

# The Topoisomerase I Inhibitor DX-8951f Is Active in a Severe Combined Immunodeficient Mouse Model of Human Acute Myelogenous Leukemia

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## ABSTRACT

The severe combined immunodeficient (SCID) mouse model of human acute myelogenous leukemia (AML) is a unique system for preclinical *in vivo* evaluation of the activity and toxicity of new agents. The topoisomerase I (topo I) inhibitor topotecan is active in patients with AML and myelodysplastic syndromes. DX-8951f is a novel topo I inhibitor with more potent antitumor effects than topotecan or CPT-11 *in vitro*. To study the *in vivo* activity of DX-8951f, 6-week-old female SCID mice received injections into the tail vein with  $2 \times 10^7$  exponentially growing KBM-3 cells. In each experiment, three to five sets of five mice were treated with DX-8951f doses ranging from 7.5 to 80 mg/kg and at schedules of 1, 3, and 5 days; a control set of five mice was treated with the drug vehicle alone. One group received DX-8951f on day 7 of the inoculation with KBM-3 (early-treatment group). To study the activity of DX-8951f in advanced disease, a second group was treated 1 month after the inoculation, when the animals were developing symptoms (late-treatment group). The study end point was the duration of survival until death from leukemia, which was assessed clinically and by the presence of the human *DQ $\alpha$*  gene in tissue samples by PCR. Six experiments were conducted with 170 animals. Survival was higher in both the early- and late-treatment groups than in untreated controls, and the treated groups had significantly less central nervous system disease. Significantly improved survival was observed in animals treated early with 60 and 80 mg/kg as a single injection, with 15 and 20 mg/kg over 3 days, and with 7.5 and 10 mg/kg over 5 days. In the late-disease model (treatment starting on days 28–35), improved survival was observed with a single dose of 80 or 20 mg/kg over 5 days. Dose escalation was limited by dilution problems at the

1-day schedule and by toxicity (mainly gastrointestinal) of the prolonged schedules. Both efficacy and toxicity were dose schedule dependent, increasing with higher doses and prolonged exposure. By establishing the antileukemic activity of DX-8951f against human AML transplanted into SCID mice at doses below the LD<sub>10</sub>, our data provide a rationale for clinical evaluation of the drug in patients with AML and favor the use of prolonged administration.

## INTRODUCTION

In recent studies, the significant activity of the topo<sup>2</sup> I inhibitor topotecan we found in patients with AML and myelodysplastic syndromes (1–3) suggested that targeting of the topo I enzyme may represent an important mechanism of antileukemic activity.

DX-8951f, a hexacyclic synthetic water-soluble derivative of camptothecin, is a novel topo I inhibitor. *In vitro*, DX-8951f is active against a wide spectrum of human malignant cell lines and against the P388 mouse leukemia (4, 5). In terms of tumor cell growth inhibition, topo I activity inhibition, and DNA fragmentation, DX-8951f is more potent than the other topo I inhibitors, SN-38 and topotecan (4, 5). Moreover, cell lines cross-resistant to CPT-11 and topotecan retain sensitivity to DX-8951f (4, 6, 7). Studies of DX-8951f in nude mice engrafted with various human solid tumor cell lines confirmed the drug's antitumor activity and, showing that myelosuppression is the dose-limiting toxicity of DX-8951f, further suggested its potential activity in treating leukemia (4, 5, 8).

We have described previously a SCID mouse model of human AML using the KBM-3 cell line, which is derived from a patient with acute myelomonocytic leukemia (9). We used this model in preclinical studies to establish activity and to assist us in designing Phases I and II leukemia studies with new drugs such as tallimustine or 9-aminocamptothecin (10–12). In the study reported here, we used the SCID mouse model of AML to evaluate the antileukemic activity of different DX-8951f dose schedules.

## MATERIALS AND METHODS

**Cells.** The KBM-3 cell line, derived in our laboratory from a patient with relapsed acute myelomonocytic leukemia (13), retains the phenotypic and genotypic characterization of acute myelomonocytic leukemia. KBM-3 cells engraft and disseminate in SCID mice in a manner similar to that observed in AML in humans (9). KBM-3 cells were expanded and frozen in

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<sup>2</sup> The abbreviations used are: topo, topoisomerase; AML, acute myelogenous leukemia; SCID, severe combined immunodeficient; GI, gastrointestinal.

liquid nitrogen in a large number of samples to avoid the use of different passages in consecutive experiments. After thawing, cells were maintained in culture as described and passaged fewer than three times before transplantation. We have shown previously that injection of  $1 \times 10^7$  or more cells killed all recipient mice within 6–10 weeks (9). Exponentially growing KBM-3 cells with 95% viability were harvested and washed in PBS before transplantation into SCID mice.

**Preparation of SCID Mice for Transplantation of KBM-3 Cells.** Female ICR SCID mice, 6 weeks of age, were obtained from a commercial breeder (Taconic Farms, Germantown, NY) and kept in a pathogen-free environment in the animal facility of The University of Texas M. D. Anderson Cancer Center. The animals were housed in microisolator cages and fed a sterile pellet diet and water, without antibiotics. The facilities are approved by the American Association for Accreditation of Laboratory Animal Care in accordance with current regulations and standards of the United States Department of Agriculture and Department of Health. Unconditioned SCID mice received injections of  $2 \times 10^7$  KBM-3 cells suspended in 0.2 ml of PBS into the tail vein.

**Drug and Treatment Schedule.** Daiichi Pharmaceutical Corp. (Montvale, NJ) supplied DX-8951f as a freeze-dried powder. After reconstitution in 0.9% NaCl USP, DX-8951f was injected into the tail vein of animals starting 7 days (“early disease”) or 28–35 days (“late disease”) after leukemia transplantation. The late-disease model reproduces the clinical situation of advanced disease, because in our experience, animals developed symptoms of leukemia during the fourth week of transplantation. The early-disease model reproduces the clinical situation of minimal disease. Experiments were conducted in sets of 30 mice. In each experiment, groups of five mice were randomly assigned to receive the drug vehicle (control group) or DX-8951f at five different dose schedules.

We initially evaluated a single-dose scheme at doses ranging from 20 to 80 mg/kg, based on previous toxicological studies conducted with BALB/c mice that showed the  $LD_{10}$  to be 52.4 mg/kg, with myelosuppression and GI toxicity being dose limiting. Problems with dilution of the drug precluded dose escalation  $>80$  mg/kg per injection. Prolonged schemes of administration were tested at doses ranging from 7.5 to 80 mg/kg given over 1, 3, or 5 days. All doses of DX-8951f are expressed as an anhydrous free base.

**Evaluation of Engraftment and Response.** Animals were observed daily and sacrificed when paralyzed or terminally ill. In the absence of clinically evaluable disease, mice were sacrificed 128 days after transplantation. Postmortem examination, performed in all animals, included macroscopic examination and tissue sample analysis by PCR for the presence of the *DQ $\alpha$*  human gene as described previously (9, 14). In addition to the analysis of samples of all macroscopically detectable tumors, systematic sampling of bone marrow, lungs, spleen, liver, and brain was done at necropsy. In cases of *DQ $\alpha$* -negative samples, true negativity was confirmed by PCR using primers for the murine *L-7* gene as described (15).

Engraftment was established on the basis of: (a) clinical evidence of leukemia defined by tumors or paraplegia [shown previously to be related to subarachnoidal space infiltration and more rarely to involvement of brain parenchyma involvement

Table 1 Engraftment and survival of control groups

Experiment	No. of mice	Median survival days (range)	Paraplegia <i>n</i>
1	5	44 (42–49)	4
2	5	40 (36–42)	2
3	5	37 (32–51)	3
4	5	32 (18–46)	5
5	5	32 (30–53)	4
6	5	35 (34–39)	3
Total	30	37 (18–53)	21

(9)]; and/or (b) the presence of human DNA in tissue samples obtained at necropsy.

**Statistical Analysis.** In the SCID mouse model, duration of survival is a simple, reliable marker of leukemia proliferation. Experiments were divided by total dose administered and by early- or late-disease models so that the impact of dose scheduling could be evaluated. Survival was calculated from the date of KBM-3 cell inoculation (day 0) to the date of death from leukemia, using the method of Kaplan-Meier (16). To provide adequate numbers of observations, some dose levels were combined. Doses with evidence of excessive toxicity ( $LD_{50}$ ) were excluded from survival analysis. For the dose levels analyzed, the number of toxic deaths was very small, and it made little difference whether toxic deaths were censored in survival analysis. We therefore censored such deaths in the results presented here. Leukemic death was defined based on clinical, postmortem, and/or molecular evidence of leukemia. Assessment of DX-8951f antileukemic activity was based on prolonged survival of the treated mice compared with survival of untreated controls. The control group consisted of the nontreated animals in the respective early- or late-disease experiments.

## RESULTS

**Engraftment.** A total of 170 mice were included in six experiments (experiment 1, 20 animals; experiments 2–6, 30 animals each). Thirty mice served as control in the six experiments (Table 1). All controls died after a median of 37 days (range, 18–53 days) after KBM-3 cells infusion, with clinical and/or molecular evidence of leukemia corresponding to a 100% engraftment rate. Twenty-one (70%) developed paraplegia, which has been shown previously to be related to subarachnoidal space infiltration by leukemic cells (9). Twenty-one control mice (including 12 with paraplegia) had tumors at various sites including the mediastinum, retroperitoneum, mesentery, kidneys, bones, and s.c. tissues.

**Early-Disease Model.** Treatment with DX-8951f started on day 7 in four experiments (experiments 3–6). The dose escalation scheme and results are presented in Table 2 for the 100 mice treated early. Most significant toxicity was a sickly appearance (hunched back, rough coat), diarrhea, and GI bleeding, observed in 36 mice (36%). Twenty-four (24%) died within 2 weeks of treatment initiation (median, 7 days; range, 6–13 days) with diarrhea (16/24) or GI hemorrhage (3/24). Among these, none of the 19 mice studied by PCR had evidence of leukemia. Twelve mice recovered from the initial toxic effects.

A first group of mice was treated with an escalating single

Table 2 Toxicity and antileukemic activity of DX-8951f in the early-disease model

Dose total <sup>a</sup>	Daily (mg/kg)	No. of mice	Toxic deaths	Leukemic deaths	Median survival <sup>b</sup> Days (range)	Paraplegia
1-day						
20	20	10	0/10	10/10	41 (29–66)	8
40	40	5	0/5	5/5	49 (39–102)	3
50	50	5	2/5	3/5	52 (14–79)	1
60	60	5	0/5	5/5	68 (53–103)	1
80	80	5	0/5	5/5	54 (49–81)	0
3-day						
10	3.3	5	0/5	5/5	45 (36–72)	3
15	5	5	0/5	5/5	64 (57–72)	1
20	6.5	10	0/10	10/10	50 (35–72)	5
30	10	5	4/5	1/5	NE	0
40	13.3	5	1/5	3/5	111 (14–128+) <sup>d</sup>	0
80	26.5	5	4/5	1/5	NE <sup>c</sup>	0
5-day						
7.5	1.5	10	1/10	9/10	57 (16–60)	4
10	2	10	1/10	9/10	54 (17–89)	3
15	3	5	3/5	2/5	NE	0
20	4	5	3/5	2/5	NE	0
80	16	5	5/5	NE	NE	0

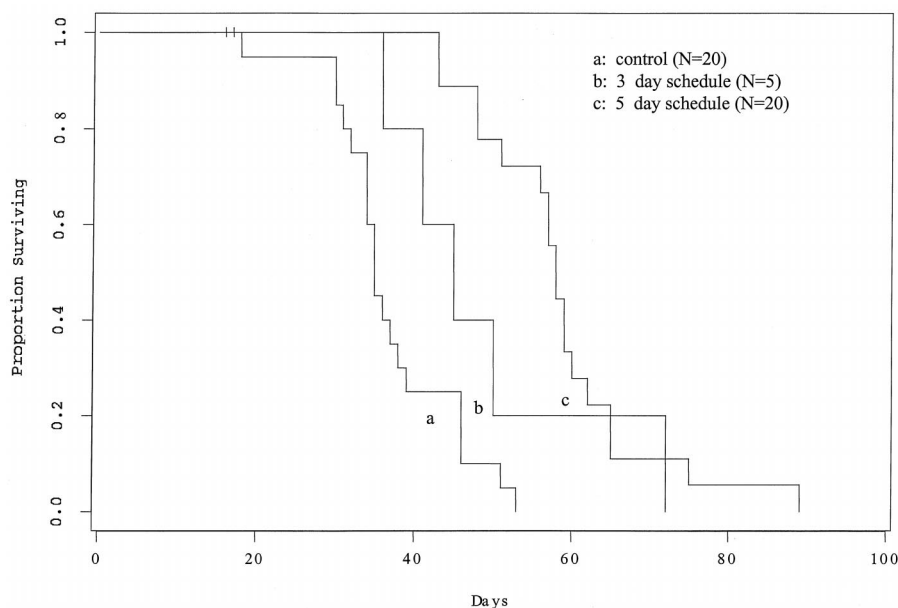
<sup>a</sup> The dose of DX-8951f is expressed as an anhydrous free base.

<sup>b</sup> Kaplan-Meier estimates for median survival.

<sup>c</sup> NE, not evaluable secondary to excessive toxicity.

<sup>d</sup> One mouse sacrificed free of disease on day 128.

Fig. 1 Survival of mice treated on day 7 with a total dose  $\leq 10$  mg/kg DX-8951f on 3- and 5-day schedules.



dose of DX-8951f ranging from 20 to 80 mg/kg (Table 2). Two toxic deaths were seen in the group receiving 50 mg/kg but not in those receiving higher doses. Survival was prolonged with increasing dose level, suggesting a dose-response effect for antileukemic activity. The solubility of the drug, which was borderline at the 80-mg/kg single-dose level, might have affected the toxicity and efficacy of the agent. The same dose range was tested using a 3-day infusion scheme and expanded to lower dose levels (10 and 15 mg/kg). The 3-day treatment scheme produced toxic deaths at a total dose of 30 mg/kg and

above, and antileukemic activity was seen at 15 mg/kg. One mouse treated with 40 mg survived until the termination of the experiment and did not show clinical or molecular evidence of residual leukemia on postmortem examination. Finally, a 5-day infusion scheme was evaluated. Because doses of 20 and 80 mg/kg initially tested produced 60–100% toxic death rates, the dose was deescalated to 7.5 mg/kg. The results showed that the toxic death rate increased progressively from 10 to 100% with increasing doses of DX-8951f. Antileukemic activity was observed at the lowest dose levels (7.5 and 10 mg/kg). Because of

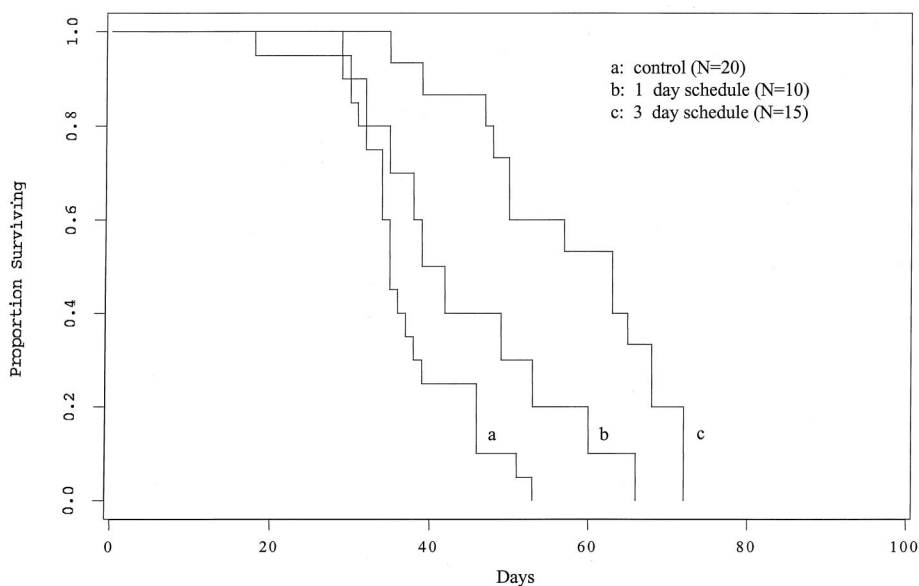


Fig. 2 Survival of mice treated on day 7 with a total dose of 15–20 mg/kg DX-8951f on 1- and 3-day schedules.

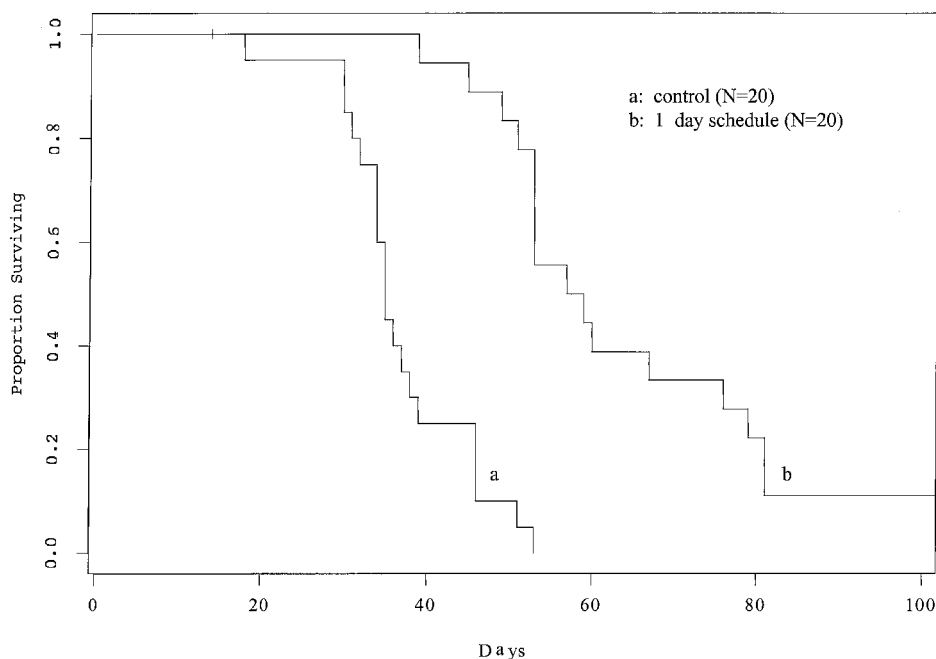


Fig. 3 Survival of mice treated on day 7 with >20 mg/kg DX-8951f.

excessive toxicity, no improvement of survival was seen at higher doses in this schedule, but the data for this group also suggested a dose-response relationship for toxicity and for antileukemic effect of DX-8951f. These results show an increase in the toxicity and the efficacy of DX-8951f with prolonged administration. The minimum dose that produced toxic deaths was 50 mg/kg for the single-injection dose, 30 mg/kg for the 3-day schedule, and 7.5 mg/kg for the 5-day schedule. Similarly, antileukemic activity was seen at doses  $\geq 60$  mg/kg for a single injection, 15 mg/kg for 3-day treatment, and 7.5 mg/kg for 5-day treatment.

Table 3 Incidence of paraplegia in the different dose schedules of the early-disease model

Total dose	Schedule	Paraplegia
$\leq 10$ mg/kg	Control	15/20
	3 days	3/5
	5 days	7/20
15–20 mg/kg	1 day	8/10
	3 days	6/15
>20 mg/kg	1 day	5/20

Table 4 Toxicity and antileukemic activity of DX-8951f in the late-disease model

Dose total <sup>a</sup>	Daily (mg/kg)	No. of mice	No. with toxicity <sup>b</sup>	Leukemic deaths	Median survival <sup>c</sup> Days (range)	Paraplegia
1-day						
20	20	5	0/5	5/5	39 (37–39)	5
50	50	5	2/5	5/5	41 (36–49)	3
80	80	5	3/5	4/5	51 (45–128+)	0
3-day						
20	6.5	5	3/5	5/5	42 (36–53)	3
50	16.5	5	5/5	2/5 <sup>d</sup>	35 (34–35)	1
5-day						
20	4	10	8/10	4/10	49 (35–128+)	2
80	16	5	5/5	5/5	42 (42–44)	1

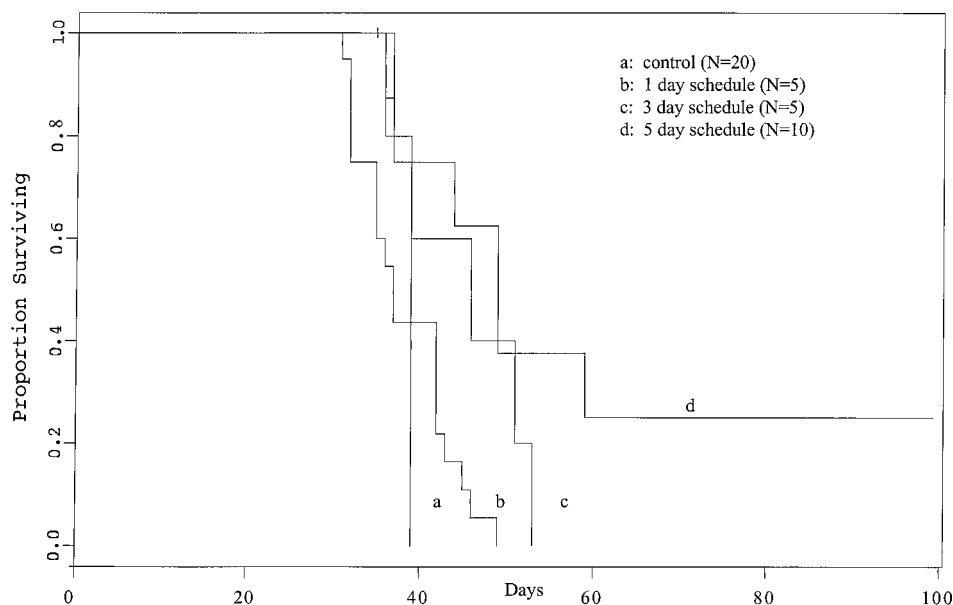
<sup>a</sup> The dose of DX-8951f is that of the anhydrous free base.

<sup>b</sup> Number of mice with toxicity, regardless of whether they died.

<sup>c</sup> Kaplan-Meier estimates for median PFS.

<sup>d</sup> Nonevaluable PCR in 3 of 5 who died.

Fig. 4 Survival of mice in the late treatment group who received 20 mg/kg DX-8951f on three different schedules.



Figs. 1 and 2 demonstrate the clear trend for longer survival with prolonged schedules for doses  $\leq 10$  mg/kg and 15–20 mg/kg, respectively. For total dose  $> 20$  mg/kg, only the 1-day schedule was evaluable because of toxicity with prolonged administration (Fig. 3).

Of note is the lower incidence of paraplegia in this group, 38.2% of the evaluable mice compared with 75% incidence of the early-treatment control group ( $P < 0.01$ ). The incidence of paraplegia decreased with the higher doses of a given schedule (Table 2). These findings were confirmed when the incidence of paraplegia was studied in the same groups of animals included in the survival curves. Trends were similar to survival experience, with generally higher rates of paraplegia associated with control groups and with shorter schedules (Table 3).

**Late-Disease Model.** In two experiments, treatment was initiated when the mice started showing signs of overt leukemia

(tumors, rough coat). Treatment started on day 35 after KBM-3 injection in experiment 1 and on day 28 after KBM-3 injection in experiment 2.

To allow comparison with animals in the early-treatment group, DX-8951f was given in doses ranging from 20 to 80 mg/kg as a single dose over 3 days or 5 days. Forty mice were treated (Table 4), and 10 served as control. Of the 26 mice that developed toxicity, 16 died within 1 week of treatment, and 4 had no evidence of disease at necropsy or by PCR analysis of bone marrow, spleen, liver, lung, and brain tissues at the time of death. Of the 10 animals that recovered from toxicity, 2 survived until the experiment ended on day 128.

Survival curves show improved survival in the treated group compared with control. At the 20-mg/kg dose level, improved survival was associated with prolonged schedule (Fig. 4). The higher doses were excluded from analysis because of excessive toxicity. Of significance is the survival of three mice



in this group with no incidence of leukemia by PCR analysis at the time of experiment termination. One of the survivors received 20 mg/kg by a prolonged (5-day) schedule; the other two received a 1-day schedule at the higher dose (80 mg/kg).

## DISCUSSION

Phase I and II trials, the standard methods of evaluating the effectiveness of new antileukemic agents, are conducted with patients who have refractory disease or who have relapsed after undergoing intensive frontline regimens. The chances of missing signs of drug activity in such trials are significant. The reported complete remission rate of Phase I studies, <5% (17), requires new strategies to investigate the activity of new agents in chemotherapy-naïve individuals whose prognosis is poor. Preclinical models of human AML are useful for testing the most promising new agents *in vivo* and for determining effective dose schedules and combinations before clinical studies begin. The SCID mouse model has been used increasingly for this purpose, and it has helped to prioritize agents for Phase I studies. We have used our animal data on tallimustine (10) and 9-aminocamptothecin (11) in designing Phase I studies for these agents (10, 12). The results of the currently reported dose-finding study showed that DX-8951f is active in human AML. Both efficacy and toxicity are dose schedule dependent, and they increase with increasing dose and prolonged exposure. The S-phase specificity of the topo I inhibitors explains the higher cytotoxicity of the drug with prolonged administration (18). In animals treated with 9-aminocamptothecin, longer schedules were shown to improve the therapeutic index (19). The GI toxicity observed in our study is consistent with the mucositis that topo I inhibitors cause at high doses and prolonged infusions (18). Clear survival advantage was observed in animals receiving DX-8951f, with four mice in the treated group surviving until experiment termination with no evidence of leukemia clinically or by molecular analysis of tissues. A significant observation was the reduction of central nervous system disease in the treated group (41% *versus* 70% in controls;  $P < 0.01$ ). Initial pharmacological studies in animals have shown that DX-8951f does not cross the blood-brain barrier in the intact brain. This may be different in the case of meningeal infiltration by leukemia cells.

In conclusion, we showed that DX-8951f is an active antileukemic agent in the SCID mice model of human AML. Our results also suggest that prolonged schedules should be favored. The apparent activity of DX-8951f in central nervous system leukemia warrants further investigations. On the basis of the data from this study, we are conducting a Phase I study of DX-8951f in patients with advanced and/or refractory leukemia at the M. D. Anderson Cancer Center.

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