Phase I and Pharmacological Study of a New Camptothecin Derivative, Exatecan Mesylate (DX-8951f), Infused Over 30 Minutes Every Three Weeks

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ABSTRACT

Purpose: A Phase I study of exatecan, a new watersoluble camptothecin derivative, was conducted to determine the maximum tolerated dose and a recommended dose, according to an internationally standardized core protocol. Pharmacological profiles of lactone and total (lactone + carboxylate) exatecan were also investigated.

Patients and Methods: Fifteen patients with advanced solid malignancies were treated with 3, 5, and 6.65 mg/m² of exatecan infused over 30 min every 3 weeks. Concentrations of lactone, total drug, and a metabolite in plasma and urine were determined during the first course.

Results: Dose-limiting neutropenia and liver dysfunction were observed in two of six patients at 6.65 mg/m², but no grade 3 or worse diarrhea was observed. Emesis was moderate, and no grade 3 or worse nausea or vomiting were observed at a recommended dose of 5 mg/m², with moderate, and no grade 3 or worse nausea and vomiting. No grade 3 or worse diarrhea was observed. Emesis was determined during the first course.

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Conclusions: The recommended dose of exatecan infused over 30 min every 3 weeks is 5 mg/m², with a favorable toxicity profile of mild and infrequent diarrhea. Interpatient variability of pharmacokinetics was similar to or smaller than that with other camptothecin derivatives.

INTRODUCTION

Camptothecin derivatives are a unique class of anticancer agents that have an inhibitory effect on topoisomerase I activity as their mechanism of action (1–3). Among camptothecin derivatives that have been evaluated clinically, irinotecan and topotecan are the most widely used drugs for which antineoplastic activities have been clinically confirmed (4). Irinotecan in particular has been demonstrated to be superior to conventional therapies that had been widely used for colorectal cancers and now plays an indispensable role in the standard therapy (5–7). Furthermore, evidence of the superior activity of irinotecan over conventional drugs against both small and non-small cell lung cancers has accumulated (8–10).

Severe and unpredictable diarrhea caused by irinotecan, however, has hampered its clinical use. Irinotecan undergoes metabolic activation by carboxyesterase to yield the active metabolite, SN-38, which is further inactivated by uridine diphosphate glucuronosyl transferase (11). Polymorphism in these enzymes leads to pharmacokinetic interpatient variation of irinotecan and explains, at least in part, the unpredictable severe toxicity (12–14).

Exatecan is a novel synthetic camptothecin derivative with a unique hexacyclic structure (15). The compound is water soluble and does not require metabolic activation. Similar to other camptothecin derivatives, the closed lactone ring of exatecan undergoes pH-dependent hydrolysis to yield an open carboxylate form (Fig. 1). An intact lactone ring was found to be necessary for topoisomerase I inhibition. Two metabolites, UM-1 and UM-2, were found in urine after exatecan was infused to rats. In vitro experiments using human liver microsomes and microsomes from cell lines expressing human CYPs revealed that UM-1 was the major metabolite in liver microsomes and that CYP3A4 was the isoyme responsible for metabolizing exatecan to UM-1.

The inhibitory effect of exatecan on topoisomerase I activity is 3 and 10 times higher than those of SN-38 and topotecan, respectively (15, 16). In vitro experiments using various cell lines derived from solid tumors showed that exatecan was 28 times more active than SN-38 and topotecan, respectively.

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3 The abbreviations used are: SN-38, 7-ethyl-10-hydroxycamptothecin; exatecan, DX-8951f; (1S,9S)-1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-10H,13H-benzof[a]pyranol[3,4',6,7]-indolizino[1,2-b]quinoline-10,13-dione monomethanesulfonate dihydrate; CYP, cytochrome P-450; AUC, area under the time-concentration curve.
(15). It also exhibited potent activity against in vivo models of acute myelogenous leukemia of early and late stages (17). It has greater activity against human tumor xenografts than other camptothecin derivatives including irinotecan, topotecan, and lurtotecan (GG-211; Ref. 18). The spectrum of in vitro activity of exatecan is broad on tumor colony formation from freshly explanted human tumor cells, covering gastric, colon, lung, breast, head and neck, ovarian, and prostate cancers and pediatric tumors (19). Furthermore, the therapeutic ratio (maximum tolerated dose:minimum effective dose) of exatecan was 2–10 times greater than those of irinotecan and topotecan (18, 20). Finally, exatecan was effective against irinotecan-, SN-38-, and topotecan-resistant cell lines (16, 18, 21), and unlike topotecan (15, 22), exatecan was effective against a P-glycoprotein-mediated multidrug-resistant cell line (15).

On the basis of these studies showing that exatecan had more potent antitumor activity and less toxicity than other camptothecin derivatives, Phase I studies with various infusion schedules have been conducted in Japan, the United States, and Europe. Before each Phase I study was planned, a standardized core protocol for Phase I studies was defined, and protocols of all of the Phase I studies were based on the core protocol, which standardized eligibility and exclusion criteria, toxicity, and efficacy criteria, the definition of dose-limiting toxicities and the maximum tolerated dose, and supportive therapies. In this study in Japan, we conducted a Phase I study of exatecan infused over 30 min every 3 weeks to determine the maximum tolerated dose and a recommended dose. Pharmacokinetic profiles of the lactone form and total (lactone + carboxylate) drug were also investigated.

PATIENTS AND METHODS

Eligibility. Eligibility criteria included patients with histologically or cytologically confirmed solid malignant tumors that were refractory to standard therapy or for which no effective therapy was available, who were 20–74 years of age, and had an Eastern Cooperative Oncology Group performance status of 0–2. Prior chemotherapy and radiotherapy had to be completed at least 4 weeks (6 weeks for nitrosourea, mitomycin C, carboplatin, and investigational new drugs) before entry into the study, and the total field of prior radiotherapy was required to encompass <20% of hematopoietic bones. Patients were required to have a life expectancy of ≥2 months and adequate organ function, with leukocyte count ≥4,000/mm³ and <12,000/mm³, absolute neutrophil count ≥2,000/mm³, hemoglobin ≥9.0 g/dl, platelet count ≥100,000/mm³, aspartate aminotransferase and alanine aminotransferase ≤2 × normal, bilirubin ≤1.5 mg/dl, creatinine clearance ≥50 ml/min, and PaO₂ ≥60 mm Hg. Patients with diarrhea, bowel obstruction or paralysis, interstitial pneumonitis, a history of heart failure or myocardial infarction within 6 months, or a history of allergy to irinotecan or other camptothecin derivatives were ineligible. Patients with a symptomatic brain metastasis, active infection, uncontrolled diabetes mellitus, liver cirrhosis, or pregnancy were also excluded from the study.

This Phase I study was conducted in accordance with the guidelines of the Ministry of Health and Welfare, Japan. Written informed consent according to institutional and regulatory requirements was obtained from all patients, and the study was approved by the Institutional Review Board of the National Cancer Center, Japan.

Dosing and Follow-Up. Exatecan was dissolved in normal saline (100 ml) and infused i.v. over 30 min; the treatment was repeated every 3 weeks after patients recovered from the toxicities. Dogs were found to be more sensitive to exatecan than mice in preclinical toxicological studies, and the starting dose was one-third of the toxic low dose in dogs (3 mg/m²). A 100% dose escalation was planned until grade 2 nausea or vomiting or other grade 1 toxicities were observed, after which successive dose increments of 65, 50, and 40%, followed by
ing toxicities at 6.65 mg/m² was found to have an AUC three times higher than other patients treated at the same dose and a considerable level of the drug remained in plasma 48 h after the end of infusion. Therefore, additional blood samplings for pharmacokinetics were performed in this patient at 9 and 13 days after the treatment.

For pharmacodynamic analysis of the relationship between the AUC and neutropenia, the surviving fraction (SF) of neutrophils was calculated by dividing the nadir neutrophil count by the pretreatment count. Relationships between the surviving fraction versus the AUC of lactone and total exatecan were analyzed using an inhibitory sigmoid $E_{\text{max}}$ model:

$$SF = 1 - \frac{\text{AUC}'}{\text{AUC}_{50} + \text{AUC}'}$$

where $r$ is a sigmoidicity parameter and $\text{AUC}_{50}$ is a parameter corresponding to an AUC value that produced a 50% decrease in neutrophil counts. Correlation between observed SF and SF predicted by the model was evaluated using Pearson correlation coefficient.

**RESULTS**

**Dose Escalation.** Fifteen patients were treated at three dose levels, 3, 5, and 6.65 mg/m², with a total of 30 courses (median number of courses in each patient was 2, range 1–5). Demographic profiles of the patients are listed in Table 1. Fourteen of 15 patients had previously been treated with chemotherapy, with a median of two regimens (range, 1–6). Although a 100% dose escalation was planned for the first part of the dose escalation, grade 2 leukopenia, thrombocytopenia, and vomiting and grade 3 anemia and nausea were observed at the first dose level. As a result, the dose was increased by 67% to 5 mg/m², at which one of six patients developed dose-limiting neutropenia and grade 3 thrombocytopenia; the dose was then increased by 33% to 6.65 mg/m². At 6.65 mg/m², two of six patients experienced dose-limiting toxicities, grade 3 liver dysfunction with dose-limiting neutropenia in one patient, and grade 3 liver dysfunction in another. On the basis of these observations, the maximum tolerated dose was determined to be 5 mg/m².

**Hematological Toxicity.** The worst hematological toxicities observed in all courses of each patient are listed in Table 2.
Neutropenia was the principal hematological toxicity, and dose-limiting neutropenia was observed in the first course of two patients. One of six patients treated at 5 mg/m² developed grade 4 neutropenia lasting for 5 days. At the 6.65 mg/m² dose level, one patient had AUC that was three times higher than the other patients treated at the same dose and developed grade 4 neutropenia, complicated by fever. Granulocyte-colony stimulating factor was given after dose-limiting neutropenia was documented, but grade 4 neutropenia lasted for 7 days in this patient. Grade 3 thrombocytopenia was observed in the two patients who experienced dose-limiting neutropenia. The nadir of neutropenia in all patients was observed between 4 and 22 (median, 11) days after the treatment, and for thrombocytopenia the nadir was between 7 and 12 (median, 10) days after the treatment. Neutrophil counts recovered to 2000/µl by 13–17 (median, 15) days after the treatment. At a recommended dose of 5 mg/m², treatment at 3-week intervals was possible in five of six patients, and the treatment was repeated every 4 weeks in one patient.

**Table 2** Worst hematological toxicity per patient across all courses

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
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<tr>
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<td>6</td>
<td>16</td>
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</tr>
<tr>
<td>6.65</td>
<td>6</td>
<td>10</td>
<td>0/3/1/1</td>
<td>1/2/1/1</td>
<td>3/0/1/0</td>
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</tr>
</tbody>
</table>

* Dose-limiting toxicity.

**Table 3** Worst nonhematological toxicity per patient across all courses

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Liver</th>
<th>Skin</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
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<td>0/2/1/0</td>
<td>1/1/0/0</td>
<td>0/0/0/0</td>
<td>0/0/0/0</td>
<td>0/0/0/0</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>16</td>
<td>3/3/0/0</td>
<td>2/2/0/0</td>
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</tr>
<tr>
<td>6.65</td>
<td>6</td>
<td>10</td>
<td>2/2/2/0</td>
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<td>0/0/2/0</td>
<td>0/0/0/0</td>
</tr>
</tbody>
</table>

* Dose-limiting toxicities.

Nonhematological Toxicity. Nonhematological toxicities for all courses are summarized in Table 3. Nausea and vomiting as a result of treatment with exatecan in this schedule were moderate to severe. All patients treated at 3 mg/m² experienced grade 2 or 3 nausea or vomiting, and granisetron was infused i.v. prior to the administration of exatecan in all patients treated at 5 and 6.65 mg/m². Grade 3 nausea and vomiting was observed in two patients at 6.65 mg/m², but they were grade 2 or milder at 5 mg/m². Although diarrhea was one of the dose-limiting toxicities of irinotecan, diarrhea with exatecan was mild and infrequent. Grade 3 or greater diarrhea was not observed, and only one episode of grade 2 diarrhea was observed at 5 mg/m². Asymptomatic grade 3 liver dysfunction with elevations of serum levels of bilirubin and transaminases was observed in the first course of 2 patients at 6.65 mg/m². The peak levels of bilirubin were 2.7 and 1.7 mg/dl, and those for transaminases

**Fig. 2** Time courses of lactone and total exatecan and a metabolite (UM-1) in a representative patient.

**Fig. 3** Time course of the ratio of lactone concentration to total concentration. Means of the ratio in all patients are shown; bars, SD.
were 8–11 times the upper limit of the normal range; they were observed 2 or 3 days after the treatment. The levels of bilirubin and transaminases decreased to grade 1 or better by 7 days after the treatment and normalized in the second week. Two patients experienced minor and transient skin eruptions with itching sensations. Although clinically insignificant microscopic hematuria was observed in one patient, no other sign of hemorrhagic cystitis was observed.

**Pharmacology.** A pharmacokinetic investigation was performed in all patients treated in this study. Time courses of lactone and total exatecan and a metabolite (UM-1) in a representative patient treated at 5 mg/m² are shown in Fig. 2. The second peak of the concentration-time curve for exatecan was observed 5–8 h after the treatment in 10 patients. The ratio of lactone concentration to total concentration decreased from 10 h after the infusion and did not change thereafter (Fig. 3).

There was a positive correlation between body surface area versus clearance of lactone ($r^2 = 0.11$) and total drug ($r^2 = 0.12$), although these correlations were not statistically significant ($P = 0.24$ and 0.20, respectively) because of the small number of patients. The AUC of the lactone and total drug increased linearly with dose escalations (Fig. 4); clearance adjusted by body surface area of lactone ($P = 0.39$) and total drug ($P = 0.50$) did not change with dose escalations. Pharmacokinetic parameters are listed in Table 4. Concentrations of total and lactone exatecan declined in parallel during the termination phase, and the ratio of the lactone AUC to the total AUC was 0.30. Although UM-1 was detected in all patients, the AUC of UM-1 was 7% or less of the parent drug in plasma. However, the amount of UM-1 excreted in urine in 24 h was twice as much as that of the parent drug, and 25 ± 8% (mean ± SD) of the administered drug was excreted in urine as the parent compound or UM-1. One patient treated at 6.65 mg/m² had a much higher AUC than the other patients and might seem to be an outlier (Fig. 4). However, the clearances of lactone and total drug in this patient were within the 95% confidential intervals of all patients. Exatecan is metabolized to UM-1 by CYP3A4, and many drugs are known to inhibit the activity of CYP enzymes. The AUC of UM-1 in the patient was also highest among all patients, and the patient was not taking any drugs known to inhibit CYP3A4.

Neutropenia was the principal toxicity, and relationships between neutropenia versus the AUC of lactone ($AUC_{lactone}$) and the total drug ($AUC_{total}$) were investigated. Neutropenia expressed as the surviving fraction of neutrophils ($SF$) was significantly related to the $AUC_{lactone}$ ($r^2 = 0.50$, $P = 0.003$) and $AUC_{total}$ ($r^2 = 0.40$, $P = 0.012$) as shown in Fig. 5. These relationships were described by inhibitory sigmoid $E_{max}$ models: $SF = 1 - AUC_{lactone}^{0.94}/(523^{0.94} + AUC_{lactone}^{0.94})$ and $SF = 1 - AUC_{total}^{0.65}/(1518^{0.65} + AUC_{total}^{0.65})$. When the patient who had the highest AUC was excluded from the pharmacodynamic analysis, the relationship with $AUC_{lactone}$ remained significant ($r^2 = 0.29$, $P = 0.047$), whereas that with the $AUC_{total}$ was no longer significant ($r^2 = 0.16$, $P = 0.16$). When the relationships between the surviving fraction of neutrophil counts and AUC were evaluated using a linear regression model, correlations to $AUC_{lactone}$ ($r^2 = 0.50$, $P = 0.003$) and $AUC_{total}$ ($r^2 = 0.44$, $P = 0.007$) were stronger than that to the dose of exatecan ($r^2 = 0.19$, $P = 0.10$). With regard to liver dysfunction, another dose-limiting toxicity in this study, grade 3 liver dysfunction was observed in two patients who had the highest values of $AUC_{lactone}$ and $AUC_{total}$.

**Response.** Nine patients had stable disease, and six patients had disease progression. No complete or partial responses were observed in this study.

**DISCUSSION**

Dose-limiting toxicities of exatecan administered over 30 min every 3 weeks were neutropenia and liver dysfunction and were observed in two of six patients treated at 6.65 mg/m²; the recommended dose was 5 mg/m². Exatecan is being developed with the expectation of enhancing the antitumor activity of camptothecin derivatives and of reducing the severe toxicity of irinotecan, especially the unpredictable diarrhea.

The principal toxicity of exatecan was neutropenia, but it was easily managed and complicated by fever in only one patient, who had the highest drug exposure. Neutropenia did not preclude the planned every-3-week administration in five of six patients treated at the recommended dose of 5 mg/m², and treatment could be repeated every 4 weeks in the remaining patient.

Dose-limiting liver dysfunction was observed in two patients treated at 6.65 mg/m² in this study. However, only six patients were treated at this dose, and the confidence interval for the rate of the toxicity was large. Furthermore, it was asymptomatic and might not be dose-limiting, unless blood chemistries...
are measured 2 or 3 days after the treatment. In this study, blood chemistries were measured within a week after the first administration of exatecan in 14 of 15 patients, and liver dysfunction was recorded in three patients. However, liver dysfunction was transient and normalized in the second week. Therefore, intrapatient dose escalation with careful monitoring might be optionally performed in Phase II studies. A notable feature of the toxicity profile of exatecan was that diarrhea was infrequent and mild. In marked contrast to irinotecan, severe diarrhea was not observed in this study. Diarrhea is dose limiting and sometimes fatal in treatment with irinotecan, and extensive use of loperamide is necessary when diarrhea begins after irinotecan administration (25–27). This did not happen in this study of exatecan, and only one episode of grade 2 diarrhea was observed at 5 mg/m².

The number of patients in this study was small, and the confidence interval for toxicity rates was large. However, another Phase I study of exatecan, administered using the same schedule as our study, has been conducted in France, and similar results were observed (28). Doses ranging from 4 to 7.1 mg/m² were evaluated in the French study, and the recommended dose and toxicities were similar to those of our study. The recommended dose was 5.3 mg/m² in the French study (5 mg/m² in our study), and neutropenia was dose limiting. Similar to our study, grade 3 or greater diarrhea was not observed in their study. Liver dysfunction was not observed in their study, but as mentioned previously, this might be related to the timing and frequency of the measurements of blood chemistry. In a Phase I study of exatecan using a daily-times-five schedule, liver dysfunction was also observed (29). Although the concentration of the lactone form was not measured in the French study, the clearance and the half-life of the total drug was 2.4 l/h/m² and 7.7 h, respectively, and close to values obtained in our study (2.1 l/h/m² and 10.9 h). These observations suggest that there are no large interethnic differences in the pharmacokinetics or pharmacodynamics of exatecan. However, the numbers of patients treated in both studies were small, and a large population should be evaluated before making definitive conclusions on interethnic differences.

Unlike irinotecan, exatecan does not require metabolic activation, which may be beneficial in reducing the interpatient variability of pharmacokinetics of the active compounds. In a Phase I study of irinotecan administered every 3 weeks, the coefficient of variation of the lactone AUC of SN-38 was large, ranging from 63 to 105% when therapeutic doses of 240–345 mg/m² of irinotecan were administered (30). Similarly, the coefficient of variation of the lactone AUC of SN-38 was 60–106% in children receiving a 1-h infusion of irinotecan (31). In a pharmacological study of irinotecan at a weekly dose of 100 mg/m², the coefficient of variation was reported to be 34% (32). These figures were larger than or similar to the moderate coefficient of variation of the AUC of lactone exatecan in this study (36% for the recommended dose; 5 mg/m²). Similarly, the variability of the lactone AUC of exatecan seemed to be less than that of topotecan administered over 30 min (51%; Ref. 33). The second peak in the concentration-time curve was observed in 10 of 15 patients in this study, which might suggest enterohepatic recirculation. Rebound concentrations were also ob-

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Total (lactone + carboxylate)</th>
<th>Exatecan</th>
<th>Urinary excretion</th>
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<tbody>
<tr>
<td></td>
<td>AUC (ng h/ml)</td>
<td>AUC (ng h/ml)</td>
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</tr>
<tr>
<td></td>
<td>T₁/₂ (h)</td>
<td>Vdss (l/m²)</td>
<td>Cl (l/h/m²)</td>
</tr>
<tr>
<td></td>
<td>Cmax (mg/m²)</td>
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</table>

| No. of patients | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatecan Vdss | Exatecan Cl | Exatecan Cmax | Exatecan T₁/₂ | Exatekan...
served in other camptothecin derivatives, irinotecan and SN-38 (34, 35).

The activity of camptothecin derivatives depends on a closed lactone ring structure (36), which quickly hydrolyzes in aqueous solution at physiological pH to generate an inactive ring-opened carboxylate, in a reversible and nonenzymatic fashion (37, 38). The lactone and carboxylate forms exist at an equilibrium depending on pH; theoretically, there should be minimal interpatient variability in the lactone:carboxylate ratio if the equilibrium depends only on pH. If the interpatient variability in the ratio was actually minimal, measurements of total concentration may be sufficient for future pharmacological investigations. However, interpatient variability of the ratio of the lactone AUC to the total AUC of exatecan had a coefficient of variation of 27%. This variability was similar to that of SN-38 (33%; Ref. 30) similar to or smaller than that of topotecan (33–44%; Ref. 33, 39) and smaller than that of 9-aminocamptothecin (54%; Ref. 40).

Exposure to the active lactone form of camptothecin derivatives theoretically explains the pharmacodynamic relationship better than exposure to the total drug. When relationships of neutropenia to drug exposure were compared between the lactone and total drug, a better relationship was reported for the lactone in a pharmacological study of 9-aminocamptothecin that had large interpatient variability of the lactone:total concentration ratio (40). On the other hand, the pharmacodynamic relationship with the total topotecan was slightly better than or similar to that with the lactone topotecan (33, 41). The lactone form of camptothecin derivatives hydrolyzes rapidly during sample handling, potentially leading to inaccurate measurements. This may artificially increase the interpatient variability of the lactone concentrations and complicate the interpretation of the pharmacodynamics. In this study, neutropenia was related to drug exposure to the lactone only slightly more than exposure to the total drug (Fig. 5), and the small difference did not seem to be clinically relevant. This might suggest that cumbersome measurements of lactone concentrations would not be necessary in pharmacological studies of exatecan. However the number of patients was limited in this study, and studies with larger numbers of patients should determine whether the total concentration can substitute for the lactone concentration in the pharmacodynamic analysis of exatecan.

There was a tendency toward a positive correlation between body surface area and clearance of lactone or total drug. However, the correlation was weak ($r^2 = 0.11$ and 0.12 for lactone and total drug, respectively), and the number of patients in this study was limited. Therefore, clinical significance of the correlation was unclear, and further studies are needed to investigate whether exatecan can be administered based on body surface area without increasing variability of drug exposure and toxicities.

In conclusion, exatecan was a well-tolerated drug with a favorable toxicity profile compared with irinotecan. Interpatient variability of pharmacokinetics was similar to or smaller than other camptothecin derivatives. Although objective complete or partial responses were not observed in this study, exatecan showed greater antitumor activity than other camptothecin derivatives in preclinical studies and antitumor responses have been observed in clinical Phase I studies of exatecan using other administration schedules. Further clinical studies are warranted.

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Phase I and Pharmacological Study of a New Camptothecin Derivative, Exatecan Mesylate (DX-8951f), Infused Over 30 Minutes Every Three Weeks

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