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ORIGINAL ARTICLE

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A phase II study of intravenous exatecan mesylate (DX-8951f) administered daily for 5 days every 3 weeks to patients with advanced ovarian, tubal or peritoneal cancer resistant to platinum, taxane and topotecan

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Abstract *Background*: DX-8951f is a water-soluble camptothecin derivative with greater in vivo and in vitro activity than topotecan or irinotecan. The objectives of this phase II study were to determine the antitumor activity, safety and pharmacokinetic profile of DX-8951f administered intravenously for five consecutive days, every 3 weeks in patients with advanced ovarian, tubal and peritoneal cancer resistant to platinum, taxane and topotecan. *Methods*: Enrolled in the study at The University of Texas M. D. Anderson Cancer Center were 16 patients with measurable cancer resistant to platinum, taxane and topotecan. All 16 patients were assessable for safety and 15 for efficacy analyses. Treatment consisted of a daily infusion of DX-8951f at 0.3 mg/m^2 per day (except for one minimally pretreated patient who started at 0.5 mg/m^2 per day) over 30 min for five consecutive days every 3 weeks. The pharmacokinetic and excretory profiles of DX-8951, the anhydrous form of DX-8951f, were also characterized. *Results*: Disease was stable in 7 of 16 patients (44%) (4 minor response and 3 stable disease). The median time to tumor progression was 43 days (95% CI 37–92 days). The median overall survival was 117 days (95% CI 90–279 days). The main toxic effect was neutropenia and leukopenia with 50% of patients experiencing grade 3 or 4 neutropenia and leukopenia. One episode of neutropenic fever was observed. Grade 3 or more anemia and thrombocytopenia were seen in 25% and 13% of patients, respectively. Grade 3 nonhematologic side effects included nausea (25% of patients) and fatigue (19%). Other side effects were not more than grade 2, and included gastrointestinal dysfunction, stomatitis, dermatitis, alopecia, liver dysfunction and drug fever. DX-8951 displayed linear pharmacokinetic characteristics at the doses administered. The average plasma clearance, total volume of distribution, and terminal elimination half-life were 2.1 l/h per m^2, 20 l/m^2 and 9.5 h, respectively. *Conclusions*: DX-8951f administered parenterally as a single agent daily at a dose of either 0.5 or 0.3 mg/m^2 per day for 5 days is feasible in patients with advanced ovarian, tubal and peritoneal cancer resistant to platinum, taxane and topotecan. Although no responses were observed, a significant number of patients had stable disease with a decrease in CA-125 levels. In this heavily pretreated population, DX-8951f has clinically relevant hematologic and gastrointestinal toxicities in about 25% of patients. DX-8951 appeared to have linear pharmacokinetic characteristics on the basis of multiple administrations.

Keywords Camptothecin · Ovarian neoplasm · Topotecan resistance · Pharmacokinetics · Exatecan mesylate · DX-8951

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Introduction

Most women affected with epithelial ovarian, fallopian and primary peritoneal carcinoma present with advanced disease, usually at stage III or IV [1]. For patients with stage III disease and in some with stage IV disease, the primary tumor is maximally debulked before initiation of chemotherapy [2]. Standard chemotherapy

treatment consists of a platinum and taxane-based regimen, which offers a 70% response rate [3]. The disease usually recurs after a disease-free interval of a few months to years. Treatment reinduction with a platinum compound is often attempted, but eventually the disease becomes refractory to platinum. Topotecan is approved for second-line therapy of recurrent ovarian cancer [4]. Hence most patients are platinum, taxane and topotecan resistant when the disease progresses.

DX-8951f is a synthetic derivative of camptothecin, a natural alkaloid extracted from the bark and leaves of the tree, *Camptotheca acuminata* [5]. The activity of the drug is linked to its lactone form, which is in equilibrium with a carboxylate (open E ring) form. The equilibrium favors the carboxylate form at physiologic pH. The chemical structure of DX-8951f has been modified to render the molecule water soluble by adding a ring structure between rings A (in position 9) and B (in position 7), and a fluor in position 11 [6]. DX-8951f has shown both high in vitro potency against a series of 32 malignant cell lines and significant topoisomerase I inhibition [7]. The antiproliferative activity of DX-8951f in this system was 28 times greater than that of topotecan, and the antiproliferative activity of DX-8951f was about seven times greater than that of SN-38 (an active metabolite of irinotecan). Because of the demonstration of greater activity of DX-8951f than other camptothecin derivatives at equimolar concentrations in these preclinical studies [8], this phase II study was initiated.

The main objectives of this phase II trial were (1) to determine the antitumor activity of DX-8951f when administered as a 30-min infusion daily for 5 days to patients with advanced ovarian, tubal and peritoneal cancer resistant to platinum, taxane and topotecan, (2) to establish the safety profile of DX-8951f, and (3) to evaluate the pharmacokinetics and metabolism of the anhydrous form of DX-8951f (DX-8951) in plasma.

Patients and methods

Patients

Patients aged 18 years or over who had histologically confirmed advanced ovarian, tubal or peritoneal cancer resistant to platinum, taxanes and topotecan were eligible for this study provided that they met the following criteria: (1) a performance status of 2 or less on the ECOG scale and a life expectancy 12 weeks or more; (2) measurable tumor (pleural effusions, ascites, and osseous metastases were not considered measurable, and lesions located in previously irradiated areas were excluded from the final evaluation); (3) a neutrophil count of ≥1500 cells/μl, a platelet count of ≥100,000 cells/μl, a serum creatinine level of ≤ 1.5 mg/dl, and a total bilirubin level of ≤ 1.5 mg/dl; (4) at least 4 weeks since prior surgery, radiation or chemotherapy; and (5) provision of signed informed consent. Disease that progressed while the patient was on chemotherapy, that recurred within 6 months after discontinuation of chemotherapy or persistent macroscopic disease after six assessable cycles of chemotherapy if the last two cycles had no measurable change in disease was considered "resistant".

Exclusion criteria included: (1) evaluable disease only; (2) concurrent radiotherapy, surgery or chemotherapy; (3) women with the potential to become pregnant, unless utilizing birth control; (4) known brain metastases; (5) previous or current malignancies (except in situ carcinoma of the cervix or non-melanoma cancer of the skin); (6) psychosis or mental disability or incompetence to give informed consent; (7) concurrent life-threatening illness; (8) receipt of any investigational drug within 28 days prior to receipt of DX-8951f; or (9) history of allergy to camptothecin derivatives.

Before entry, a complete medical history was recorded and a physical examination done. Performance status was noted and lesions measured. A complete blood cell count and relevant blood chemistries, including a CA-125, were determined. Chest radiography and other indicated imaging studies were done as needed and repeated at the end of course 2 and every other course thereafter. Before each course, a clinical examination and a blood chemistry survey were required. Complete blood cell counts were performed weekly.

Treatment

Upon registration, patients were stratified according to their cancer treatment history. Minimally pretreated patients were started at a dose of 0.5 mg/m^2 per day. Heavily pretreated patients were defined as those who had had more than six courses of alkylating agent-containing chemotherapy or more than four courses of carboplatin, radiation therapy to >25% of hematopoietic reserves, two or more courses of mitomycin C or a nitrosourea. Heavily pretreated patients were given a starting dose of 0.3 mg/m^2 per day. Doses were altered ±0.1 mg/m^2 per day after the first course depending on toxicities.

Daiichi Pharmaceutical Corporation supplied DX-8951f for parenteral use in vials containing 2 mg lyophilized powder. The vials containing DX-8951f were stored in a refrigerator (2–8°C) and protected from light in a closed package. After reconstitution with normal saline, DX-8951f is stable for at least 24 h under ambient conditions of light and temperature. Each vial was reconstituted with 0.9% NaCl to obtain a stock 0.5 mg/ml solution. The appropriate volume of stock solution to yield the required dose was diluted in a PVC infusion bag with sterile 0.9% NaCl to a total volume of 100 ml for clinical use. One course of DX-8951f consisted of a 30-min infusion daily for five consecutive days. Treatments were repeated every 21 days. Treatment delays to allow recovery from toxic effects could not exceed 2 weeks.

Reductions of dose were allowed to prevent excessive toxicity. Subsequent doses were reduced by one dose level and given only upon bone marrow recovery in case of (1) asymptomatic ANC <500/μl (grade 4 neutropenia) lasting more than 5 days, (2) neutropenic fever with ANC <500/μl (grade 4 neutropenia), (3) platelet count <25,000/μl, (4) significant delays because of ANC <1500/μl (grade 2 or more neutropenia) or platelets <100,000/μl on day 28, or (5) grade 3 or more nonhematologic toxicity (or grade 2 neurotoxicity).

Dose escalation was permitted after the first course if the following conditions were met: (1) absolute neutrophil count nadir from the previous course was >1000/μl; (2) platelet nadir from the previous course was >100,000/μl; (3) maximum nonhematologic toxicity experienced by the patient during any previous course was grade 1 (excluding any grade of alopecia, local vein reaction or grade 2 nausea or vomiting); and (4) recovery from previous course toxicity had occurred by day 22.

Treatment was given for at least two courses unless there was rapidly progressive disease, in which case it was discontinued after one course. Continuation of treatment was dependent on the patient's response and tolerance, usually until progression of disease occurred. Therapy was discontinued in patients who experienced unacceptable toxicity.

Assessment of response

All patients who received at least five daily infusions (one course) of DX-8951f were considered evaluable for efficacy analysis. Response was assessed according to modified SWOG response criteria [9].

Development of an effusion and ascites (nonevaluable disease) was considered progressive disease. Radiographic studies were reviewed by the principal investigator (C.F.V.) and a radiologist (E.L.). Response, survival, and time to tumor progression were measured from the start of DX-8951f administration.

Sampling schedule and analytical assay

Pharmacokinetic blood samples were collected from each patient during the first course of DX-8951f. Serial blood samples were collected over 24 h on day 1 and over 2 h on day 5. On day 1, samples were taken before the start of the infusion (time 0), at 0.48 h (29 min into the infusion), once during each of the following sampling time windows (0.5–2 h, 4–8 h) and at 24 h (prior to the start of infusion on day 2) after the end of the infusion. On day 5, samples were taken before the start of the infusion (time 0), at 0.48 h (29 min into the infusion) and after the end of the infusion within the sampling time window 0.5–2 h. The blood draws taken during the sampling time windows 0.5–2 h and 4–8 h were obtained at specific times according to a randomization scheme (0.5, 1, 1.5, 2 and 4, and 4.5, 5, 6, 7 and 8 h).

The blood was collected into a heparinized tube and centrifuged at 3000 rpm for 15 min to separate out the plasma. The plasma was then transferred to a sample tube and frozen immediately at −20°C. All the collected plasma was labeled and forwarded to MDS Pharma Services (Montreal, Canada) for analysis. DX-8951 was analyzed in plasma using a validated HPLC method [10]. The lower limit of quantitation was 0.201 ng/ml.

Pharmacokinetic analysis

Pharmacokinetics were evaluated using standard compartmental approaches [11]. Linear pharmacokinetic models including two- and three-compartments were investigated for their quality of fit using maximum likelihood analysis with ADAPT-II [12]. The simplest model that best fitted the plasma concentrations of DX-8951f was a two-compartment pharmacokinetic model (Fig. 1). A three-compartment model did not significantly improve the fit based on visual inspection of the graphs and evaluation of pertinent indicators of "goodness of fit". The model discrimination process in our evaluation was based on the minimization of the values of the Akaike information criterion test, of the objective function, and of the residual variability [13]. An additional criterion considered in the discrimination process was the maximization of the average coefficient of determination. Pharmacokinetic parameters were calculated using a population pharmacokinetic methodology, the iterative two-stage methodology (IT2S) [14]. This method was necessary due to the limited sampling of the study design and to ensure the robustness of the results. Parameters defined and fitted by the two-compartment model were: Vc (central volume of distribution, l/m^2), Vp (peripheral volume of distribution, l/m^2), CLd (distributional clearance, $l/h/m^2$), and CL (total clearance, $l/h/m^2$). During the population analysis, the clearances (CL and CLd) and the volumes of distribution (Vc and Vp) were fitted to the average observed patient body surface area of 1.81 m^2. All plasma concentrations of DX-8951 were modeled simultaneously in each subject using a weighting procedure of $W_j = 1/S_j^2$ (where W_j is the weight associated with each individual concentration-time point j). The variance S_j^2 (variance calculated for each time point j) was calculated for each observation using the equation $S_j^2 = (a + b*Y)^2$, where a and b represent the additive and proportional error of this variance model, and Y the observed plasma concentrations of DX8951f.

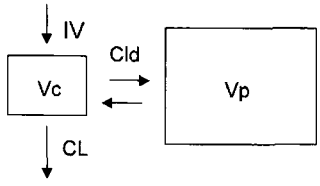

Fig. 1 Graphical representation of the structural pharmacokinetic model (*CL* total plasma clearance, *Cld* distributional clearance, *Vc* central volume of distribution, *Vp* peripheral volume of distribution, *IV* infusion of DX8951f)

Statistical analysis

Simon's optimal two-stage design was employed [15]. The null hypothesis was that the overall response rate was ≤ 5% vs the alternative hypothesis that the overall would be ≥20%. At the first stage, 14 evaluable patients were enrolled. As no responses occurred the trial was terminated. This design yielded ≥0.90 probability of a positive result if the true response rate was ≥20%. It yielded a ≥0.90 probability of a negative result if the true response rate was ≤ 5% with a ≥0.54 probability of early negative stopping. Treatment toxicity and survival were also determined [16].

Results

Patient characteristics

The characteristics of 16 eligible patients enrolled in the study are detailed in Table 1. Of these 16 patients, 13 had histologically confirmed papillary serous carcinoma, 2 had tumors of mixed morphology and 1 had clear-cell carcinoma, and 14 had tumors originating in the ovary and 2 had tumors originating in the peritoneum. All patients but two had high-grade carcinoma. One patient had a history of breast cancer more than 5 years prior to enrollment in this study. She had no evidence of breast cancer recurrence at enrollment. The median number of prior chemotherapy regimens was five (range two to eight). The patients had a median of two prior surgeries (range one to five) related to their disease process. Three patients received prior radiation on the pelvis. Two patients had participated in a gene therapy study. Of the 16 patients enrolled in the trial, 15 were heavily pretreated and 1 was minimally pretreated.

Table 1 Patient characteristics

Number of patients entered	16
Number of patients evaluable	
For safety	16
For efficacy	15
Age (years)	
Median	56
Range	33–65
ECOG performance status	
0	8
1	5
2	3
Number of patients who had prior treatments	
Chemotherapy	16
Platinum + taxane	16
Topotecan	16
Hormonotherapy	0
Immunotherapy	2
Radiotherapy	3
Surgery	16

Table 2 Response

Response	No. of patients (%)	Median CA-125 response (%)	Time to disease progression (weeks)
Minor response	4 (25%)	−85, −56, −56, −43	29, 24, 14, 8
Stable disease	3 (19%)	−61, −31, +90	14, 13, 10
Progressive disease	8 (50%)	+27 (range −27 to +168)	–
Unknown[a]	1 (6%)		
Total	16 (100%)		

[a]One patient did not return for follow-up

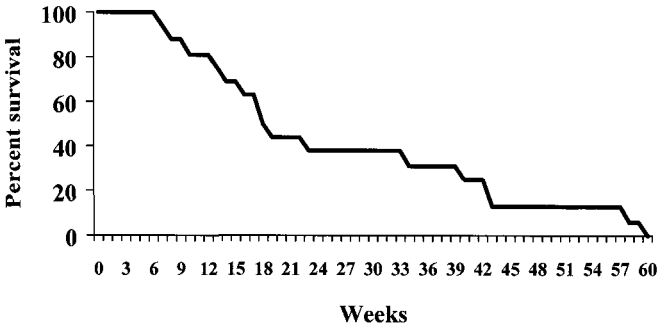

Fig. 2 Kaplan-Meier curve showing overall survival

Response

All 16 patients were evaluable for toxicity and 15 were evaluable for response. One patient did not return for follow-up after completing 5 days of treatment with DX-8951f on course one. The median number of treatment courses for all patients was 2 with a mean of 2.8 courses (range 1 to 9 courses). Complete or partial remission was not observed. Of the 15 evaluable patients, 4 achieved a minor response, 3 had stable disease and 8 showed evidence of progressive disease (Table 2). The median time to tumor progression was 43.0 days (95% CI 37–92 days) for 16 evaluable patients, and for the 7 patients who achieved either minor response or stable disease the median time to tumor progression was 100 days (range 58 to 210 days). One of these patients had a 23% reduction in the size of her tumor, but qualified for a serologic remission with a sustained 83% reduction in the levels of CA-125 lasting 25 weeks, as per the criteria described by Rustin et al. [17]. Eight patients had progressive disease after receiving at least one course of therapy. Four patients each had >50% and >25% non-sustained reduction in CA-125 levels, respectively. The median survival was 117 days (95% CI 90–279 days; Fig. 2).

Toxicity

All 16 patients who received DX-8951f could be evaluated for toxicity (Table 3). A total of 45 administered courses were evaluated. Of the 16 evaluable patients, 50% experienced grade 3 or 4 neutropenia and leukopenia. One episode of neutropenic fever was observed, and 25% and 13% of patients presented with grade 3 or more anemia and thrombocytopenia, respectively. Other

Table 3 Number of patients presenting with at least one toxic effect ($n=16$)

Toxic effect	Grade				Total (%)	Grade 3+4 (%)
	1	2	3	4		
Neutropenia	1	4	5	3	13 (81)	8 (50)
Leukopenia	2	5	6	2	15 (94)	8 (50)
Anemia	0	9	4	0	13 (81)	4 (25)
Thrombocytopenia	7	1	2	0	10 (63)	2 (13)
Intestinal obstruction	0	0	5	0	5 (31)	5 (31)
Nausea	2	6	4	0	12 (75)	4 (25)
Vomiting	2	4	3	0	9 (56)	3 (19)
Dehydration	0	3	3	0	6 (38)	3 (19)
Anorexia	1	2	0	0	3 (19)	0
Diarrhea	1	8	0	0	9 (56)	0
Weight loss	1	1	0	0	2 (13)	0
Stomatitis	1	1	0	0	2 (13)	0
Increased alkaline phosphatase	1	1	0	0	2 (13)	0
Fatigue	0	3	2	1	6 (38)	3 (19)
Drug fever	1	0	0	0	1 (6)	0
Neutropenic fever	0	0	1	0	1 (6)	1 (6)
Infection	0	2	0	0	2 (13)	0
Alopecia	1	1	0	0	2 (13)	0
Sepsis	0	0	1	0	1 (6)	1 (6)

grade 3 or more nonhematologic side effects included nausea (four patients) with vomiting and dehydration, fatigue (three patients), non-neutropenic infection (one patient). Five patients developed an intestinal obstruction, most likely related to disease progression. All other side effects were grade 2 or less and included gastrointestinal dysfunction (50% of patients), weight loss (13%), increase in liver function test (13%), fatigue (19%), alopecia (13%), stomatitis (13%), and dermatitis, drug fever, and dysuria (one patient each or 6%). In ten patients receiving multiple courses, the starting dose was 0.3 mg/m^2 per day for 5 days every 3 weeks. This dose was increased to 0.4 mg/m^2 per day for 5 days in four patients. In the patient treated at 0.5 mg/m^2 per day for 5 days, the dose was escalated to 0.6 mg/m^2 per day. Only one patient required a permanent dose reduction to 0.2 mg/m^2 per day for 5 days.

Pharmacokinetics

Of the 16 patients enrolled in the study, 12 had their pharmacokinetic profile assessed with a population-based approach. The results are summarized in Table 4. Figure 3 shows a "spaghetti" plot of all of the fitted and

Table 4 Pharmacokinetic parameters of DX-8951f (n = 12) (*CL* total plasma clearance, *Cld* distributional clearance, *Vc* central volume of distribution, *Vp* peripheral volume of distribution, λ_z-*HL* terminal elimination half-life)

Parameter	Average	CV%
CL (l/h/m^2)	2.1	64.7
Cld (l/h/m^2)	5.6	37.4
Vc (l/m^2)	7.1	28.1
Vp (l/m^2)	12.9	45.8
Vss (l/m^2)	20.0	36.0
λ_z-HL (h)	9.5	36.3

observed concentration time points for every patient in this study.

The pharmacokinetic behavior of DX-8951 has been shown previously [10] to be linear between the administered doses. This means that the plasma clearance (CL) and volume of distribution (Vss) does not change between the lowest and highest dose groups. This was again seen in this patient population. In addition, DX-8951 was associated with a terminal elimination half-life (λ_z-HL) of 9.5 h, a total body clearance (CL) of 2.1 l/h/m^2, and a total volume of distribution (Vss) of 20 l/m^2. These values are consistent with those seen when DX-8951 was administered in patients suffering from advanced solid malignancies [18].

Discussion

DX-8951f is a camptothecin analog with better in vitro and in vivo activity than topotecan or irinotecan. DX-8951f has been tested in six different phase I studies in patients with various refractory cancers. The dose-limiting toxicity is hematologic with grade 4 neutropenia and more rarely thrombocytopenia. Transient grade 3 liver function test anomalies (elevation of transaminases) have been observed in some studies [19, 20]. Other toxic effects are anemia, nausea and vomiting, diarrhea, fever, alopecia, fatigue, and malaise. Antitumor activity has been observed in non-small-cell lung cancer, ovarian cancer, endometrial cancer, colon cancer, hepatoma, thymoma, and small-cell carcinoma of the bladder [18, 21, 22]. Treatment could be tolerated for many months in patients with responding or stable disease.

In our study, patients with advanced ovarian, tubal and peritoneal carcinomas resistant to platinum, taxane and topotecan were treated with DX-8951f. Minor response combined with stable disease was observed in about 44% of patients for a median duration of 100 days (range 58 to 210 days). Overall survival was 117 days (95% CI 90–279 days). All patients who achieved stabilization of disease were heavily pretreated and resistant to platinum, taxane and topotecan. In a similarly refractory population who had not been pretreated with topotecan, treatment with another camptothecin analog, rubitecan, yielded a 7% remission rate [23]. Observed toxicity was similar to that reported for other DX-8951f studies. Because of bowel compromise related to peritoneal carcinomatosis, gastrointestinal side effects were prominent.

A relationship has been demonstrated between AUC and Cmax and severity of neutropenia and gastrointestinal toxicity [24]. Plasma levels reach cytotoxic concentrations. Drug concentrations exceeding biologically relevant concentrations (> 0.435 to 4.35 ng/ml) were sustained in patients for prolonged periods, with Cmax values averaging 52 ng/ml and 77 ng/ml at 0.3 and 0.5 mg/m^2 per day, respectively (the recommended phase II doses for heavily and minimally pretreated patients) [18]. The AUC (lactone/total drug) ratio is around 30% and the terminal elimination half-life between 6 and 9 h. Plasma pharmacokinetics showed large interpatient variations. In the present study, Cmax and half-life values were similar. The average Cmax after

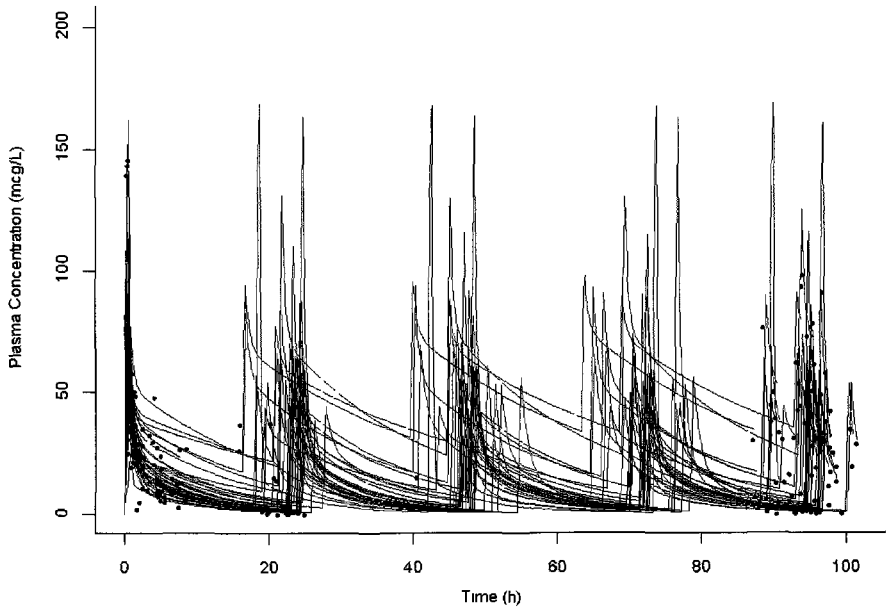

Fig. 3 Observed (*points*) and fitted (*continuous lines*) concentrations for each subject over the 5 days of administration ("spaghetti" plot)

single administration was 34 ng/ml at 0.3 mg/m^2 per day. The average terminal elimination half-life was 9.5 h. The residual variability in plasma concentrations derived by the compartmental pharmacokinetic model was 12.2%. This includes the intraindividual variability, all experimental errors (errors in dosing, errors in analysis, etc.) and errors arising from the pharmacokinetic modeling. Therefore, the chosen model fitted the data well. The interindividual CV% ranged from 28% to 72%. This latter variability in pharmacokinetic parameters is typical of those found for most drugs.

The antitumor activity of DX-8951f has been linked to accumulation of drug in the cells. This phenomenon seems to be at the basis of the differential activity between the different camptothecin analogs [25]. One factor that could account for the increase in antitumor effect may be related to higher membrane permeability [26]. It has been found that cytotoxicity of hexacyclic camptothecin analogs (DX-8951f-type analogs) does not always correlate with their topoisomerase I inhibitory activity, but that it does positively correlate with the calculated logP value, as an indicator of membrane permeability [27]. Of all the camptothecin analogs tested, DX-8951f has the highest calculated logP value. Furthermore, DX-8951f is able to completely overcome P-glycoprotein-mediated resistance and is hardly affected by BCRP-mediated resistance [25, 27, 28]. In a cloning in vitro system of adult and pediatric tumors, topotecan was minimally effective after a 1-h exposure but showed concentration-dependent inhibition with continuous exposure [8]. DX-8951f had definite cytotoxic activity in a concentration-dependent manner with both a 1-h and continuous exposure. Comparison of topotecan and DX-8951f showed that five of eight ovarian tumors were more sensitive to the latter. With continuous exposure, DX-8951f and topotecan were equally effective at equimolar concentrations. These data suggest that DX-8951f may have a higher therapeutic index than topotecan [7, 8] or irinotecan [29, 30]. When tested on human tumor xenografts, the antitumor activity has also been shown to be greater than with topotecan or irinotecan [29, 31, 32, 33].

In a heavily pretreated population of patients with advanced ovarian, tubal or peritoneal cancer resistant to prior platinum, taxane and topotecan, DX-8951f did not have significant activity. However, stable disease and minor response were observed, and this supports the preclinical data indicating that DX-8951f is active in topotecan- and irinotecan-resistant tumor cell lines. Therefore, DX-8951f may be as effective as other analogs such as topotecan or irinotecan when administered to patients naive to camptothecins.

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