confirmed by CT PET and skin biopsy with a PFS of 68+ months; an angioimmunoblastic T-cell lymphoma patient treated at 905 mg/m^2/day was a CRu after four courses (marrow examination declined) and withdrew from study therapy; follow-up indicated PFS of ≥14 months and patient was confirmed alive at +118 months. One patient each with cutaneous and angioimmunoblastic lymphoma had PRu, each receiving six cycles, with PFS of 5 and 6 months, respectively. These patients demonstrated "best response" aggregate reductions in lymph node size of 94% and 78%, respectively; both had been previously treated with

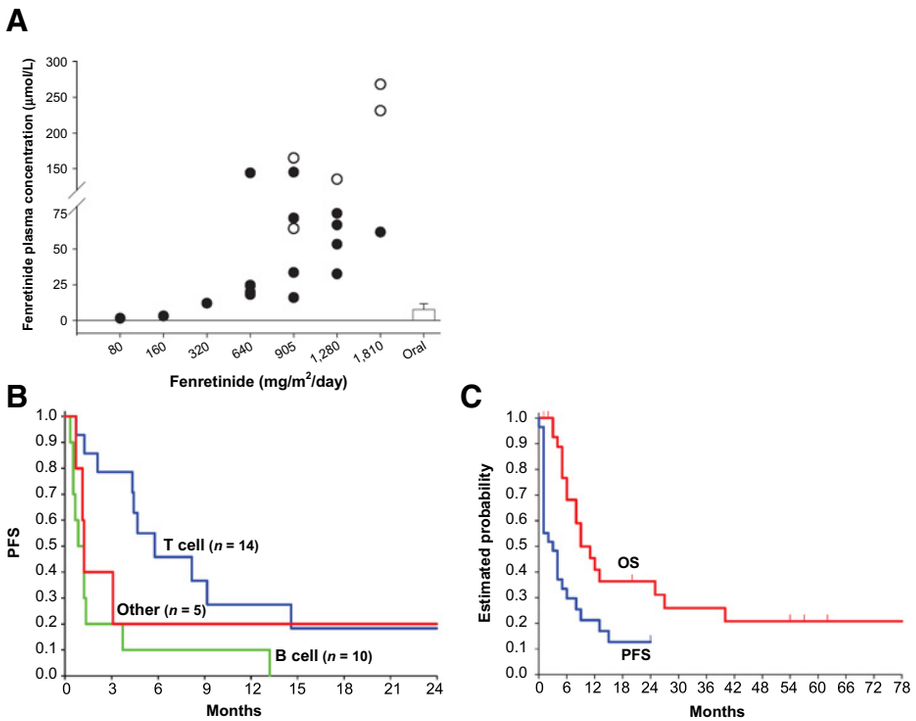

Figure 1.

A, End-infusion fenretinide plasma levels for dosing cohorts (+120 hours). Closed circles, patients completing infusion course; open circles, last plasma sample of patients with infusions stopped due to hypertriglyceridemia; Bar, reported achievable plasma levels using oral capsule dosed on 7-day schedule. **B,** PFS of evaluable patients by tumor type; peripheral T cell ($n = 14$), median 5.7 [95% confidence interval (CI), 2.1–14.6] months; mature B-cell lymphoma or leukemia ($n = 10$), median 0.8 (95% CI, 0.5–1.3) months; other hematologic malignancy ($n = 5$), median 1.2 (95% CI, 0.6–not available) months; difference in PFS between T cell and B cell, $P < 0.011$ (log-rank test). **C,** Overall survival (OS), median (95% CI): 9.3 (5.5–25.4) months, and PFS, median (95% CI): 3.0 (1.2–5.7) months, for all patients ($n = 29$) over all dose levels.

Table 3. Summary of antitumor responses

Best response	T-cell NHL, *n* (%)[a]	B-cell NHL, *n* (%)	Leukemia/myeloma/ other, *n* (%)[a]
CR/CRu	2 (17%)	0	0
PRu	2 (17%)	1 (9%)	0
SD	5 (42%)	2 (18%)	0
PD	2 (18%)	8 (73%)	4 (100%)
Inevaluable[b]	2	0	1

Abbreviation: NHL, non-Hodgkin lymphoma.
[a]Of evaluable patients.
[b]T cell: one patient withdrew after course 1, one patient lost to follow-up; one acute lymphoblastic leukemia patient proceeded to marrow transplant after three courses.

combination chemotherapy regimens and agents such as denileukin, anti-IL1 antibodies, depsipeptide, and bexaratone. Among the peripheral T-cell patients, one CR, one PRu, and one SD patient had failed previous HDACi therapy. PFS by disease type, and PFS and OS for all patients, are shown in Fig. 1B and C.

Discussion

Fenretinide emulsion obtained plasma drug levels that were 5 to 7 times higher than a previous capsule formulation (13) and demonstrated modest toxicities, including in patients of advanced age. Reversible asymptomatic hypertriglyceridemia related to the soy oil vehicle accounted for four of eight DLTs across all levels. Hypertriglyceridemia generally manifested in the first 48 hours of the first course, was detected by monitoring of nonfasting serum triglycerides, and was manageable in most patients by dose reduction. No specific pattern of predisposing factors was discernable from the limited number of such patients. Within the limitations of a phase I study, fenretinide emulsion demonstrated activity in eleven evaluable peripheral T-cell lymphomas from 905 to 1,810 mg/m^2/day, with a CR + PR + SD response rate of 82%, which is notable in the highly pretreated patients enrolled. Only one of 10 NHL B-cell malignancies responded, but half of such patients were treated at less than the MTD level, or at nontolerated dose levels, which limited interpretation. Too few patients were enrolled in other disease categories for assessment.

A recommended phase II schedule of 600 mg/m^2/day on day 1 and 1,200 mg/m^2/day on days 2 to 5, c.i.v, every 21 days, is suggested to allow potentially lipid-intolerant patients to "metabolically induce" serum lipase capacity for 24 hours prior to advancing to potentially therapeutic dosing. Pharmacokinetic analysis showed a dose-to-plasma level relationship with an expected mean steady-state fenretinide level in the 50 μmol/L range at suggested phase II dosing. The data demonstrate that intravenous delivery solved the previous problem of limited fenretinide plasma levels; this may have contributed to the encouraging responses observed. A registration-enabling, phase II study of fenretinide emulsion in relapsed/refractory peripheral T-cell lymphomas using the recommended dosing schedule above is ongoing (ClinicalTrials.gov identifier: NCT02495415).

Future studies in hematologic cancers may confirm the association between systemic fenretinide exposure and clinical outcome and/or compare survival and quality-of-life endpoints. The modest toxicities of the present formulation also suggest that trials testing fenretinide emulsion in combination with other agents could be explored, such as the current phase I trial testing fenretinide emulsion in combination with the ceramide-modulating agent, safingol (ClinicalTrials.gov identifier: NCT01553071).

Disclosure of Potential Conflicts of Interest

C.P. Reynolds is an employee of and holds ownership interest (including patents) in CerRx, Inc. B.J. Maurer is an employee of, reports receiving commercial research grants and other commercial research support from, holds ownership interest (including patents) in, and is a consultant/advisory board member for CerRx, Inc. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Mohrbacher, S. Groshen, S. Kummar, M.H. Kang, D. Tsao-Wei, C.P. Reynolds, E.M. Newman
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.M. Mohrbacher, S. Groshen
Study supervision: A.M. Mohrbacher, A.S. Yang, S. Groshen, E.M. Newman
Other (wrote the original phase I clinical protocol, enrolled and treated more than half of the patients and made the observations of activity in T-cell lymphoma patients, and then wrote the article with S. Groshen, and then extensively revised with E.M. Newman and B.J. Maurer, including pharmacokinetic data): A.M. Mohrbacher

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