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

Norbert Vey, Francis J. Giles, Hagop Kantarjian, Terry L. Smith, Miloslav Beran, and Sima Jeha

Departments of Leukemia [N. V., F. J. G., H. K., M. B.] Bio-statistics [T. L. S.], and Pediatrics [S. J.], The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

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 cells. 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 DQa 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_{90}, 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^{2} 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...
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 passed 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, German-
town, NY) and kept in a pathogen-free environment in a 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 Accred-
itation 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 trans-
plantation. The late-disease model reproduces the clinical situ-
ation 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 rang-
ing from 20 to 80 mg/kg, based on previous toxicological
studies conducted with BALB/c mice that showed the LD$_{50}$ 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 examina-
tion, performed in all animals, included macroscopic examina-
tion and tissue sample analysis by PCR for the presence of the
DQ$a$ human gene as described previously (9, 14). In addition to
the analysis of samples of all macroscopically detectable tu-
mors, systematic sampling of bone marrow, lungs, spleen, liver,
and brain was done at necropsy. In cases of $DQ$a$-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>
<thead>
<tr>
<th>Experiment</th>
<th>No. of mice</th>
<th>Median survival days (range)</th>
<th>Paraplegia $n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>44 (42–49)</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>40 (36–42)</td>
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<td>3</td>
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<td>37 (32–51)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>32 (18–46)</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>32 (30–53)</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>35 (34–39)</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>37 (18–53)</td>
<td>21</td>
</tr>
</tbody>
</table>

The late-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.

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

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sacrificed 128 days after transplantation. Postmortem examina-
tion, performed in all animals, included macroscopic examina-
tion and tissue sample analysis by PCR for the presence of the
DQ$a$ human gene as described previously (9, 14). In addition to
the analysis of samples of all macroscopically detectable tu-
mors, systematic sampling of bone marrow, lungs, spleen, liver,
and brain was done at necropsy. In cases of $DQ$a$-negative
samples, true negativity was confirmed by PCR using primers
for the murine L-$7$ gene as described (15).

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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

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 experi-
ments (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, mesentry, kid-
nneys, 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
treated mice. Most significant toxicity was a sickly
appearance (hunched back, rough coat), diarrhea, and GI bleed-
ing, 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

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

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

b Kaplan-Meier estimates for median survival.

c NE, not evaluable secondary to excessive toxicity.

d One mouse sacrificed free of disease on day 128.

Fig. 1 Survival of mice treated on day 7 with a total dose ≤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
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 ≥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

<table>
<thead>
<tr>
<th>Total dose</th>
<th>Schedule</th>
<th>Paraplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 mg/kg</td>
<td>Control</td>
<td>15/20</td>
</tr>
<tr>
<td>3 days</td>
<td>5 days</td>
<td>7/20</td>
</tr>
<tr>
<td>15–20 mg/kg</td>
<td>1 day</td>
<td>8/10</td>
</tr>
<tr>
<td>3 days</td>
<td>6/15</td>
<td></td>
</tr>
<tr>
<td>&gt;20 mg/kg</td>
<td>1 day</td>
<td>5/20</td>
</tr>
</tbody>
</table>

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.
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

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

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

\(a\) The dose of DX-8951f is that of the anhydrous free base.  
\(b\) Number of mice with toxicity, regardless of whether they died.  
\(c\) Kaplan-Meier estimates for median PFS.  
\(d\) Nonevaluable PCR in 3 of 5 who died.
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-naive 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.

REFERENCES

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