Phase I and Pharmacological Study of a New Camptothecin Derivative, Exatecan Mesylate (DX-8951f), Infused Over 30 Minutes Every Three Weeks¹

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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 and vomiting were observed at a recommended dose of 5 mg/m², with prophylactic use of granisetron. Pharmacokinetics were linear and had moderate variability; clearances of lactone and total drug were 6.8 ± 2.8 and 2.1 ± 1.1 (mean ± SD) l/h/m², respectively. The ratio of lactone concentration to total drug concentration in plasma decreased from 0.81 ± 0.06 at the end of infusion to 0.15 ± 0.06 10 h after the infusion. The lactone:total ratio of drug exposure was 0.30 ± 0.08, ranging from 0.16 to 0.43. Neutropenia was related to the drug exposure of both lactone and total drug.

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 carboxylesterase 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 isozyme 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 6 and 28 times more active than SN-38 and topotecan, respectively.

¹The 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[e]pyran-3’,4’,5,6,7’-indolizino[1,2-b]quinoline-10,13-dione monomethanesulfonate dihydrate; CYP, cytochrome P-450; AUC, area under the time-concentration curve.
It also exhibited potent activity against in vivo models of acute myelogenous leukemia of early and late stages. 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. 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...
33% escalation for all subsequent levels, were planned. At least 3 patients were treated at one dose level, and the dose was increased if none experienced dose-limiting toxicity. When dose-limiting toxicity was observed in 1 of 3 patients, the dose level was expanded to 6 patients, and 33% dose escalations were performed thereafter. The dose escalation was continued until 2 of the first 3 patients or 2 of the 6 patients experienced dose-limiting toxicity.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria. The dose-limiting toxicities included grade 4 neutropenia lasting for 5 days or longer, grade 4 neutropenia complicated by fever (≥38.5°C) of infection, grade 4 thrombocytopenia or anemia, and grade 3 or greater nonhematological toxicity, except for alopecia, nausea, and vomiting. Vomiting was considered to be dose limiting when grade 4 vomiting was observed after prophylactic use of granisetron. The maximum tolerated dose was defined as the highest dose resulting in dose-limiting toxicities in not more than one of six patients during the first treatment course. Antiemetics were not routinely used prophylactically until one patient experienced grade 2 vomiting, after which granisetron at a dose of 3 mg was used prophylactically in all patients.

A complete medical history, physical examination, and tumor measurement were performed and recorded prior to the therapy. Baseline values of complete blood counts with differential and platelet counts were obtained, and measurements were repeated at least twice a week after treatment. Values for serum total protein, albumin, total bilirubin, urea nitrogen, creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase, γ-GTP, alkaline phosphatase, lactate dehydrogenase, glucose, and electrolytes including sodium, potassium, chloride, and calcium were obtained prior to the therapy and were tested at least weekly after the treatment. Tumor measurement was repeated after each course and antitumor responses were assessed using the Southwest Oncology Group response criteria. All patients were treated and monitored in a hospital for the first course.

Pharmacological Study. Blood sampling for determinations of the pharmacokinetics of exatecan was conducted before and at 15 min into the exatecan infusion, at the end of infusion, 15 and 30 min, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 24, and 48 h after the end of infusion. Plasma concentrations of the lactone form and total (lactone + carboxylate) exatecan and the metabolite UM-1 were measured. Urine was sampled before the infusion, and the voided volumes and concentrations of total exatecan and UM-1 in urine were monitored for 24 h after the infusion.

The lactone form and the total concentration of exatecan were measured using high-performance liquid chromatography methods (23), and high performance liquid chromatography-mass spectrometry was used for the measurement of UM-1 concentrations (24).

Pharmacokinetic analysis was performed using a non-compartment method. The pharmacokinetics of the lactone form and total exatecan in plasma were calculated separately. The elimination constant was calculated by linear regression of the terminal log-linear part of the concentration-time curves, AUC was calculated using the linear trapezoidal rule from time zero to the last point measured and extrapolated to infinity using the elimination constant. One patient who experienced dose-limiting 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\textsubscript{max} model:

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

where \(r\) is a sigmoidicity parameter and \(AUC'_{50}\) 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.

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 were 353 and 353 U/L. Asymptomatic grade 3 liver dysfunction was observed in two patients at 5 mg/m² and in one patient at 6.65 mg/m². In two patients, the levels of liver enzyme returned to normal after dose adjustments. Asymptomatic grade 3 pancreatitis was observed in one patient at 6.65 mg/m².

**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>
</tr>
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<tr>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1/1/0/0</td>
<td>2/0/0/0</td>
<td>0/1/0/0</td>
<td>0/2/1/0</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>16</td>
<td>1/2/1/0</td>
<td>1/1/1/1</td>
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<td>0/2/0/0</td>
</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>0/2/1/0</td>
<td>2/3/0/0</td>
</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>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>4</td>
<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>
<td>1/1/0/0</td>
<td>0/1/0/0</td>
<td>0/2/0/0</td>
</tr>
<tr>
<td>6.65</td>
<td>6</td>
<td>10</td>
<td>2/2/2/0</td>
<td>1/2/2/0</td>
<td>1/0/0/0</td>
<td>0/0/2/0</td>
<td>0/0/0/0</td>
</tr>
</tbody>
</table>

* Dose-limiting toxicities.

**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 0.81 ± 0.06 (mean ± SD) at the end of infusion to 0.15 ± 0.06 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 ($AUC_{\text{lactone}}$) and the total drug ($AUC_{\text{total}}$) were investigated. Neutropenia expressed as the surviving fraction of neutrophils ($SF$) was significantly related to the $AUC_{\text{lactone}}$ ($r^2 = 0.50, P = 0.003$) and $AUC_{\text{total}}$ ($r^2 = 0.40, P = 0.012$) as shown in Fig. 5. These relationships were described by inhibitory sigmoid models: $SF = 1 - AUC_{\text{lactone}}^{0.94}/(523^{0.94} + AUC_{\text{lactone}}^{0.94})$ and $SF = 1 - AUC_{\text{total}}^{0.65}/(1518^{0.65} + AUC_{\text{total}}^{0.65})$. When the patient who had the highest AUC was excluded from the pharmacodynamic analysis, the relationship with $AUC_{\text{lactone}}$ remained significant ($r^2 = 0.29, P = 0.047$), whereas that with the $AUC_{\text{total}}$ 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 $AUC_{\text{lactone}}$ ($r^2 = 0.50, P = 0.003$) and $AUC_{\text{total}}$ ($r^2 = 0.44, P = 0.007$) 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 $AUC_{\text{lactone}}$ and $AUC_{\text{total}}$.

**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 severity of 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

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**Fig. 4** Relationship between the dose of exatecan versus the AUC of lactone ($AUC_{\text{lactone}}$) and the total drug ($AUC_{\text{total}}$). The $AUC_{\text{lactone}}$ and $AUC_{\text{total}}$ increased linearly with dose escalations.
Table 4  Pharmacokinetic profile of exatecan (mean ± SD)

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>C_{max}</th>
<th>AUC</th>
<th>T_{1/2}</th>
<th>CI</th>
<th>V_{dss}</th>
<th>C_{max}</th>
<th>AUC</th>
<th>T_{1/2}</th>
<th>CI</th>
<th>V_{dss}</th>
<th>Exatecan</th>
<th>UM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(ng/ml)</td>
<td>(ng × h/ml)</td>
<td>(h)</td>
<td>(l/h/m²)</td>
<td>(l/m²)</td>
<td>(ng/ml)</td>
<td>(ng × h/ml)</td>
<td>(h)</td>
<td>(l/h/m²)</td>
<td>(l/m²)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>258 ± 43</td>
<td>464 ± 60</td>
<td>10.3</td>
<td>6.5 ± 0.8</td>
<td>45 ± 13</td>
<td>320 ± 40</td>
<td>1836 ± 812</td>
<td>10.2</td>
<td>1.9 ± 0.9</td>
<td>20 ± 7</td>
<td>0.29 ± 0.12</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>440 ± 137</td>
<td>663 ± 240</td>
<td>8.4</td>
<td>8.5 ± 3.2</td>
<td>36 ± 11</td>
<td>565 ± 147</td>
<td>2092 ± 965</td>
<td>10.2</td>
<td>2.8 ± 1.2</td>
<td>25 ± 7</td>
<td>0.33 ± 0.05</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>6.65</td>
<td>6</td>
<td>664 ± 149</td>
<td>1591 ± 1058</td>
<td>10.7</td>
<td>5.3 ± 2.3</td>
<td>36 ± 13</td>
<td>779 ± 160</td>
<td>7004 ± 6922</td>
<td>12.2</td>
<td>1.6 ± 0.9</td>
<td>20 ± 10</td>
<td>0.28 ± 0.09</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>9.6 ± 2.8</td>
<td>38 ± 12</td>
<td>10.9</td>
<td>2.1 ± 1.1</td>
<td>22 ± 8</td>
<td>0.30 ± 0.08</td>
<td>0.04 ± 0.01</td>
<td>8.7 ± 4.2</td>
<td>16.0 ± 4.5</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

\(^a\) C_{max}, the maximum concentration; \(^b\) T_{1/2}, half life; CI, clearance; V_{dss}, distribution volume at the steady state.

Harmonic mean.
erved 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 to total AUC of exatecan (34, 35). On the other hand, the pharmacodynamic relationship with the total topotecan was slightly better than or similar to that with the lactone topotecan (33, 34). 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.

REFERENCES


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

Hironobu Minami, Hirofumi Fujii, Tadahiko Igarashi, et al.


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