Phase I and Pharmacokinetic Study of DX-8951f (Exatecan Mesylate), a Hexacyclic Camptothecin, on a Daily-Times-Five Schedule in Patients with Advanced Leukemia

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ABSTRACT

Purpose: DX-8951f is a novel hexacyclic camptothecin-analogue topoisomerase I inhibitor with both in vitro antileukemic activity and myelosuppression as a dose-limiting toxicity in solid tumor Phase I studies. DX-8951f is active in a human acute myeloid leukemia (AML) severe combined immunodeficient mouse model. In a leukemia Phase I study, we investigated the toxicity profile and pharmacokinetics of DX-8951f in patients with primary refractory or relapsed AML or acute lymphocytic leukemia, myelodysplastic syndromes, or chronic myelogenous leukemia in blast phase (CML-BP).

Experimental Design: DX-8951f was given as an i.v. infusion over 30 min daily for 5 or 7 days. The starting dose was 0.6 mg/m²/day for 5 days (3.0 mg/m²/course). Courses were given every 3–4 weeks according to toxicity and antileukemic efficacy.

Results: Twenty-five patients (AML, 21 patients; myelodysplastic syndrome, 1 patient; acute lymphocytic leukemia, 2 patients; CML-BP, 1 patient) were treated. Stomatitis was the dose-limiting toxicity, occurring in two of two patients treated at 1.35 mg/m²/day for 5 days, two of three treated at 1.2 mg/m²/day for 5 days, and one of six treated at 0.9 mg/m²/day for 7 days. The recommended Phase II dose was 0.9 mg/m²/day for 5 days. The pharmacokinetics of DX-8951f was linear and well fit by a two-compartment model.

Conclusions: Phase II studies are warranted to further define the activity of DX-8951f in patients with hematological malignancies.

INTRODUCTION

Novel agents are required to improve the prognosis of patients with hematological malignancies. Camptothecin, an alkaloid isolated from the Chinese tree Camptotheca acuminata, has a cytotoxic effect mediated through interference with the catalytic cycle of DNA topo I enzyme and stabilization of the covalent DNA–enzyme complex by inhibiting DNA religation (1–4). The reversible drug–enzyme–DNA ternary complex causes arrest of the replication fork and formation of single-strand DNA breaks during DNA synthesis (5). Initial clinical studies of camptothecin were halted because of severe and unpredictable adverse effects (6, 7). Camptothecin derivatives, including irinotecan (CPT-11) and topotecan, were developed to improve the toxicity profile and poor aqueous solubility of the parent drug (8, 9). Topotecan administered as a single agent has significant antileukemic activity in patients with AML and MDS (9–17). We have recently reported on its activity as a component of combination regimes in these patients (18–20). Further development of novel topotecan inhibitors was spurred by the spectrum of potencies of this class of drugs in terms of enzyme inhibition, antiproliferative activity, toxicities, and pharmacological properties (21–24). One such novel agent is the hexacyclic camptothecin derivative DX-8951f (15,9S)-1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzene-d(1H)-pyrano-[3′,4′:6,7]indolizino[1,2-b]quinoline-10,13-dione monomethane sulfonate (salt), dihydrate, exatecan mesylate; Daiichi Pharmaceutical Co, Ltd, Tokyo, Japan (Fig. 1; Refs. 25–28).

Many camptothecins require enzymatic activation that may accentuate interindividual variability in their pharmacological behavior, antiproliferative activity, and toxicities (21–23, 29, 30). DX-8951f is water-soluble and does not require enzymatic activation (25). DX-8951f is a more potent top I inhibitor, and causes more DNA fragmentation, than do camptothecin, topotecan, or 10-hydroxy-7-ethylcamptothecin (SN-38), the active metabolite of irinotecan (25, 27, 31). DX-8951f is 3- and 10-fold

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3 The abbreviations used are: top I, topoisomerase I; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; SCID, severe combined immunodeficient; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CML-BP, chronic myelogenous leukemia in blast phase; PGP, P-glycoprotein; CR, complete remission; PR, partial remission; HI, hematological improvement; MLI, marrow leukemia infiltrate; PK, pharmacokinetic(s); IT2S, iterative two-stage methodology; CV, coefficient of variation; ara-C, cytosine arabinoside.
more potent than SN-38 and topotecan, respectively, at inhibiting topo I extracted from murine P388 leukemia cells (25, 27). In a study of camptothecin analogues against a panel of 32 cancer cell lines, including hematopoietic neoplasms, the IC50 (concentration that inhibits 50%) values of DX-8951f averaged 6- and 28-fold lower than SN-38 and topotecan, respectively (25). In the human tumor cloning assay, DX-8951f and topote-
can were not completely cross-resistant, with cell lines cross-resistant to CPT-11 and topotecan retaining sensitivity to DX-8951f (28). Unlike topotecan, 9-aminocamptothecin, and SN-38, DX-8951f is not a substrate for multidrug transporter PGP and has cytotoxic activity against tumor cell lines and xenografts with acquired multidrug resistance (MDR) conferred by PGP overexpression (27, 28, 31–35).

We have previously reported on the activity of DX-8951f in a human AML SCID mouse model (36, 37). This activity was schedule-dependent, and DX-8951f had significant activity against central nervous system leukemia in this model (37, 38). On the basis of this SCID mouse data, we conducted a Phase I study of DX-8951f in adult and pediatric patients with primary refractory or relapsed AML or ALL, MDS, or CML-BP. The starting dose and schedule were chosen based on the overall toxicities and specifically on the pattern and degree of myelo-suppression seen in solid tumor Phase 1 studies of DX-8951f (39–42).

PATIENTS AND METHODS

Patient Selection. Patients with refractory MDS (refractory anemia with excess blasts, refractory anemia with excess blasts in Transformation, or chronic myelomonocytic leukemia), AML, ALL, or CML-BP were eligible. Eligibility criteria were: Eastern Cooperative Oncology Group performance score of ≤ 2; serum bilirubin of ≤ 1.5 mg/dl; alanine aminotransferase (ALT) or aspartate aminotransferase levels (AST) < two times the upper limit of normal (ULN), serum creatinine ≤ 1.5 mg/dl, and no chemotherapy and/or radiation therapy for 2 weeks before entering this study with recovery from the toxic effects of that therapy. Patients with AML included those receiving first salvage with primary refractory disease, a first CR duration of less than 12 months, or those receiving second or subsequent salvage therapy. All of the patients gave signed informed consent indicating that they were aware of the investigational nature of this study in keeping with the policies of the M. D. Anderson Cancer Center.

Dosage and Drug Administration. DX-8951f was given as a 30-min i.v. infusion once per day for 5 consecutive days, once every 21–28 days. DX-8951f, the methane sulfonic salt of DX8951, was supplied by Daiichi Pharmaceutical Corporation (Montvale, NJ) in vials containing 2 mg of lyophilized drug, (calculated as the anhydrous free-base equivalent, 50 or 125 mg of maltose monohydrate), and a proper quantity of hydrochloric acid (pH 3.3 to 4.7). The drug was diluted in the vial with 0.9% saline solution to obtain a 0.5-mg/ml stock solution. An appropriate volume of the stock solution, to yield the required dose, was further diluted in a polyvinyl chloride infusion bag with 0.9% saline solution to a total volume of 100 ml, which was administered over 30 min. The starting dose of DX-8951f was 0.6 mg/m² daily for 5 days, i.e., 3.0 mg/m² per course.

Treatment was given on an out-patient basis unless the patient was an in-patient for other reasons. Toxicity was graded on a scale of 0 to 4 using the Common Toxicity Criteria, Version 2.0, of the National Cancer Institute. All of the patients who received at least one dose of DX-8951f were considered evaluable for toxicity.
Patients were assessed on each day of therapy, and at least three times weekly and as clinically indicated while on protocol. DX-8951f doses were increased by 50% per level until grade 2 toxicity occurred; then doses were increased by 30–35% (depending on ease of dose “rounding”) until MTD was determined. MTD was defined as the dose level at which no more than two of six patients experienced DLT, with the next higher dose level having at least two of three or six patients encountering DLT. Any Grade 3 or worse extramedullary adverse event was considered a DLT.

Response Criteria. CR was defined as normalization of the blood and bone marrow with 5% or less blasts, normocellular or hypercellular bone marrow, a granulocyte count above 10⁹/liter and a platelet count above 100 × 10⁹/liter. Patients who met these criteria but still had 6–25% marrow blasts were considered to have a PR. HI was defined as for CR, but with platelet counts remaining below 100 × 10⁹/liter. Other responses were considered as failures and categorized as: (a) early death if death occurred within 2 weeks from start of therapy; (b) aplastic death if death occurred during therapy without evidence of hematological recovery and with less than 20% MLI (percentage of blasts × marrow cellularity; (c) secondary resistance if MLI was reduced below 20% but increased later; and (d) primary resistance if MLI did not decrease below 20%.

PK. The PK of DX-8951f were determined during the first course of therapy in all of the consenting patients. Heparinzied blood samples were collected on day 1 before the start of infusion (time 0), at 29 min (1 min before the end of DX-8951f infusion), at 1, 4, and 24 h from the end of infusion; samples were collected on day 5 immediately before the start of infusion (time 0), and at 1 h from the end of infusion. The limited sampling time points were determined based on PK results obtained in prior Phase I studies performed in solid tumors. Blood was immediately centrifuged at 3000 rpm for 15 min, and plasma was transferred to 1.5-ml sample tubes and stored at −20°C until needed for analysis. All of the collected plasma samples were analyzed at MDS Pharma Services in Montreal, Canada. DX-8951 in plasma was quantified using a validated high-performance liquid chromatography method (43, 44). The lower limit of DX-8951 quantification was 0.20 ng/ml.

PK Analyses. PK parameters were characterized using compartmental analyses of data obtained from 18 patients (72%) who consented to give PK specimens. Total DX-8951 plasma concentration data were also analyzed using model-dependent methods. After visual inspection of plasma concentration-time curves, individual data sets were fit with either two- or three-compartment models using nonlinear least-squares regression (45). The goodness of model fit (i.e., two- versus three-compartment model) was guided by inspection of the weighted sum of squares, dispersion of the residuals, SEs of the fitted PK parameters, and the Akaike information criterion (46). The parameters were systematically superior in fitting all of the plasma concentrations when estimated by the two-compartmental model and were, thus, used as prior values for the population PK analysis. The population PK analysis was performed using an IT2S. All of the concentrations were modeled using a weighting procedure of \( W_j^2 = \frac{1}{SE_j^2} \), where the variance of \( SE_j^2 \) was calculated for each observation using the equation \( SE_j^2 = (a + b \cdot Y_j)^2 \), where \( a \) and \( b \) are the intercept and slope of each variance model. The slope (\( b \)) is the residual variability associated with each concentration (i.e., the sum of the intrapatient variability and the sum of all experimental errors), and the intercept (\( a \)) is related to the limit of detection of the analytic assay. Estimates from previous studies were used as beginning priors and were updated iteratively during the population PK analysis (VARUP; IT2S) until stable values were found.

Pharmacodynamic Analysis. The relationship between the maximum observed decrease in which blood count (WBCs) at nadir compared with baseline values versus the exposure of patients to DX-8951 [area under the curve (area-under the time curve from time zero to infinity).] was determined by using an inhibitory Emax model.

RESULTS

Patient Characteristics. The characteristics of the 25 patients treated on study are shown in Table 1. Their median age was 54 years (range, 11–76 years); and performance status was 0 or 1 in 12 patients (48%) and 2 in 14 (52%) patients. Twenty-one patients had AML. A total of 25 patients received 27 courses of therapy (i.e., 2 patients received an additional course). DX-8951f was given as second salvage to 11 AML patients, fourth or more salvage to 4 patients. Six patients with AML received DX-8951f as their first salvage attempt; two after a first CR lasting less than 6 months, two with a first CR of 6–12 months, and two with primary refractory disease. All of the patients with AML had previously received intermediate- or high-dose ara-C as part of induction, consolidation, or salvage therapy. Two patients with ALL were given DX-8951f as a third or subsequent salvage attempt for refractory disease, and one patient with refractory CML-BP received DX-8951f as a first salvage attempt.

Toxicity. The dose escalation scheme of DX-8951f is shown in Table 2. DLT was initially defined at the 1.35 mg/m² day-×-5-day dosage (two of two patients having grade 3 grade three stomatitis) and then also at the 1.2 mg/m²/day-×-5-days
dosage (two of three patients having grade 4 stomatitis). With
the absence of grade 3 toxicity at the next lower dose level, we
defined 0.9 mg/m²/daily for 5 days as the MTD. We then
assessed a 0.9 mg/m²/daily-for-7-days schedule to investigate
whether a more prolonged regimen would allow an increase in
the total dosage administered. However at this dose level, two of
six evaluable patients experienced grade 3 toxicities: one expe-
rienced stomatitis, and the other experienced weakness. Fifteen
patients had 18 febrile episodes during the first course of ther-
rapy. These included six episodes of fever of unknown origin;
five pneumonias; and three septicemic episodes. Two patients
received a second course of DX-8951f that was begun at 28 and
36 days after the start of course 1. No grade 3 toxicities occurred
in these second courses.

Response. Twenty-four patients (96%) were evaluable
for response; overall responses were as per Table 3. One patient
had a HI; one patient had a PR, whereas no CRs were observed
in this study. Neither of the patients with ALL showed a
significant response. WBC nadir occurred between days 9 and
16, with a tendency to recover thereafter. (Fig. 2).

PK and Pharmacodynamic Studies. Representative
plasma concentration-time profiles are shown in Fig. 3, and
mean total DX-8951 PK parameters derived using a compart-
mental method are listed in Table 4. The PK of total DX-8951
on day 1 were characterized by a moderately large volume of
distribution at steady-state averaging 14.36 liter/m² (CV,
30.08%) and a mean elimination t½ of 8.75 h (CV, 48.34%).
There were no significant differences (P > 0.05) between PK
parameters derived from paired concentration data sets obtained
on days 1 and 5; mean CL values were 1.86 (CV, 56%) and 2.05
(CV, 72%) liter/h/m², respectively. Because there was no evi-
dence of nonlinear drug elimination, nor autoinduction, nor
inhibition of drug clearance based on visual inspection of indi-
vidual plasma concentration-time curves, linear PK models were
evaluated for quality of fit. A two-compartment model was
systematically superior in fitting all of the plasma concentration-
time data sets for total DX-8951 on both days 1 and 5. There-
fore, PK parameters derived from the biexponential model were
used to develop a population PK model using an IT2S approach.
A representative patient’s plasma concentration data fit to this
population model are shown in Fig. 3. Pertinent PK parameters
derived from this model were nearly identical to those derived using noncompartmental methods in a previous Phase I study, with mean CL and t½ values of 2.13 liter/h/m²
(CV, 60%) and 9.87 h (CV, 77%), respectively (12, 19, 29).
Mean values for volume of the central compartment (Vc)
and volume of distribution at steady-state were 2.40 liter/m² (CV,
40%) and 19.0 liter/m² (CV, 23%), respectively.

Table 2 Toxicities by dose level of DX-8951f

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients</th>
<th>Mucositis</th>
<th>Nausea/ Vomiting</th>
<th>Diarrhea</th>
<th>Skin</th>
<th>CNS</th>
<th>Other</th>
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<tbody>
<tr>
<td>0.6 X 5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9 X 5</td>
<td>9</td>
<td>2 (3)</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 X 5</td>
<td>3</td>
<td>4 (2)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9 X 7</td>
<td>7</td>
<td>3 (1)</td>
<td></td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.35 X 5</td>
<td>2</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a CNS, central nervous system.

Table 3 Response to DX-8951f treatment (n = 25)

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>HI</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Early death</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Aplastic death</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Secondary resistance</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Primary resistance</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Inevaluable</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Resistance type (primary versus secondary) unknown</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 2 Changes in WBC counts (n = 25 patients) after administration of DX-8951f (mean ± SD).
DX-8951f Phase I in Leukemia

![Graph](https://example.com/graph.png)

**Fig. 3** Observed (...) and model-predicted (-) plasma concentrations versus time for representative patient.

WBC counts were well explained by an inhibitory Emax model. The Emax (maximal decrease in WBC precursor production in bone marrow) for the WBC nadir compared with the predose value was 89% and the DX-8951 exposure (AUC<sub>50</sub>) associated with one-half of the Emax value was 57 μg/h/liter (Fig. 4).

**DISCUSSION**

The topo I inhibitors are a potent class of antileukemic agents (12, 19, 29). DX-8951f, a hexacyclic synthetic water-soluble derivative of camptothecin, is a novel topo I inhibitor (25). The antitumor activities of DX-8951f have been studied both in vitro and in vivo in a number of different model systems (31, 47). DX-8951f was approximately 3 times more potent than SN-38 (the active metabolite of CPT-11), 10 times more potent than topotecan, and 20 times more potent than camptothecin as an inhibitor of topo 1 in vitro and 5 times more potent than SN-38 as an inhibitor of DNA synthesis (25, 31). In cell-based cytotoxicity assays, DX-8951f was 3–10 times more active than SN-38, topotecan, or camptothecin in its antiproliferative activity against a wide range of breast, colon, gastrointestinal, and lung human tumor cell lines (25, 27).

Toxicology studies in mice, rats, and dogs have shown that hematopoietic, gastrointestinal, lymphatic, and reproductive tissues are most prone to the adverse effects of DX-8951f (48). Noncumulative myelosuppression has been the principal dose-limiting effect of DX-8951f in both single- and multiple-dosing regimen studies in both rodents and dogs. There is considerable interspecies differences in drug tolerance, with dogs being more susceptible to toxicity than mice or rats. In dog and rodent pharmacology studies using 14C-DX-8951f and high-performance liquid chromatography for differential quantification of lactone and total drug, the half-life (t<sub>1/2</sub>) of the lactone ranged from ~20 to 30 min, and systemic exposure to the lactone was ~50% of total drug exposure. In rats treated with a single i.v. dose of 14C-DX-8951f, urine and fecal recovery averaged 15 and 78% of the administered dose, respectively. Hydroxylated metabolites predominated after coinubation of DX-8951f and human liver microsomes in vitro, and the rate of metabolite formation was decreased by inhibitors of CYP3A; the use of known CYP3A inhibitors was avoided in patients in the currently reported study. DX-8951f is highly plasma protein in both rats and dogs; spectrometric studies indicate that the lactone is selectively stabilized by albumin under physiological conditions.

The requirement of many camptothecins for enzymatic activation accentuates interindividual variability in their behavior. However, DX-8951f does not require enzymatic activation (25). Additionally, the broad preclinical antitumor spectrum of DX-8951f may be partially attributable to its not being a PGP substrate, in contrast to topotecan, 9-aminocamptothecin, and SN-38 (27). In addition, the antitumor activity of DX-8951f is similar against human pancreatic cancers and their respective sublines with acquired resistance to CPT-11 in vivo and SN-38 in vitro (27, 28). We thus considered DX-8951f to be potentially active in topotecan-resistant AML, an important consideration because topotecan is a component of some front-line AML regimens (20).

We have recently reported on the efficacy and toxic effects of DX8951f in a human AML SCID mouse model (37). Six-week-old female ICR SCID mice were given injections of 20 × 10⁶ viable KBM3 cells in the tail vein. The mice were then divided into groups of five and treated with different doses of DX-8951f 7 days after inoculation. Animals dying within 2 weeks from treatment had no molecular evidence of leukemia and were counted as toxic deaths. In control groups, all of the animals died of disseminated leukemia with a median survival of 35–37 days. With a single 20 mg/kg dose of DX8951f, no survival advantage was seen. Median survival improved with single doses of 40 and 50 mg/kg and was significantly prolonged at 60 mg/kg as compared with the control group. Further dose escalation was technically not feasible. Toxicity data suggest schedule-dependent effects because the same total dose of 20 mg/kg produced three of five deaths when given over a period of 5 days in contrast to none in five animals when given over a period of 1 or 3 days. The 20-mg/kg dose was well tolerated but was not effective in the one-day schedule. When given in a three-day schedule, a total dose of 20 mg/kg was still well tolerated and survival was significantly improved. In a five-day schedule the 20-mg/kg dose was toxic and did not prolong survival. DX-8951f had dose-schedule-dependent activity and toxicity in this AML in vivo model, as has been recently observed with other topo I inhibitors (49, 50).

Rowinsky et al. (39) have recently reported on a solid tumor Phase 1 study of DX-8951f given on the same schedule as the currently reported study. The MTD, defined as the highest dose level at which the incidence of DLT did not exceed 20%, was calculated separately for minimally pretreated (MP) and heavily pretreated (HP) patients. Thirty-six patients were treated with 130 courses of DX-8951f at six dose levels ranging from 0.1 to 0.6 mg/m²/day. Brief, noncumulative neutropenia was the most common toxicity observed. Severe myelosuppression was the DLT in both MP and HP patients. Nonhematological toxicities (nausea, vomiting, and diarrhea) were rarely severe. The recommended doses for Phase II studies of DX-8951f as a 30-min infusion daily for 5 days every 3 weeks were 0.5 and 0.3 mg/m²/day, respectively, for MP and HP patients with solid tumors.

In the currently reported Phase 1 study of DX-8951f in patients with leukemia, the MTD was 0.9 mg/m²/daily for 5 days with stomatitis being the DLT at higher doses. This represents an approximate doubling of the MTD established in
patients with solid tumors (39, 41, 48, 51). Although stomatitis was the DLT on this study, it was not a feature of the toxicity of DX8951f that was given on a variety of schedules in Phase I studies in patients with solid tumors, in whom lower doses were defined as the MTD on the basis of myelosuppression (39, 40, 42, 51). Stomatitis is a relatively pronounced toxicity in hematological malignancies and to place its activity in the context of topotecan (53, 54), 9-aminocamptothecin, (55) 9-nitrocamptothecin, (56), and NX-211 (57), all of which have antileukemic activity.

Because of the limited number of evaluable subject profiles in certain dosing groups, results have to be interpreted with caution. Nevertheless, the total plasma clearance (Cl) and volume of the central compartment (Vc) appeared to be the same between dosing groups. Patients treated at the dose of 1.25 mg/m²/day had more severe (Grade 4) DLT (stomatitis) than patients receiving the stopping dose of 1.35 mg/m²/day.

A 53-year-old male with AML and a −5, −7 blast karyotype achieved a PR after he received DX-8951f as second salvage therapy. The patient had primary refractory disease and had failed to achieve a response to either prior cyclophosphamide, ara-C, and topotecan (CAT) or dolostatin therapy. A 51-year-old female with AML and a trisomy 8, −5, −7 blast karyotype achieved a HI after she received DX-8951f as first salvage therapy. Her initial CR duration after induction therapy with CAT was 14 weeks.

Although it is very difficult to comment on the relative activity of DX-8951f in comparison with that of other topo I inhibitors in patients with acute leukemia based on the data from this Phase I study, it is noteworthy that both of the responding patients had failed prior topotecan therapy. Phase II studies are warranted to define the activity of DX-8951f in patients with hematological malignancies and to place its activity in the context of topotecan (53, 54), 9-amino camptothecin, (55) 9-nitrocamptothecin, (56), and NX-211 (57), all of which have antileukemic activity.

**REFERENCES**


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