A Phase I and Pharmacokinetic Study of Exatecan Mesylate Administered as a Protracted 21-Day Infusion in Patients with Advanced Solid Malignancies


ABSTRACT

Purpose: The purpose of this study was to assess the feasibility of administering exatecan, a water-soluble, potent camptothecin analogue, as a protracted 21-day continuous i.v. infusion (CIVI). The study also sought to determine the maximum tolerated dose (MTD) of exatecan on a 21-day CIVI schedule, characterize its pharmacokinetic behavior, and seek preliminary evidence of anticancer activity.

Experimental Design: Exatecan dose-schedule development was performed in two stages using the modified Continual Reassessment Method and single patient cohorts. First, patients with advanced solid malignancies were treated with exatecan (0.15 mg/m²/day) as a CIVI for 5 days, and the duration of the CIVI was incrementally increased from 5 to 21 days. In the second stage of the study, the dose was incrementally increased to derive a tolerable dose of exatecan administered as 21-day CIVI. The MTD was defined for both minimally pretreated (MP) and heavily pretreated (HP) patients as the highest dose level at which the incidence of dose-limiting toxicity does not exceed 20%.

Results: Thirty-one patients were treated with 100 courses of exatecan at 6 dose-schedule levels. The incidence of the principal dose-limiting toxicities, neutropenia and thrombocytopenia, was unacceptably high at exatecan doses exceeding 0.15 mg/m²/day as a 21-day CIVI, which was determined to be the MTD for both MP and HP patients. The pharmacokinetics of exatecan were dose-proportional, and mean [coefficient of variation (percentage) steady-state concentration (plasma concentration at steady-state)] values ranged from 6.88 (80.6) to 19.41 (74.2) ng/ml at exatecan dose levels ranging from 0.15 to 0.30 mg/m²/day, which are similar to IC₅₀ values against human tumor cell lines treated for shorter periods. Mean pharmacokinetic parameters for total exatecan derived from a compartmental model included clearance and volume of distribution values of 1.39 (86.9) liters/h/m² and 39.66 (197.4) liters, respectively. Two HP patients with non-small cell lung and unknown primary carcinomas had partial responses, and objective evidence of anticancer activity and clinical benefit were noted in several other individuals.

Conclusions: The administration of exatecan as a 21-day CIVI at doses as high as 0.15 mg/m²/day is safe and feasible for both MP and HP patients. The characteristics of the myelosuppressive effects of exatecan on this schedule, the paucity of severe nonhematological toxicities, and documented anticancer activity in several drug-refractory malignancies warrant further evaluation of the merits of administering exatecan by either a CIVI or alternate drug delivery systems to achieve protracted systemic exposure.

INTRODUCTION

The rationale for developing the hexacyclic camptothecin analogue exatecan (DX-8951f; 1S,9S)-1-amino-9-ethyl-1,2-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3′,4′:6,7]-indolizinol[1,2-b]quinoline-10,13(9H,15H)-dione monomethanesulfonate dihydrate; exatecan mesylate; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan; Fig. 1) is based on its favorable physicochemical features, which may portend a greater therapeutic advantage than other camptothecin analogues (1–3). Unlike irinotecan, exatecan is inherently active and does not require enzymatic activation, which may accentuate the fundamentally large interindividual variability in the pharmacological and toxicological profiles of camptothecin analogues (1–4). Exatecan is also a more potent inhibitor of topo³
I than either camptothecin, topotecan, or SN-38 (10-hydroxy-7-ethylcamptothecin), the active metabolite of irinotecan (4–9). It is 3- and 10-fold more potent than SN-38 and topotecan, respectively, at inhibiting topo I extracted from murine P388 leukemia cells, with IC50 values of 0.975, 2.71, 9.52, and 23.5 μg/ml for exatecan, SN-38, topotecan, and camptothecin, respectively (5). In addition, IC50 values against a panel of 32 human cancer cell lines averaged 6- and 28-fold lower than those of SN-38 and topotecan, respectively (5). Exatecan has demonstrated impressive activity against human tumor xenografts of colon, lung, breast, renal, and gastric origin, and its efficacy has generally been superior to those of topotecan and irinotecan (5, 9). Although impressive activity has been observed on both single- and divided-dosing schedules, superior efficacy against human tumor xenografts has generally been noted with divided-dosing schedules (4, 5, 9).

The impressive preclinical antitumor spectra of exatecan may be due, in part, to the fact that it is not a substrate for the Pgp multidrug transporter, in contrast to topotecan, 9-amino-camptothecin, and SN-38, which are weak Pgp substrates (10–13). The lack of cross-resistance of Pgp-overexpressing neoplasms is suggested by the comparable activity of exatecan against human lung cancer PC-6 and its Pgp-overexpressing variant, PC-6/vincristine (6). Similarly, exatecan possesses roughly equivalent potencies against PC-6 and a SN-38-resistant subline characterized by impaired SN-38 accumulation without Pgp overexpression, and the antitumor activities of exatecan were similar against human pancreatic cancers SUIT-2 and KP-1N and their respective sublines with acquired resistance to irinotecan in vivo and SN-38 in vitro, presumably due to reduced levels of topo I mRNA and protein (8). Although the significance of its lack of Pgp substrate affinity is unclear, exatecan is a known substrate for breast cancer resistance protein, which appears to confer drug resistance in vitro (14, 15).

The feasibility of administering exatecan on a broad range of dose schedules has been evaluated in Phase I studies in patients with advanced solid malignancies (4, 16–18). The principal DLT on all schedules has been myelosuppression, and severe nonhematological effects have been uncommon. Although objective antitumor activity has been observed with exatecan on several schedules in Phase I and II evaluations, the preponderance of activity has been associated with divided-dosing schedules. In addition to tumor regressions reported in Phase I studies in several types of lower and upper gastrointestinal malignancies, small and non-small cell lung cancers, and refractory acute leukemias, prominent and consistent antitumor activity has been noted in Phase II evaluations in untreated and previously treated patients with advanced pancreatic, hepatocellular, and biliary carcinomas (4, 16–21).

The prominent schedule-dependent antineoplastic activity noted with exatecan in preclinical studies, the impressive clinical results achieved with divided-dosing schedules to date, and the intriguing clinical activity with other topo I-targeting agents, particularly topotecan, administered as a protracted infusion served, in part, as the rationale for evaluating the feasibility of administering exatecan as a protracted CIVI (22–24). Another reason for evaluating exatecan as a protracted infusion is that the toxicological and pharmacokinetic information ascertainment from these studies could potentially serve as a foundation for developmental studies of DE-310, a novel slow-release polymer of exatecan undergoing staggered development with exatecan (25).

The principal objectives of this Phase I and pharmacokinetic study were to: (a) determine the MTD of exatecan in patients with advanced malignancies by first progressively prolonging the duration of the CIVI from 5 to 21 days and then successively increasing the exatecan dose; (b) characterize the toxicities associated with exatecan on protracted dose schedules; (c) determine whether biologically relevant pharmacological parameters can be achieved; (d) identify the recommended dose for Phase II development; and (e) seek preliminary evidence for antitumor activity.

**PATIENTS AND METHODS**

**Patient Selection.** Patients with histologically confirmed advanced solid malignancies that failed to respond to standard therapy or for whom adequate therapy was not available were eligible for this study. Eligibility criteria also included: age ≥ 18 years; a WHO performance status ≤ 2 (ambulatory and capable of self-care); no prior chemotherapy or wide-field radiation therapy within 4 weeks of treatment (6 weeks for nitrosoureas and mitomycin C); adequate hematopoietic (ANC ≥ 1500/μl, hemoglobin level ≥ 8.5 g/dl, platelet count ≥ 100,000/μl), hepatic [total bilirubin ≤ 1.5 mg/dl, transaminases ≤ 2.5 times the institutional normal upper limit (<5 times the institutional

**Lactone**

**Carboxylate**

*Fig. 1 Structure of the active exatecan lactone (left) undergoing reversible pH-dependent hydrolysis to its inactive open-ring form (right).*
upper normal limit if due to liver metastases), and renal (creatinine ≤ 2.0 mg/dl) functions; measurable or evaluable disease; prothrombin time ≤ 1.5 times the institutional upper normal limit; no chronic enteropathy or no recent onset of diarrhea defined as an excess of 2–3 stools/day above the normal frequency in the past 4 weeks; and no coexisting medical problem of sufficient severity to limit compliance with the study. Because preclinical studies had suggested that exatecan is metabolized by CYP3A P450 enzymes, patients were instructed to avoid a list of medications, foods, and beverages that could potentially modulate this enzyme system. These medications, foods, and beverages were discontinued if they were determined to not be absolutely necessary and/or if substitutions were available. All medications were recorded in the case report form. Patients gave written informed consent according to federal and institutional guidelines before treatment.

**Dosage and Drug Administration.** Exatecan was administered as a 5–21-day CIVI. This dose- and schedule-finding study was performed in two stages. In the first stage, a daily dose of 0.15 mg/m²/day (equivalent to one-third of the toxic dose low in dogs) was held constant as the infusion duration was progressively increased from 5 to 10, 10 to 15, and 15 to 21 days in cohorts of new patients. Treatment was repeated every 3 weeks (5- or 10-day infusions) or 4 weeks (15- or 21-day infusions). Three patients were to be treated at the first dose-schedule level, with a minimum of a single patient to be treated at each successive infusion duration. In the second stage, the dose was progressively increased. If less than grade 2 toxicity was observed in either stage of the study, the infusion duration was increased, or the dose was doubled in each new patient with a cohort size of one until a grade 2 or higher toxicity was observed. At this time, the cohort size was increased to a minimum of three patients, and the dose was increased according to a modified version of the mCRM (26). The MTD was defined *a priori* as the highest dose at which a maximum of 20% of patients experienced DLT during the first course. In the event of DLT during the first course, the posterior distribution of the parameter determining the dose-toxicity curve was recalculated, and patients were to be treated at the dose closest to the current estimate of the MTD according to the mCRM. The investigators’ judgment could take precedence over the mCRM at any time. Intraindividual dose reduction by one level was permitted for individuals who experienced DLT. The MTD was to be defined separately for MP patients and HP patients if it appeared that HP patients were more susceptible to DLT. HP patients were defined *a priori* as those who had been previously treated with >6 courses of alkylating agent-containing chemotherapy (or >4 courses of carboplatin, ≥2 courses of mitomycin C or a nitrosourea, or radiation therapy to >25% of hematopoietic reserves (with whole pelvic radiation equivalent to radiation to 30%)); During the exatecan infusion, DLT was defined as the following: (a) grade 3 nonhematological toxicity (excluding nausea or vomiting); (b) any grade 4 vomiting with maximum supportive care; (c) ≥ grade 3 neutropenia (ANC ≤ 1000/μl); (d) ≥ grade 3 thrombocytopenia (platelets ≤ 50,000/μl); and (e) grade 4 anemia (hemoglobin < 6.5 g/dl). In the period following treatment, DLT was defined differently for neutropenia [grade 4 (ANC < 500/μl)] lasting longer than 5 days or associated with fever (≥38.5°C) and thrombocytopenia (platelet count < 25,000/μl) and any delay in treatment longer than 2 weeks due to unresolved toxicity. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (27).

Exatecan mesylate (DX-8951f), the methane sulfonic salt of DX8951, was supplied by Daiichi Pharmaceutical Corp. (Montvale, NJ) in vials containing 2 or 5 mg of lyophilized drug, calculated as the anhydrous free base equivalent, 50 or 125 mg of maltose (monohydrate), and a proper quantity of hydrochloric acid (pH 3.3–4.7). The drug was diluted in the vial with 0.9% saline solution, USP, to obtain a 0.5 mg/ml stock solution. The appropriate volume of the stock solution was diluted with 0.9% saline solution, USP, in a polyvinyl chloride infusion bag to yield an infusion volume with a final drug concentration range of 0.00029–0.02 mg/ml administered as a CIVI over 24–120 h, which was the range permissible according to stability data at the time of the study, through a central venous catheter using an ambulatory programmable peristaltic infusion pump.

**Pretreatment and Follow-Up Studies.** Histories that included recording of performance status and concurrent medications, physical examinations, and routine laboratory evaluations were performed pretreatment and weekly. Routine laboratory evaluations included complete blood counts, differential WBC counts, electrolytes, blood urinary nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, hepatic transaminases, prothrombin time, and urinalysis. Pretreatment studies also included an electrocardiogram and relevant radiological studies for evaluation of all measurable or evaluable sites of malignancy, as well as an assessment of relevant tumor markers. Radiological studies for disease status assessments were repeated after every other course or as needed to confirm response. Patients were able to continue treatment if they did not develop progressive disease. A complete response was scored if there was disappearance of all active disease on two successive measurements separated by a minimum period of 4 weeks, and a PR required at least a 50% reduction in the sum of the product of the bidimensional measurements of all lesions documented.
separated by at least 4 weeks. Malignant disease fluctuations in patients with evaluable disease were described qualitatively. Any concurrent increase in the size of any lesion by $\geq 25\%$ or the appearance of any new lesion was considered disease progression.

**Plasma and Urine Sampling and Assay.** Blood samples in heparinized tubes were collected before the infusion and at 1, 2, 3, 4, 5, 10, 15, and 21 days after initiation of the infusion. The last sample was collected at least 30 min before discontinuing the infusion. The samples were centrifuged at 3000 rpm for 15 min immediately after collection. Next, the plasma was transferred to a sample tube, which was frozen at $-20^\circ C$ until assayed for the total anhydrous free base form of exatecan. Urine was collected continuously for 48 h in 0–24- and 24–48-h aliquots. After the urine collections were shaken, 50-ml aliquots were drawn off at the end of each collection and frozen at $-20^\circ C$ in a labeled sample tube.

Separation and analysis of the plasma and urine samples were accomplished by reverse-phase high performance liquid chromatography after solid-phase extraction as described previously (16). The lower limit of quantitation of exatecan was 0.20 ng/ml in plasma and 2.50 ng/ml in urine. Both interassay and intra-assay coefficients of variation were identical to those described previously (14).

**Pharmacokinetic Analysis.** Individual total exatecan plasma concentration data were analyzed by noncompartmental methods (28). The mean $C_{\text{ss}}$ was calculated as the mean of the observed $C_{\text{ss}}$ values, and total plasma CL was calculated by dividing the dose by $C_{\text{ss}}$. Parameter values were expressed as mean values [CV (percentage)]. Plasma concentration data were also analyzed using model-dependent methods (28–30). A linear two-compartment model, which performed well in previous studies of exatecan administered as protracted infusion, was used to fit the data (16). Individual parameter estimates were derived using ADAPT-II (ADAPT-II Release 4; Biomedical Simulations Resource, University of Southern California, Los Angeles, CA) using maximum likelihood analysis (31). The “goodness” of model fit was guided by inspection of the weighted sum of squares, dispersion of the residuals, SEs of the fitted pharmacokinetic parameters, and the Akaike information criterion (32).

The relationships between indices of exatecan exposure ($C_{\text{ss}}$ and AUC) and myelosuppression in the first course were explored. Relevant parameters of myelosuppression that were evaluated included nadir absolute blood count values and percentage decrements in the ANC and platelet counts, which were calculated as follows: 100 × ([pretreatment counts – nadir counts]/pretreatment counts). The relationships between exatecan $C_{\text{ss}}$ and AUC and hematological toxicity were described using the sigmoidal $E_{\text{max}}$ model of drug action ($i.e.$, percentage change hematological parameter $= E_{\text{max}} \times \text{parameter}^\gamma/\text{parameter}^\gamma + \text{parameter}^\gamma$; Ref. 30), where the $E_{\text{max}}$ was fixed at 100%, and parameter $\gamma_{\text{so}}$ is the parameter at which the effect is 50% of the maximal effect. The exponent $\gamma$ is a constant that describes the sigmoidicity of the curve. The sigmoidal $E_{\text{max}}$ model was fit to the data by nonlinear least squares regression.

The coefficient of determination ($R^2$) and the SEs for the estimated parameters were used as measures of goodness of fit for the pharmacodynamics model.

### RESULTS

**General**

Thirty-one patients, whose pertinent characteristics are displayed in Table 1, received 100 total courses of exatecan administered as a protracted 5–21-day CIVI according to the dose-schedule escalation scheme outlined in Table 2. Three first courses were not fully evaluable for toxicity due to early premature disruption of treatment for reasons unrelated to exatecan toxicity. The median number of courses received was 3 (range, 1–15). Seven patients required dose reduction by one level due to intolerable toxicity in either the first course (four patients) or subsequent courses (three patients).

The duration of the exatecan infusion was incrementally increased from 5 to 21 days at a constant dose of 0.15 mg/m$^2$/day in both MP and HP patients as a single group. At exatecan infusion durations shorter than 21 days, patients had either no or negligible toxicity, with the exception of an atypical dose-limiting event in a HP patient at the first dose level, 0.15

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**Table 2 Dose-escalation scheme**

<table>
<thead>
<tr>
<th>Exatecan dose level</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Patients with DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mg/m$^2$/day × days)</td>
<td>(evaluable)</td>
<td>(evaluable)</td>
<td>First courses</td>
</tr>
<tr>
<td>No.</td>
<td>New</td>
<td>Reduced to level</td>
<td>Total</td>
</tr>
<tr>
<td>1</td>
<td>0.15</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
<td>21</td>
<td>16 (13)$^b$</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>0.23</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>31 (28)$^a$</td>
<td>100 (97)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Initial dose reduced to this level because of DLT at previous dose.

$^b$ Three infusions terminated prematurely for reasons unrelated to exatecan.

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mg/m²/day for 5 days. The patient was an outlier relative to other patients in the cohort from both toxicological and pharmacological standpoints, experiencing grade 4 neutropenia, fever, and grade 3 thrombocytopenia, whereas no hematological toxicity of any grade had been noted in three other patients treated at this same dose level. The atypical toxicological behavior was associated with substantially lower CL than the other patients, possibly due to chronic and concurrent ingestion of Essiac tea. Treatment with exatecan doses exceeding 0.15 mg/m²/day for 21 days produced an unacceptably high rate of dose-limiting events in first courses in both HP and MP patients. In contrast, repetitive treatment with 0.15 mg/m²/day exatecan for 21 days was well tolerated and was determined to be the MTD for both HP and MP patients.

**Toxicity**

**Hematological Toxicity.** Both neutropenia and thrombocytopenia were the principal toxicities of exatecan administered as a 5–21-day infusion. The distributions of National Cancer Institute grades of neutropenia and thrombocytopenia and dose-limiting hematological events, as functions of both dose level and the extent of prior therapy, are displayed in Table 3. Both ANC and platelet count nadirs were typically experienced from days 10–15, 15–21, 15–21, and 15–28 when exatecan was administered over 5, 10, 15, and 21 days, respectively. Except for the single patient who had been chronically and concurrently ingesting Essiac tea, as discussed previously, clinically significant hematological events were not noted in any patient treated with exatecan at doses of at least 0.15 mg/m²/day for less than 21 days. At doses exceeding 0.15 mg/m²/day for 21 days, the incidence of dose-limiting hematological events was unacceptably high. Dose-limiting hematological events were experienced in the first courses of four of six patients and two of three patients after treatment with exatecan dose-schedules of 0.23 and 0.30 mg/m²/day for 21 days, respectively. At the 0.30 mg/m²/day dose level, severe hematological toxicity occurred during the 21-day CIVI in two patients, resulting in premature discontinuation of treatment. The severity of myelosuppression was similar in HP and MP patients. In contrast, dose-limiting hematological events were noted in only 2 of 14 (14%) new MP and HP patients in 3 of 59 (5%) courses at the 0.15 mg/m²/day for 21 days dose level. At this dose level, treatment delays due to unresolved neutropenia or thrombocytopenia were not noted, and there was no evidence of a cumulative effect of exatecan on ANC and platelet count nadirs in both MP and HP patients.

Severe anemia occurred less frequently than neutropenia and was most often noted concomitantly with severe neutropenia and/or thrombocytopenia. Anemia, possibly related to exatecan, was generally mild or moderate. However, severe (grade 3) anemia, which required RBC transfusions, was noted in 6 of 28 (21%) evaluable patients, without any apparent predilection for HP patients.

**Nonhematological Toxicity.** Nonhematological toxicities were relatively uncommon. Gastrointestinal toxicities, which were generally mild to moderate in severity, predominated. Diarrhea was experienced by four (13%) patients at some time during treatment. Severe (grade 3) diarrhea associated with dose-limiting myelosuppression was encountered by two of three MP patients at the highest dose level, 0.30 mg/m²/day for 21 days. At the 0.15 mg/m²/day for 21 days dose level, 1 of 14 (7%) evaluable patients experienced diarrhea. Prior treatment with fluoropyrimidine- and irinotecan-containing regimens did not appear to be a determinant for this toxicity. Except for one sporadic episode of grade 3 vomiting in a patient who had not yet received optimal antiemetic premedication along with exatecan treatment at the 0.3 mg/m²/day for 21 days dose level, nausea and vomiting were always mild or moderate in severity. At the 0.15 mg/m²/day for 21 days dose level, five (29%) and two (6%) patients experienced grade 1 and grade 2 nausea and/or vomiting, respectively. Nausea and vomiting were managed successfully, and recurrences were prevented with prochlorperazine or serotonin 5-hydroxytryptamine receptor antagonists.

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**Table 3** Hematological toxicity

<table>
<thead>
<tr>
<th>Exatecan dose level (mg/m²/day × days)</th>
<th>Extent of prior treatment (evaluable)</th>
<th>No. of patients (evaluable)</th>
<th>No. of courses (first course) with toxicity</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 1–2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>0.075 × 5 HP</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.15 × 5 MP</td>
<td>4 (4)</td>
<td>15 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.15 × 10 HP</td>
<td>1 (1)</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.15 × 15 HP</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.075 × 21 MP</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.12 × 21 HP</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.15 × 21 Total</td>
<td>20 (18)</td>
<td>59 (56)</td>
<td>23 (7)</td>
<td>1 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>0.23 × 21 Total</td>
<td>6 (6)</td>
<td>8 (8)</td>
<td>19 (3)</td>
<td>1 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>10 (8)</td>
<td>17 (16)</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.30 × 21 Total</td>
<td>3 (3)</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*One patient each at the 0.15 (MP) and 0.23 (HP) mg/m²/day for 21 days dose levels experienced grade 3 neutropenia in course 1, which did not fully recover until day 42.*
Phase I Study of Exatecan

received one course of exatecan, 0.15 mg/m²/day for 21 days, chemotherapy with hematopoietic stem cell support. The patient who had received extensive prior therapy including high-dose tases was observed in a patient with metastatic breast cancer individuals. A 20% reduction in the size of measurable metas-
level. Additionally, objective benefit was noted in several other total courses of exatecan at the 0.15 mg/m²/day for 21 days. The episode was associated with grade 4 neutropenia, grade 3 thrombocytopenia, and concurrent Gram-negative bacteremia; however, the relative contributions of exatecan, disease progression, and a concurrent bacteremic epi-
se in the etiology of this event are unknown.

**Antitumor Activity.** Twenty-eight and three patients had measurable and evaluable disease, respectively. Two pa-
tients had major objective responses. A 69-year-old male with advanced non-small cell lung cancer that was refractory to prior chemotherapy consisting of carboplatin and paclitaxel experi-
enced a PR characterized by a 64% reduction in measurable lung involvement that lasted for 4 months. He received five courses of exatecan at the 0.15 mg/m²/day for 10 days dose level. A 57-year-old female with carcinoma of unknown primary with endometrial features and clearly refractory to prior chemotherapy consisting of carboplatin and paclitaxel also had a PR. The patient experienced an 89% reduction in measurable disease lasting 9 months, during which time she received nine total courses of exatecan at the 0.15 mg/m²/day for 21 days dose level. Additionally, objective benefit was noted in several other individuals. A 20% reduction in the size of measurable metastases was observed in a patient with metastatic breast cancer who had received extensive prior therapy including high-dose chemotherapy with hematopoietic stem cell support. The patient received one course of exatecan, 0.15 mg/m²/day for 21 days, and declined further treatment. A minor (18%) reduction in measurable disease lasting 7 months also occurred in a patient with metastatic colorectal carcinoma whose disease had pro-
gressed during treatment with irinotecan and 5-fluorouracil. The patient had been treated with exatecan at the 0.15 mg/m²/day for 5 days dose level. Of the 12 patients who received prior treatment with chemotherapy agents targeting topo I, this patient was the only subject who experienced any degree of objective dis-

gression. Lastly, a 52-year-old male with an advanced malignant thymoma that had never responded to various thera-
ties had substantial radiographic and symptomatic improvement that enabled him to discontinue his dependence on oxygen. Both radiographic and clinical improvement persisted for 12 months, during which time he was treated with 12 courses of exatecan at 0.15–0.23 mg/m²/day for 21 days.

**Pharmacokinetic and Pharmacodynamic Studies.** Twenty-nine of the 31 patients had blood sampling performed for pharmacokinetic studies. Representative plasma total exatecan concentration-time profiles are shown in Fig. 2. An inspection of the scatterplots of dose versus either C_s or AUC revealed significant overlap in C_s and AUC values within the narrow dose range of 0.15–0.30 mg/m²/day (Fig. 3, A and B). Pertinent pharmacokinetic parameters for all 29 patients who had blood sampling performed are listed in Table 4. Despite the limited number of dose levels studied, pharmacokinetics appeared dose proportional, and CL was dose independent. The patient who chronically imbibed Essiac tea was a clear outlier from both pharmacological and toxicological perspectives. After treatment with exatecan at the lowest dose-schedule level, 0.15 mg/m²/day for 5 days, the patient developed severe neutropenia and thrombocytopenia, whereas no other patient treated with exatecan at this dose-schedule level developed severe toxicity. The patient’s CL was markedly lower, and resultant C_s was markedly higher than those of other patients in the study. No further DLT occurred in this patient after dose reduction to 0.075 mg/m²/day and discontinuation of Essiac tea ingestion. Model-derived compartmental pharmacokinetic parameters for all patients are listed in Table 5. Interestingly, although body surface area, ideal body weight, and actual body weight were evaluated as covariates for model derivation, the final model used body surface area because it was superior to the other potential variates at predicting and describing the pharmacoki-
netics of exatecan. Other significant covariants incorporated into the final model were the use of concurrent CYP1A2 inhibitors, gender, calculated creatinine CL, serum bilirubin, and aspartate aminotransferase. The pharmacokinetics of exatecan were characterized by a moderately large V_ss, averaging 39.66 (197.4) liters and a mean elimination t_1/2 of 27.45 h (CV, 131.2%; median, 11.27 h; range, 3.98–152.67). Mean CL was 1.39 (86.9), of which 7.2% was accounted for by renal disposition.

The magnitude of the effects of exatecan on both neutro-
phils and platelets was related to pharmacokinetic parameters.
reflecting total drug exposure. Scatterplots and relationships between percentage decrements in blood cell counts and nadirs and exatecan AUC values are depicted in Fig. 4, A–D, whereas respective scatterplots and relationships referable to Cs are shown in Fig. 5, A–D. Relationships between percentage decrements in blood cell counts and both Cs and AUC values were best, albeit loosely, described by sigmoidal E\text{max} models \[ R^2 = 0.1845 \] and \[ R^2 = 0.2574 \], respectively.

With these models, the exatecan AUC and Cs values predicted to yield 50% decrements in ANC and platelets were 1948.5 \( \text{g-h/liter} \) and 1.76 ng/ml, respectively. Respectively AUC and Cs values predicted to yield 50% decrements in platelet counts were 3586.53 \( \text{g-h/liter} \) and 9.25 ng/liter. Interestingly, the ranges of pharmacokinetic parameters associated with any given degree of myelosuppression in the first course were similar among HP and MP patients.

**DISCUSSION**

Exatecan was developed to exploit physicochemical properties that may result in superior anticancer activity, less toxicity, reduced interindividual variability, and greater overall feasibility than other topo I-targeting agents in clinical use (1–9). Furthermore, exatecan is an intrinsically active compound, rather than a prodrug, which assuages concerns about interindividual variability in prodrug activation that could increase the fundamentally large interindividual variability in the toxicological, pharmacokinetic, and anticancer profiles of the camptothecin analogues (1–4). In early clinical evaluations to date, exatecan has demonstrated impressive activity in several drug-refractory malignancies, including advanced acute leukemias and carcinomas of the lung, pancreas, liver, and biliary tract, and Phase III studies are in progress (4, 20, 21). Although schedule dependence was not as prominent with exatecan in preclinical studies relative to other camptothecin analogues, the cumulative results of these studies indicate that maximal anticancer activity is achieved with divided dosing schedules (4–9). These results, in addition to the preponderance of anticancer activity noted with divided dosing schedules in early clinical trials, have served, in part, as the rationale for developing exatecan administered on a 30-min infusion daily for 5-day-every-3-week schedule (4, 15–21). A further extension of preclinical and

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**Table 4** Pertinent exatecan pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Exatecan dose (mg/m(^2)/day)</th>
<th>No. of patients</th>
<th>( C_{\text{s}} ) (ng/ml)</th>
<th>CL (liters/h/m(^2))</th>
<th>AUC (( \mu \text{g-h/liter} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>21</td>
<td>5.06 (1.90–24.18)</td>
<td>1.24 (0.26–3.30)</td>
<td>121 (45–580)</td>
</tr>
<tr>
<td>Mean (% CV)</td>
<td></td>
<td>6.88 (80.6)</td>
<td>1.33 (55.0)</td>
<td>165.9 (80.0)</td>
</tr>
<tr>
<td>0.23</td>
<td>5</td>
<td>7.49 (2.27–12.45)</td>
<td>1.28 (0.77–4.22)</td>
<td>180 (55–299)</td>
</tr>
<tr>
<td>Mean (% CV)</td>
<td></td>
<td>6.96 (54.8)</td>
<td>1.90 (72.1)</td>
<td>167.1 (54.8)</td>
</tr>
<tr>
<td>0.3</td>
<td>3</td>
<td>13.55 (8.85–35.82)</td>
<td>0.92 (0.35–1.41)</td>
<td>325 (212–860)</td>
</tr>
<tr>
<td>Mean (% CV)</td>
<td></td>
<td>19.41 (74.2)</td>
<td>0.895 (59.5)</td>
<td>465.8 (74.2)</td>
</tr>
</tbody>
</table>

**Table 5** Pharmacokinetic parameters (compartmental analysis)

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>CL (liters/h/m(^2))</th>
<th>Mean</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL_{NR} (liters/h)(^a)</td>
<td>29</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>CL_{NR} (liters/h)(^a)</td>
<td>29</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>CL_{I} (liters/h)</td>
<td>29</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>CL_{I} (liters/h)</td>
<td>29</td>
<td>7.45</td>
</tr>
<tr>
<td></td>
<td>V_{C} (liters)</td>
<td>29</td>
<td>39.66</td>
</tr>
<tr>
<td></td>
<td>V_{C} (liters)</td>
<td>29</td>
<td>10.90</td>
</tr>
<tr>
<td></td>
<td>V_{P} (liters)</td>
<td>28</td>
<td>29.79</td>
</tr>
</tbody>
</table>

\(^a\) CL_{NR}, nonrenal clearance; CL_{I}, renal clearance; CL_{I}, distributional clearance; V_{C}, central volume of distribution; V_{P}, peripheral volume of distribution.

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**Fig. 3** Scatterplots showing the distributions of total exatecan Cs values (left) and AUC values (right) as a function of exatecan dose.
clinical observations aimed at maximizing the anticancer activity of exatecan includes an evaluation of exatecan as a protracted CIVI. This approach is further supported by evaluations of the water-soluble topo I-targeting agent topotecan on a 21-day CIVI schedule, which has resulted in prominent anticancer activity to date (1–3, 22–24). The present study was performed to determine the feasibility of administering exatecan as a 21-day CIVI every 28 days and to determine whether biologically relevant drug exposure is achieved with exatecan on a protracted schedule. Furthermore, an assessment of the feasibility of a protracted exatecan schedule, as well as characterizing the pharmacokinetic and toxicological profiles of the agent, was anticipated to lay a foundation for further investigations with slow-release polymers of exatecan such as DE-310 (25).

As predicted from preclinical and early clinical studies, myelosuppression was the principal DLT of exatecan in the present study (4, 16, 21, 33). Both neutropenia and thrombocytopenia were the principal DLTs of exatecan on a 21-day CIVI schedule, whereas isolated neutropenia principally precluded dose escalation of exatecan on alternate schedules. The incidence of dose-limiting hematological events, including protracted neutropenia, neutropenia associated with fever, severe thrombocytopenia, and delayed recovery of blood cell counts, was unacceptably high at exatecan doses exceeding 0.15 mg/m²/day as a 21-day CIVI. At the 0.23 and 0.30 mg/m²/day for 21 days dose levels, four of six patients and two of three patients experienced DLT in their first course of treatment. Although the 0.30 mg/m²/day for 21 days dose level was considered intolerable for MP and HP patients alike based on the high rate of DLTs in MP patients, and the 0.23 mg/m²/day dose level was not definitively determined to be intolerable for MP patients, there did not appear to be a sufficient absolute difference between the 0.15 and 0.23 mg/m²/day doses to warrant additional patient accrual to determine the tolerance of the 0.23 mg/m²/day for 21 days dose level in MP patients. In contrast, the 0.15 mg/m²/day for 21 days dose level was well tolerated by both MP and HP patients. Furthermore, the steep dose-toxicity relationship associated with the topo I-targeting agents, in general, mandates that the selection of doses for broad disease-directed studies incorporate a sufficiently wide margin of safety. At the 0.15 mg/m²/day for 21 days dose level, dose-limiting hematological events occurred in 2 of 14 (14%) evaluable patients in course 1 and in 3 of 59 (5%) total courses. The dose intensity for MP patients treated with exatecan at the 0.15 mg/m²/day for 21 days dose level was comparable (94%) with that of MP patients treated at the MTD, 0.5 mg/m²/day, on a 30-min infusion daily for 5 days (16). However, the dose intensity for HP patients treated with exatecan at 0.15 mg/m²/day for 21 days dose level was comparable (94%) with that of MP patients treated at the MTD, 0.5 mg/m²/day, on a 30-min infusion daily for 5 days (16). However, the dose intensity for HP patients treated with exatecan at 0.15 mg/m²/day for 21 days was 158% of the MTD (0.3 mg/m²/day) established for HP patients on the daily for 5-day schedule. Furthermore, nonhematological effects, which were similar in nature to those reported in previous trials of exatecan, were minimal, and severe nonhematological toxicity was not observed at the 0.15 mg/m²/day for 21 days dose level. The early onset and resolution of cytopenias, the low rate of severe hematological events requiring treatment delay, and the lack of cumulative myelosuppression with repetitive treatment indicate that immature hematopoietic precursors are not significantly affected by exatecan and that 0.15 mg/m²/day is an appropriate starting dose for both MP and HP patients. Nevertheless, treatment with exatecan at these doses should be limited to patients with good performance status and organ function similar to those in the present study until patients who are potentially at higher risk for toxicity are studied.

Because preclinical evaluations demonstrated nearly iden-
tical toxicokinetic profiles in various animal species and previous Phase I trials of exatecan in humans, the strategy of using the mCRM and assigning single patients to treatment at exatecan dose levels was used in the present study to minimize the numbers of patients treated at dose-schedule levels significantly lower than the MTD (16, 26). These measures, in addition to the use of a starting dose equivalent to one-third of the highest dose that did not cause severe irreversible toxicity in dogs, proved to be safe and highly efficient in this study because they resulted in the need for small numbers of both dose escalation steps and patients before relevant biological activity was encountered. In essence, the close proximity of the starting dose to the dose associated with a relevant degree of toxicity precluded derivation of major benefit from the assignment of single patients to nontoxic dose levels because single patients were able to be treated at only two dose levels, obviating the need to treat four total patients with exatecan at subtherapeutic dose levels.

The principal pharmacokinetic characteristics of total exatecan, including its dose proportionality, fit to a two-compartment model, a moderately large $V_{ss}$ (mean, 39.66 liters), and substantial interindividual variability in CL resemble those reported for exatecan administered on less protracted schedules (4, 16–21). Renal CL of the parent compound was also negligible (mean, 7.2%), which is consistent with previous reports (4, 14, 16). In rodents, exatecan is extensively metabolized by hepatic P450 systems, particularly P450 CYP3A and CYP1A, followed by biliary excretion, and similar disposition processes appear to be operative in humans (4, 33). The preliminary results of a detailed pharmacological study designed to evaluate the impact of interindividual variability in P450 isoforms, as assessed by $[^{14}C]$erythromycin and caffeine metabolism, on the pharmacokinetic and toxicological profiles of exatecan suggest that similar disposition processes are operative in humans. It can be speculated that the chronic and concurrent ingestion of Essiac tea may have been responsible for the uniquely severe toxicity and substantially low CL of total drug in the first patient treated at the first dose level. Except for extensive prior myelosuppressive therapy (albeit no more extensive than that of other HP patients in the study), this subject had no readily identifiable predisposing determinants for hematological toxicity. Nevertheless, the composition of Essiac tea is complex and highly variable, even among similar lots from the same supplier (34, 35). Most preparations have a stable base composition of burdock root, sheep sorrel, rhubarb root, and slippery elm bark, but kelp, blessed thistle, red clover, watercress, and other ingredients are occasionally added. Based on a review of the literature, it may be stated that neither Essiac tea itself nor its components are known to affect specific cytochrome P450 metabolizing processes. However, extracts of many herbal preparations are known to induce or inhibit cytochrome P450 systems (36). It can be speculated that Essiac tea would be much less likely to affect the equilibrium between the lactone and opened-ring species of exetacan, which might contribute to toxicity, because the equilibrium is largely dependent on pH and the magnitude and consistency of binding proteins to a much lesser degree. In any case, the unanticipated and profound toxicity as well as the reduced CL in the first study patient underscores the need for rigorous documentation of concurrent medications in clinical evaluations of novel therapeutics. Nevertheless, routine adoption of a policy that empirically restricts the use of herbal remedies in clinical evaluations would be imprudent. It is important to note that the preliminary results of the pharmacological study reflect the complexity of the interactions between exatecan and other herbal remedies, and further research is needed to fully understand the mechanisms behind these interactions.

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4 C. Takimoto, unpublished observations.
any specific type of concurrent medication may not be appropriate in Phase I trials because rigorous toxicological and pharmacokinetic assessments render this setting ideal to provide firm proof of drug-drug interactions.

Although the maximum tolerated daily dose of exatecan on a 21-day CIVI schedule is approximately 33% of that for exatecan administered as a 30-min infusion daily for 5 days, $C_{50}$ values achieved on the protracted CIVI schedule averaged 6.88 (80.6) ng/ml, which are similar to IC$_{50}$ values achieved in vitro after treatment of human tumor cell lines with exatecan for shorter periods (4, 5). In a study of the cytotoxic effects of exatecan against a panel of 32 human solid and hematopoietic cancer cell lines treated for 72 h, IC$_{50}$ values averaged 2.02, 2.92, 1.53, 0.88, and 4.33 ng/ml against breast, colon, stomach, lung, and other neoplasms, respectively (4, 5). For both topotecan and exatecan, $C_{50}$ values achieved on protracted 21-day CIVI schedules are similar to IC$_{50}$ values achieved in vitro against human tumor cell lines (3–5, 22). Because rather impressive clinical activity has been reported with topotecan administered as a 21-day CIVI, somewhat optimistic projections regarding the potential clinical utility of exatecan on a protracted schedule may be rendered based on the toxicokinetic similarities between exatecan and topotecan. Furthermore, Hochster et al. demonstrated that patients receiving topotecan as a 21-day CIVI had progressive decrements in the percentages of free topo I in peripheral blood mononuclear cells in weeks 1, 2, and 3 (23). This observation indicates that incremental drug effects occur during the entire duration of treatment and supports a mechanistic rationale for clinical evaluations of topo T-targeting agents on protracted schedules (22, 24).

Although exatecan lactone was not measured in this study, the lactone:total ratio of exatecan was reported elsewhere to be roughly constant (1, 3, 37–40). The cumulative results of pharmacological studies of camptothecin analogues, in which parallel measurements of both total drug and lactone were performed, indicate that the pharmacokinetics and pharmacodynamics of the lactone and total drug are similar because the ratio of the lactone:total drug remains roughly constant (1, 3, 37–40). These results may be attributed to the fact that the open-ring carboxylate, albeit inherently inactive, serves as a pH-dependent reservoir for the lactone, as is the case for topotecan (1, 23). This observation indicates that incremental drug effects occur during the entire duration of treatment and supports a mechanistic rationale for clinical evaluations of topo T-targeting agents on protracted schedules (22, 24).

The antitumor activity observed in patients with various drug-refractory malignancies is encouraging and provides further impetus for evaluating the merits of protracted exatecan administration schedules. Although such schedules are often considered cumbersome from a feasibility standpoint, the pharmacological parameters achieved in the present study may serve as benchmarks for evaluating alternate exatecan formulations and delivery systems designed to achieve protracted drug exposure in a less cumbersome fashion. For example, the preliminary clinical results with DE-310, a macromolecular exatecan polymer that is designed to gradually release active drug over several weeks, suggest that pharmacologically relevant parameters similar to those achieved with the 21-day CIVI schedule may also be achieved after a single treatment (25). Nevertheless, the ultimate clinical activity of exatecan administered on a 21-day CIVI schedule or in conjunction with novel delivery systems will be defined only in appropriate clinical trials. However, the specific pattern of myelotoxicity, relative paucity of nonhematological toxicity, and the activity against several types of neoplasms warrant further disease-directed evaluations of exatecan on this schedule.

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A Phase I and Pharmocokinetic Study of Exatecan Mesylate Administered as a Protracted 21-Day Infusion in Patients with Advanced Solid Malignancies


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