A Phase I, Randomized, Open-Label, Parallel-Cohort, Dose-Finding Study of Elacridar (GF120918) and Oral Topotecan in Cancer Patients

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Abstract

Purpose: Breast cancer resistance protein (ABCG2) substantially limits the oral bioavailability of topotecan. Coadministration with elacridar, an inhibitor of breast cancer resistance protein–mediated drug transport, increases the bioavailability of topotecan. The aim of this study was to establish the lowest effective dose of elacridar to obtain maximum oral bioavailability of topotecan and to determine the optimal schedule of coadministration of oral topotecan and elacridar. In the second part of this study, dose-limiting toxicities and maximum tolerated dose of oral topotecan coadministered with elacridar, at a daily times five regimen administered every 21 days, were established.

Experimental Design: In part I, 20 patients were randomized to receive 100, 300, 500, 700, or 1,000 mg of elacridar on days 1 and 8 1 h before or simultaneously with 2.0 mg oral topotecan, which was also randomized. On day 15, all patients were treated with 1.5 mg/m^2 i.v. topotecan. In part II of the study, patients were treated daily with oral topotecan and with the lowest effective dose of elacridar following from part I. The maximum tolerated dose and dose-limiting toxicity were determined in cohorts of three patients. Blood samples were taken on days 1, 8, and 15 of part I and on day 1 of cycles 1 and 2 of part II.

Results: Complete apparent oral bioavailability of topotecan (102 $\pm$ 7%) for all treatment arms with elacridar in both schedules was seen in part I. In the topotecan dose escalation part, two dose-limiting toxicities were seen at the 2.5 mg topotecan dose level.

Conclusion: The recommended schedule is 2.0 mg oral topotecan plus 100 mg elacridar administered concomitantly daily times five every 21 days.

Topotecan applied i.v. is licensed for the treatment of small cell lung cancer after failure of first-line chemotherapy and for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. Preclinical and clinical studies with topoisomerase I inhibitors have shown an increased antitumor efficacy with protracted exposure at low concentrations (1–7). Based on these findings, phase I and II studies were undertaken with daily times five oral treatment and low-dose continuous infusion in cancer patients (1, 8–10). However, topotecan has moderate and variable oral bioavailability of 42 $\pm$ 13% (10, 11). This was unexpected as topotecan is water soluble, forms a chemically stable equilibrium between the lactone and the carboxylate form under physiologic conditions, and lacks significant systemic first-pass metabolism (12). Furthermore, in these early studies, only short treatment schedules of up to 5 days were feasible due to gastrointestinal side effects possibly resulting from unabsorbed topotecan (13). In a study by Ma et al., it was shown that topotecan is a substrate not only for P-glycoprotein, as previously reported by Chen et al., but also for breast cancer resistance protein (MXR, ABCG2; refs. 14–16). Maliepaard et al. (17) showed that this transporter is ubiquitously expressed in human tissues (e.g., in the epithelium of the small intestine and colon and in the liver canalicular membrane). In a study by Jonker et al. (18), *mdr 1a/1b (-/-) P-glycoprotein* knockout mice and *wild-type* mice were treated with oral topotecan in combination with elacridar (GF120918), a combined breast cancer resistance protein/P-glycoprotein inhibitor. The systemic exposure to orally applied topotecan increased almost 7- and 10-fold, respectively, in these mice. Because the affinity of topotecan for P-glycoprotein is low, the affinity of topotecan for breast cancer resistance protein is the most plausible explanation for the limited absorption of oral

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topotecan (15). These data resulted in a proof of concept study by Kruijtzer et al. (19) in which topotecan was combined with elacridar. In this study, the oral bioavailability of topotecan increased from 40.0% when administered without elacridar to 97.1% with elacridar. Elacridar had only a minor effect on the elimination as it decreased the systemic clearance of topotecan i.v. by only 10%. Based on these results, the current study, which comprised two parts, was designed. In the first part, the primary objectives were to determine the minimum dose of elacridar resulting in maximum oral bioavailability of topotecan and to determine whether the drugs should be given concomitantly or with a 1-h time interval. In part II, the dose-limiting toxicities and maximum tolerated dose of oral topotecan when coadministered with a fixed dose of elacridar for 5 days, every 21 days, were determined.

Materials and Methods

Patient selection. Patients with histologic proof of cancer for whom no standard therapy of proven benefit existed were eligible for the study. Previous radiotherapy, surgery, or chemotherapy was allowed but treatment had to be stopped at least 4 weeks before study entry, and any resulting toxicities had to be resolved before study entry. Patients had to have acceptable bone marrow (WBC $>3.0 \times 10^9$/L; absolute neutrophil count $>1{,}500 \times 10^9$/L; platelets $>100 \times 10^9$/L) and liver (aspartate aminotransferase/alanine aminotransferase and alkaline phosphatase $\leq 2\times$ upper limit of normal unless explained by liver metastases then $\leq 5\times$ upper limit of normal was accepted) function. Serum albumin had to be ≥ 25 g/L and serum creatinine had to be ≤ 130 μmol/L or clearance had to be ≥ 60 mL/min. All patients had to have a Zubrod-Eastern Cooperative Oncology Group-WHO performance status of ≤ 2. Patients were excluded if they suffered from uncontrolled infectious disease, neurologic disease, or motility disorders that could influence the absorption of study drugs. Patients with symptomatic brain metastases were not eligible. Further exclusion criteria were concomitant use of known multidrug resistance–converting drugs, H2 receptor antagonists, or proton pump inhibitors. The trial was approved by the ethics committee of both institutes, and all patients gave written informed consent before study enrollment.

Toxicity and response evaluation. Baseline evaluation within 2 weeks before study drug administration included a complete medical history and physical examination, WHO performance status, ophthalmologic examination, blood count, biochemical profile, serum tumor markers, tumor evaluation using appropriate radiographic imaging, and adverse event assessment. Within 72 h before first treatment, vital signs, 12-lead electrocardiogram, hematology, clinical chemistry, urinalysis, and serum pregnancy test were completed. Hematology, biochemical profiles, performance status, 12-lead electrocardiogram and vital signs, radiological assessment, weight, and body surface area were assessed after the first course or within 5 days of day 21 of subsequent courses.

On days 1 and 8 of part I and on day 1 of part II, an electrocardiogram and vital signs assessment were obtained before dose and at ~3 h after oral topotecan dose on day I of part II. On day 15 of part I, an ophthalmologic exam was repeated and weight and body surface area were determined. Adverse event assessment was done every week. Tumor measurements were done every course of part II of the study by examination with the same radiological method used at baseline. In patients with measurable disease, response to therapy was assessed according to Response Evaluation Criteria in Solid Tumors criteria (20). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (21). Patients received a 0.25 mg/m^2/d dose reduction if the patient suffered from severe or prolonged grade 4 neutropenia (neutrophils $<500 \times 10^9$/L) and fever or infection or grade 4 neutropenia lasting 7 days. Furthermore, a dose reduction was required if toxicities required a delay in the next course. These toxicities were defined as grade 2 (or worse) neutropenia (neutrophils $<1{,}500 \times 10^9$/L) or grade 3/4 nonhematologic toxicity, with the exception of grade 3 nausea, grade 3/4 vomiting, and alopecia.

Drug administration. Topotecan and elacridar were supplied by GlaxoSmithKline. Topotecan was supplied as capsules containing topotecan hydrochloride equivalent to 1.0 and 0.25 mg of the

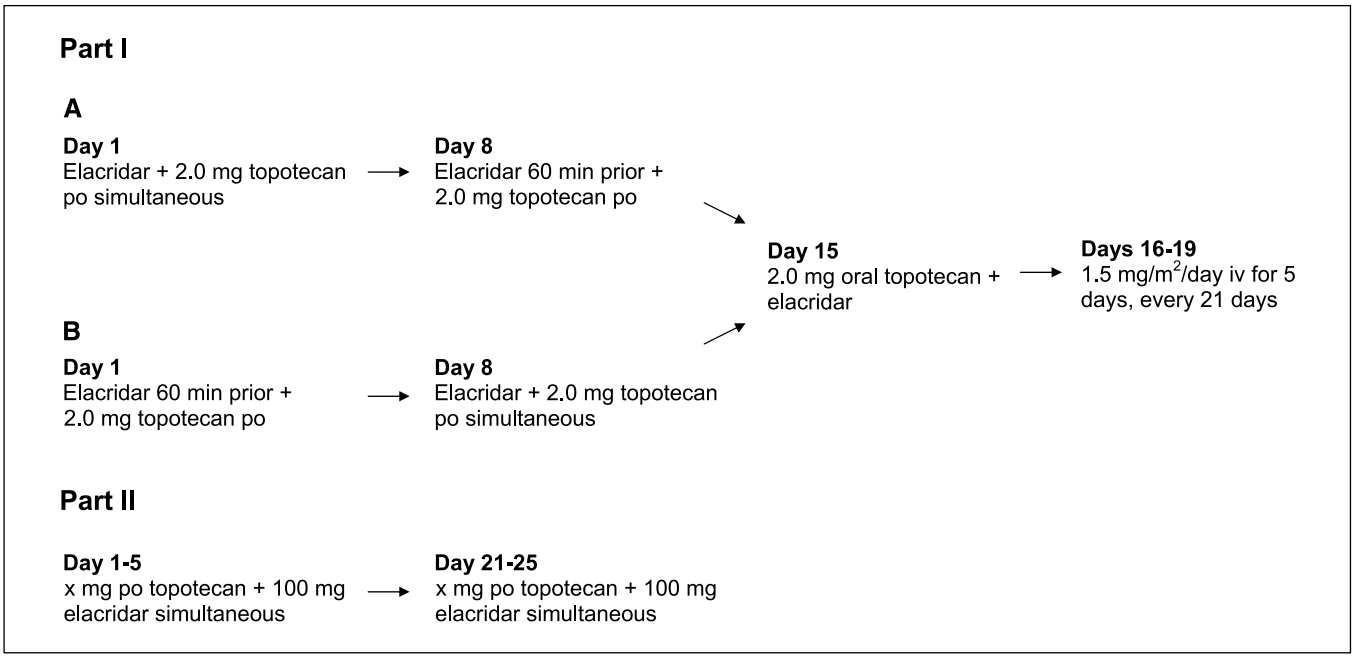

Fig. 1. Study administration schedule.

Table 1. Patient characteristics

	Part I	Part II
No. patients	24	15
Completed, *n* (%)	19 (79)	7 (47)
Prematurely discontinued, *n* (%)	5 (21)	8 (53)
Male/female, *n* (%)	8/16 (33/67)	11/4 (73/27)
Performance status		
0	10	6
1	11	9
2	3	
Median age (y)	55.5	55.0
Range	27-75	27-69
Tumor type		
Bladder carcinoma	1	1
Gastric carcinoma	1	1
Gallbladder carcinoma	1	
Skin cancer, squamous cell carcinoma	1	
Endometrium adenocarcinoma	1	
Ovarian adenocarcinoma	7	2
Primary tumor unknown		
Adenocarcinoma	1	
Squamous cell carcinoma	1	
Pancreas carcinoma	1	2
NSCLC	6	
SCLC	3	
Renal		1
Tonsil carcinoma		1
Cardia carcinoma		2
Appendix carcinoma		2
Thyroid carcinoma		1
M. Hodgkin		1
Colon carcinoma		1
Prior therapy		
None	1	0
Chemotherapy	22	12
Radiotherapy	3	4
Surgery	13	11

Abbreviations: NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

anhydrous free base. Elacridar was administered as tablets containing 100 mg elacridar as the hydrochloride salt. Topotecan i.v. was supplied in vials containing 4 mg of topotecan as the free base.

Patients and methods. In part I of the study, a planned number of 20 patients were randomized to receive orally 1,000, 700, 500, 300, or 100 mg of elacridar coadministered with 2.0 mg oral topotecan on days 1 and 8. Administration of topotecan and elacridar was either simultaneously, or elacridar was administered 60 min before topotecan, according to randomization. Both groups were treated with 2.0 mg topotecan i.v. on day 15 and subsequently with 1.5 mg/m^2 i.v. on days 16 to 19.

In part II, patients received oral topotecan daily times five every 21 days, coadministered with the lowest pharmacologically effective dose of elacridar following results of part I. The initial dose of topotecan was 1.0 mg with dose escalation of 0.5 mg increments if tolerated up to a maximum daily dose of 4.0 mg. Cohorts of three patients were treated at each dose level until a dose-limiting toxicity was observed, and at least six patients were treated at the maximum tolerated dose. After the first dose-limiting toxicity occurred, an additional three patients were treated at the same dose level.

Standard breakfasts before study drug administration were only required on pharmacokinetic sampling days for each patient over the initial 24 h after dose. On dosing days when pharmacokinetic samples were not collected, study drug administration should take place 30 min after breakfast; however, breakfast was not standardized. Patients in part I could continue standard i.v. therapy, 1.5 mg/m^2 for 5 days every 21 days, and patients in part II could continue the same oral dose of topotecan and elacridar as trial medication, for 5 days every 21 days, if considered in the patients' best interest (see Fig. 1).

Pharmacokinetic sample collection, processing, and storage procedures. Whole blood samples of 5 mL were collected in heparinized tubes on days 1, 8, and 15 for part I and on day 1 of cycles 1 and 2 of part II of study. Topotecan blood sample collection times were on days 1 and 8 of part I and on day 1 of cycles 1 and 2 of part II: before dose and 15, 30, 45, 60, and 90 min and 2, 4, 6, 8, 10, and 24 h after oral intake of topotecan. On day 15 of part I, blood sampling took place before dose; 15 min after start of the topotecan infusion; before the end of the topotecan infusion; and 15, 30, 45, 60, and 90 min and 2, 4, 6, 8, 10, and 24 h after the end of topotecan infusion. Elacridar collection times were (only on days 1 and 8 of part I) -60 min and -30 min (only these two samples if elacridar was given 60 min before topotecan); before topotecan dose; and 30, 60, and 90 min and 2, 4, 6, 8, 10, and 24 h after oral administration of topotecan. Samples were collected and treated as described earlier (22). In brief, 1 mL of cold methanol of -30°C was added to 1 mL of plasma to retain the ratio between lactone and carboxylate of topotecan. Plasma samples were assayed for topotecan lactone, for total topotecan, and for elacridar (only in part I) using validated liquid chromatography-tandem mass spectrometry methods (23, 24).

The area under the plasma concentration-time curve (AUC) was determined using the linear trapezoidal rule for all incremental trapezoids arising from increasing concentrations and logarithmic trapezoidal rule for those arising from decreasing concentrations using WinNonlin version 3.0 (Pharsight Corp.). For part I of the study, the apparent bioavailability of oral topotecan with elacridar was calculated by dividing the AUC after oral administration by the AUC of topotecan after i.v. administration of the drug. The maximal drug concentration (C_{max}) and time to maximal drug concentration (T_{max}) were obtained directly from the experimental data for total topotecan and its lactone form and for elacridar. Other variables that were determined were the total plasma clearance and the terminal half-life ($t_{1/2}$) of topotecan lactone and elacridar after i.v. and oral administration.

The apparent oral bioavailability (F) and the interpatient variability [coefficient of variation (%CV)] of total topotecan and topotecan lactone are calculated according to the following formulas:

$$F = \frac{AUC_{oral}}{AUC_{iv}} \times 100\%$$

$$\%CV = \frac{SD}{mean} \times 100\%$$

Statistical analysis. In part I, multivariate analysis was done to examine the effects on oral bioavailability of the within-subject factor (simultaneous or 60-min interval between elacridar and topotecan), the between-subjects factor (dose of elacridar at five levels), and the interaction of these two factors. A polynomial model in dose was fit to the oral bioavailability estimates.

Point and 95% confidence interval estimates of interpatient variability of bioavailability were obtained.

Results

Safety. A total of 39 patients was entered onto this study (see Table 1). During the first phase of the study, all doses of elacridar administered in combination with a fixed dose of 2 mg oral topotecan were well tolerated. Two drug-related severe side effects were observed: febrile neutropenia grade 3 and hemoptysis with thrombocytopenia grade 4. Each of these

events occurred during cycles of daily times five i.v. topotecan therapy and was not related to the oral application of topotecan plus elacridar. Other toxicities that were reported were of gastrointestinal origin, especially nausea and vomiting, and hematologic, especially anemia and neutropenia. These toxicities were mostly of Common Toxicity Criteria grade 1 and never exceeded Common Toxicity Criteria grade 2, except for one patient who had grade 3 vomiting. Toxicities clearly associated with elacridar were not observed.

In part II, most nonhematologic toxicities were reported as grade 1 to 2 across all dose levels. One grade 3 fatigue, one grade 3 constipation, and two grade 3 vomiting were reported at the 2.0 mg dose level. The most frequently reported toxicities were fatigue, nausea, constipation, and anorexia. Only three patients had grade 1 to 2 diarrhea, which did not result in interruption of intake of topotecan. In part II, initially three patients were recruited at each dose level (see Table 2A and B). Two dose-limiting toxicities were seen at the 2.5 mg topotecan

Table 2. Toxicities that were possibly, probably, or definitely related to study drugs

Maximum severity NCI-CTC grade		Cohort				
	Grade	A	B	C	D	Total
A. Maximum hematologic toxicity profile in part II (n = 15) for all cycles						
Dose (mg)		1	1.5	2.0	2.5	
n		3	3	6	3	15
Anemia	1	—	—	1	—	1
	2	1	—	3	2	6
	3	—	—	1	—	1
Leukopenia	1	—	—	1	—	1
	2	—	—	—	2	2
	3	—	—	2	—	2
	4	—	—	—	1	1
Neutropenia	1	—	—	—	—	—
	2	—	—	1	1	2
	3	—	1	2	2	5
	4	—	—	—	1	2
Thrombocytopenia	1	—	1	1	—	2
	2	1	1	1	2	5
	3	—	—	1	—	1
	4	—	—	—	1	1
B. Maximum nonhematologic toxicity profile in part II (n = 15) for all cycles						
Dose (mg)		1	1.5	2.0	2.5	
n		3	3	6	3	15
Gastrointestinal disorders						
Abdominal distention	1	—	—	1	—	1
Abdominal pain	1	2	1	—	1	4
	2	—	—	1	1	2
Constipation	1	—	1	3	1	5
	2	—	—	—	1	1
	3	—	—	1	—	1
Diarrhea	1	—	1	2	—	3
	2	—	—	1	—	1
Nausea	1	2	3	2	2	9
	2	—	—	1	—	1
Stomatitis	1	—	—	—	1	1
Vomiting	1	1	—	1	1	3
	2	—	—	—	—	—
	3	—	—	2	—	1
General disorders and administration site conditions						
Fatigue	1	1	1	1	—	2
	2	—	1	1	3	5
	3	—	—	1	—	1
Malaise	1	—	—	—	—	—
	2	—	1	—	—	1
Pyrexia	1	—	—	—	1	1
	2	—	—	1	1	2
Skin and s.c. tissue disorders						
Alopecia	1	1	—	2	1	3
	2	—	—	2	1	3
Metabolism and nutrition disorders						
Anorexia	1	—	1	3	1	5
	2	—	—	—	1	1

NOTE: Toxicities were possibly, probably, or definitely related to study medication.
Abbreviation: NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table 3. Part I: pharmacokinetic variables of total topotecan (lactone plus carboxylate)

	Total topotecan				
	Simultaneous administration				
	A	B	C	D	E
n	4	4	3*	2	4
Dose (mg) elacridar	100	300	500	700	1,000
F[‡]	102.3 (91.5-114.4)	98.4 (67.5-143.4)	106.6 (64.4-176.5)	87.6 (15.7-488.3)	110.2 (94.3-128.7)
%CV[§]	7	25	21	19	10
AUC_∞ (μg·h/L)	86.8 (60.4-124.8)	71.8 (42.4-121.6)	77.6 (57.0-105.7)	97.7 (40.5-235.4)	89.0 (59.7-132.8)
CL (L/h)					
C_{max} (μg/L)	12.3 (7.0-21.6)	11.9 (9.2-15.4)	12.1 (6.9-21.1)	12.1 (1.7-87.1)	13.9 (10.9-17.7)
V_d (L)					
T_{max} (h)[‖]	2.01 (1.95-4.02)	3.01 (2.02-4.00)	1.29 (0.62-4.00)	2.00 (0.53-2.03)	1.77 (1.50-4.03)

NOTE: Data are presented as geometric mean (95% confidence interval).
Abbreviation: CL, clearance.
*For the C_{max}, the number of patients used to calculate the value was 4.
† For the AUC_∞, C_{max}, and T_{max}, the number of patients used to calculate the value was 4.
‡ Expressed as geometric mean ± 95% confidence interval.
§ %CV is calculated by dividing the SD by the mean.
‖ T_{max} is expressed as median (range).

dose level: one grade 4 febrile neutropenia and a grade 4 neutropenia >5 days combined with a thrombocytopenia grade 4. Of the next three patients at the 2.0 mg dose level of topotecan, two developed a dose-limiting toxicity: one patient suffered from fatigue and ileus and the other patient had grade 3 neutropenia, vomiting, thrombocytopenia, leucopenia, and dehydration. However, only toxicities in the latter patient were related to the study drug, and consequently, the 2.0 mg dose level was found safe for future testing. Therefore, the maximum tolerated dose was determined to be at 2.0 mg oral topotecan combined with a dose of 100 mg elacridar. Gastrointestinal toxicity was minimal and the combination was well tolerated.

Response. In part I of study, four patients prematurely discontinued the study. Three patients due to progressive disease and one patient left the study on request. Responses were not measured in part I, as patients received only oral topotecan at one occasion. Of the 15 patients who were entered in part II, all were assessable for response; however, no complete or partial response was reported. One patient with ovarian cancer experienced a decrease in CA125 at cycles 2 and 3 at the 2.5 mg dose level. Two patients had stable disease (<6 months): one of them suffered from advanced renal cell cancer and was treated with 1.5 mg topotecan and one had advanced gastric cancer and received 1.0 mg topotecan.

Pharmacokinetics. Plasma pharmacokinetic variables $t_{1/2}$, k_{el}, AUC_{last}, V_d, C_{max}, and T_{max} for part I and part II of study are summarized in Tables 3, 4, 5, 6, and 7. Of the 24 patients in part I, 4 went off study before completion of kinetics and were replaced. Two of these patients had progressive disease and one patient had a course delay >2 weeks because of fever. In three other patients, no lactone samples were collected, and from

Table 4. Part I: pharmacokinetic variables of topotecan lactone

	Topotecan lactone				
	Simultaneous administration				
	A	B	C	D	E
n	3*	4	3	3	3
Dose (mg) elacridar	100	300	500	700	1,000
F	101.2 (81.4-125.8)	92.1 (70.4-120.5)	109.9	90.1	111.4 (74.9-165.9)
%CV	9	17	20	16	16
AUC_∞ (μg·h/L)	29.6 (21.0-41.7)	23.7 (16.4-34.1)	27.9	29.0 (9.6-87.4)	31.0 (20.3-47.2)
CL (L/h)					
C_{max} (μg/L)	6.7 (2.9-15.4)	5.7 (3.7-8.9)	10.4 (2.8-38.6)	6.1 (0.4-95.5)	7.3 (2.5-20.8)
V_d (L)					
$t_{1/2}$ (h)	2.69 (2.27-3.18)	2.82 (1.62-4.92)	3.78	5.17 (1.71-15.56)	3.74 (1.85-7.56)
T_{max} (h)	2.0 (1.95-4.02)	1.76 (1.52-2.00)	0.76 (0.28-0.80)	2.03 (0.53-2.03)	2.03 (0.98-4.03)

NOTE: Data are presented as mean ± SD. For the AUC_∞, the number of patients used to calculate the value was 3. For the T_{max} and $t_{1/2}$, the number of patients used to calculate the value was 3.
*For the AUC_∞, C_{max}, T_{max}, and $t_{1/2}$, the number of patients used to calculate the value was 4.
† For the C_{max} and T_{max}, the number of patients used to calculate the value was 16.

Table 3. Part I: pharmacokinetic variables of total topotecan (lactone plus carboxylate) (Cont'd)

	Total topotecan					
	Sequential administration					
	A	B	C	D	E	I.v. topotecan
n	4	4	4	3 †	4	19
Dose (mg) elacridar	100	300	500	700	1,000	
F ‡	107.2 (82.0-140.2)	101.0 (79.0-129.2)	109.6 (89.0-135.0)	80.5 (57.4-112.8)	109.4 (88.9-134.6)	
%CV§	18	15	13	13	13	
AUC_∞ (μg·h/L)	91.0 (62.6-132.3)	73.7 (58.9-92.3)	81.6 (61.6-108.1)	77.2 (43.7-136.5)	88.4 (60.4-129.4)	78.6 (72.5-85.1)
CL (L/h)						25.8 ± 4.25
C_{max} (μg/L)	16.2 (11.4-22.9)	11.3 (8.9-14.3)	13.2 (7.3-23.7)	10.1 (4.0-25.3)	15.0 (12.4-18.1)	30.1 (27.7-32.7)
V_d (L)						106 (97.8-114.4)
T_{max} (h)‖	1.26 (0.58-2.30)	2.01 (1.97-4.02)	1.76 (1.00-3.97)	4.00 (0.95-4.18)	1.75 (1.50-2.00)	0.50 (0.25-0.57)

another patient, no total topotecan samples were collected. One patient was excluded because of deviations from sampling times.

Results in Tables 3 and 4 reveal a complete apparent oral bioavailability (F) of topotecan for all treatment arms of elacridar for both schedules (see Figs. 2 and 3). The mean %CV for F ranged between 7% and 25% for all groups and was 17% for topotecan i.v. These data reflect the low interpatient variability after oral administration.

No statistically significant difference in F between administration either simultaneously or sequentially was observed for either total topotecan (P = 0.71) or for topotecan lactone (P = 0.55). In addition, no significant effect of the dose of elacridar on the apparent bioavailability of topotecan was observed (P = 0.22) for total topotecan and (P = 0.25) for topotecan lactone.

No dose-schedule interaction was observed in part I of the study for topotecan (P = 0.81) and for topotecan lactone (P = 0.18), indicating that randomization of schedule either simultaneously or sequentially did not influence the kinetics of the administered doses of topotecan.

Based on these results, the lowest pharmacologically effective and safe dose of elacridar of 100 mg was selected for simultaneous administration with topotecan in study part II. The pharmacokinetic values of elacridar are presented in Table 5 and Fig. 4A and B. The mean %CV for the AUC_{last} of elacridar ranged between 11% and 116%, indicating a high variability.

In part II, no samples were collected from two patients on day 21 of study due to progressive disease. A linear relationship was found between the administered dose of topotecan and the AUC_∞ for total topotecan (slope, 1.01; 90% confidence interval, 0.12-1.89) and topotecan lactone (slope, 1.38; 90% confidence interval, 0.74-2.03) for which data of cycle 1 of part II were used. In addition, a linear relationship was observed between C_{max} of topotecan and dose (slope, 1.25; 90% confidence interval, 0.51-1.98). The $t_{1/2}$ did not differ significantly between the oral treatment groups and the i.v. administration (see Tables 6 and 7).

Discussion

These results reveal that administration of 100 mg elacridar combined with oral topotecan results in complete apparent bioavailability of topotecan. Moreover, the data showed a consistently low interpatient variability in the bioavailability across all treatment groups. The mean %CV for the apparent oral bioavailability ranged between 7% and 25% for oral dosing and was 17% for the AUC of topotecan when administered i.v. Additionally, these data confirmed that dosing of elacridar and oral topotecan simultaneously results in similar increases in the apparent bioavailability of oral topotecan as when these agents are given sequentially at an interval between elacridar and topotecan of 60 min. The lowest dose of elacridar tested, 100 mg, resulted in a similar increase in the apparent

Table 4. Part I: pharmacokinetic variables of topotecan lactone (Cont'd)

	Topotecan lactone					
	Sequential administration					
	A	B	C	D	E	I.v. topotecan
n	3*	4	3	3	3	15 †
Dose (mg) elacridar	100	300	500	700	1,000	
F	111.8 (82.9-150.9)	97.6 (77.2-123.3)	111.2 (96.2-128.6)	75.1	104.4 (59.2-184.1)	
%CV	12	14	6	13	23	
AUC_∞ (μg·h/L)	32.1 (23.5-43.8)	25.1 (18.9-33.3)	30.2 (18.2-50.1)	24.1 (8.4-69.3)	29.0 (18.9-44.5)	27.2 (24.7-30.0)
CL (L/h)						73.5 (66.7-80.9)
C_{max} (μg/L)	10.9 (8.0-14.9)	5.9 (4.9-7.2)	8.9 (2.9-27.)	4.9 (0.5-45.1)	9.7 (8.3-11.5)	23.4 (20.5-26.6)
V_d (L)						175 (162-190)
$t_{1/2}$ (h)	3.23 (2.36-4.42)	3.35 (2.36-4.76)	2.93 (2.07-4.14)	4.74 (1.15-19.43)	3.36 (1.45-7.78)	2.82 (2.62-3.03)
T_{max} (h)	1.15 (0.58-1.63)	1.50 (1.13-2.03)	0.76 (0.75-1.50)	2.00 (0.95-4.18)	1.53 (1.00-1.53)	0.4 (0.25-0.57)

Table 5. Part I: pharmacokinetic variables of elacridar

	Elacridar				
	Simultaneous administration				
	A	B	C	D	E
Dose (mg)	100	300	500	700	1,000
n	4	4	4*	4	4
AUC_{last} ‡ (μg·h/L)	1,168 (252-5,404)	895 (434-1,847)	1,544* (1-463,537)	1,300 (770-2,195)	2,109 (1,771-2,511)
%CV of AUC_{last}	116	49	79	31	11
C_{max} (μg/L)	81.4 (19.2-345)	66.6 (38.2-116)	100 (41.7-241)	97.8 (55.8-171)	140 (114-171)
T_{max} (h)	6.0 (4.0-8.0)	4.0 (2.0-4.1)	4.0 (2.1-8.0)	4.1 (4.0-8.4)	6.0 (6.0-8.2)

NOTE: Data are presented as mean ± SD.
*For AUC_{last}, the number of patients used to calculate the value was 2.
† For T_{max}, AUC_{last}, and C_{max}, the number of patients used to calculate the value was 4.
‡ Determined by calculation of AUC by the linear-logarithmic trapezoid rule up to the last measured time point.

bioavailability of oral topotecan as the higher doses of elacridar. Lower doses of elacridar could not be tested at this moment as the minimal tablet strength is currently 100 mg.

A previous study showed that elacridar almost completely reversed breast cancer resistance protein–mediated resistance to the camptothecins at 100 nmol/L (25). Absorption of both topotecan and elacridar was rapid as already at the first sample taken at 15 min after intake of topotecan and 30 min of elacridar relatively high plasma concentrations could be measured. T_{max} for elacridar was reached after 2 h and even after up to 8 h in some patients, reflecting a large interpatient variability. The dissolution of elacridar is variable, which at least partly explains the observed variability in its pharmacokinetics. At the different doses of elacridar, similar apparent bioavailabilities of total topotecan and topotecan lactone were observed. These data suggest that a dose of 100 mg elacridar administered simultaneously with oral topotecan is a suitable dose to be selected for the dose escalation part of study. However, it cannot be excluded that an even lower dose of elacridar is equally effective. This would nevertheless require a different formulation of the currently available 100 mg capsule of elacridar. Interestingly, it was shown that the apparent oral bioavailability was ~100% and, in some patients, even slightly higher than 100%. This can be explained by the contribution of

Table 6. Part II: pharmacokinetic variables of total (lactone plus carboxylate) topotecan

	Total topotecan			
	A	B	C	D
Cycle 1				
Dose (mg)	1.0	1.5	2.0	2.5
n	3	3	6	3
AUC_∞* (μg·h/L)	39.2 (13.6-113.4)	49.7 (26.3-94.1)	51.0 (24.6-105.8)	98.9 (30.4-321.1)
%CV	38	27	61	51
CL/F (L/h)	25.5 (8.8-73.6)	30.2 (15.9-57.1)	39.2 (18.9-81.4)	25.3 (7.8-82.1)
C_{max} (μg/L)	4.5 (2.4-8.7)	8.1 (4.1-16.2)	8.0 (4.2-15.3)	14.2 (7.2-28.1)
k_{el} (h^{-1})	0.160 (0.075-0.341)	0.190 (0.079-0.457)	0.231 (0.165-0.325)	0.156 (0.118-0.205)
V_d/F (L)	159 (54-473)	159 (83-306)	169 (92-313)	163 (66-402)
$t_{1/2}$ (h)	4.33 (2.03-9.21)	3.65 (1.52-8.79)	2.99 (2.14-4.20)	4.46 (3.38-5.88)
T_{max} (h)	4.03 (2.00-4.03)	1.90 (1.50-2.08)	2.00 (2.00-4.00)	4.00 (2.03-4.25)
Cycle 2				
Dose (mg)	1.0	1.5	2.0	2.5
n	1	3	6	1
AUC_∞* (μg·h/L)	28.1	58.7 (23.0-150.0)	70.9 (44.0-114.0)	65.4
%CV		41	53	
CL/F (L/h)	35.6	25.5 (10.0-65.3)	28.2 (17.5-45.4)	38.2
C_{max} (μg/L)	4.4	8.8 (3.2-24.1)	9.7 (5.6-17.0)	11.2
k_{el} (h^{-1})	0.261	0.170 (0.105-0.276)	0.159 (0.137-0.185)	0.166
V_d/F (L)	136	150 (38-596)	177 (122-257)	230
$t_{1/2}$ (h)	2.65	4.07 (2.51-6.60)	4.35 (3.75-5.05)	4.17
T_{max} (h)	4.00	2.00 (2.00-2.23)	4.00 (2.00-6.03)	2.00

NOTE: Data are presented as mean ± SD. F followed from part I elacridar simultaneously with topotecan (see Table 5).
*Determined by calculation of AUC by the linear-logarithmic trapezoid method up to the last measured time point with extrapolation to infinity using the terminal rate constant k_{el}.

Table 5. Part I: pharmacokinetic variables of elacridar (Cont'd)

Elacridar				
Sequential administration				
A	B	C	D	E
100	300	500	700	1,000
4	4	4	3[†]	4
935 (205-4,260)	975 (579-1,642)	1,353 (451-4,054)	956 (571-1,602)	2,629 (1,660-4,166)
77	35	63	28	32
62.9 (13.0-305)	81.5 (55.0-120.7)	104.3 (52.6-206.9)	97.2 (49.6-190.3)	185 (138.3-247.7)
7.2 (7.0-11.0)	6.0 (2.0-7.1)	4.5 (2.0-7.0)	3.1 (2.5-5.2)	6.0 (3.0-9.1)

intrapatient variability, which may result in a calculated apparent bioavailability of >100%. Furthermore, in our previous study, we found that elacridar slightly reduced systemic clearance of topotecan by an average of 10% (19). This may also contribute to an overestimation of the true bioavailability.

In the dose escalation part of the study, the combination of elacridar with oral topotecan was well tolerated and adverse events were as observed in our previous study (19). No dose-limiting diarrhea was reported, as was the case for oral topotecan monotherapy (26, 27). We speculate that topotecan has a local effect on the intestinal mucosa, and in combination with elacridar, the intestinal absorption is increased, which may affect the toxicity profile. Furthermore, dose-limiting hematologic toxicities were as observed after i.v. administration of topotecan: neutropenia and thrombocytopenia. In analogy of studies with topotecan i.v., the AUC of topotecan lactone was related to the nadirs in thrombocytes and in absolute neutrophil count (28–30). In this study, no significant relationship between the AUC of total topotecan and the presence of absolute neutrophil count or thrombocytopenia was found. This may be explained by the relatively small data set of the study.

Pharmacokinetic analysis of these data showed a significant linear correlation between the administered dose of topotecan and the AUC_∞ for total topotecan and topotecan lactone and between the C_{max} of topotecan. C_{max} of topotecan lactone was not linearly correlated with dose. This could be due to the limited number of patients available for pharmacokinetics in two patient groups (Table 7).

In conclusion, administration of 100 mg elacridar combined with oral topotecan results in complete apparent oral bioavailability of topotecan. The recommended oral dose of topotecan in combination with elacridar administered simultaneously is 2.0 mg daily times five every 21 days. Phase II studies are indicated to assess the activity of the combination of topotecan plus elacridar.

Table 7. Part II: pharmacokinetic variables of topotecan lactone

	Topotecan lactone			
	A	B	C	D
Cycle 1				
Dose (mg)	1.0	1.5	2.0	2.5
n	3	3	6	3
AUC_∞ (μg·h/L)	9.9 (4.3-23.0)	16.9 (11.8-24.2)	21.9 (13.4-35.8)	35.2 (11.1-112.0)
%CV	30	14	51	48
CL/F (L/h)	100.9 (43.6-233.8)	88.7 (62.1-126.6)	91.3 (55.9-149.1)	71.0 (22.3-226.1)
C_{max} (μg/L)	1.5 (1.0-2.3)	4.7 (2.0-11.2)	4.6 (2.4-9.0)	8.5 (2.9-24.7)
k_{el} (h^{-1})	0.188 (0.059-0.596)	0.163 (0.023-1.158)	0.180 (0.091-0.359)	0.226 (0.075-0.681)
V_d/F (L)	537 (346-832)	546 (104-2852)	506 (228-1122)	314 (153-644)
$t_{1/2}$ (h)	3.69 (1.16-11.68)	4.27 (0.60-30.38)	3.84 (1.93-7.65)	3.06 (1.02-9.21)
T_{max} (h)	4.03 (1.5-6.0)	2.00 (0.97-2.08)	1.75 (1.00-2.05)	2.03 (2.00-2.22)
Cycle 2				
Dose (mg)	1.0	1.5	2.0	2.5
n	1	3	6	1
AUC_∞ (μg·h/L)	7.4	21.9 (9.8-49.1)	26.5 (16.4-42.9)	32.4
%CV		32	50	
CL/F (L/h)	135.1	68.6 (30.6-153.7)	75.4 (46.6-122.0)	77.1
C_{max} (μg/L)	1.5	5.0 (1.8-13.8)	4.6 (2.9-7.3)	7.1
k_{el} (h^{-1})	0.286	0.159 (0.024-1.075)	0.178 (0.102-0.311)	0.102
V_d/F (L)	473	430 (71-2620)	423 (249-719)	756
$t_{1/2}$ (h)	2.43	4.35 (0.65-29.31)	3.89 (2.23-6.78)	6.80
T_{max} (h)	2.0	1.57 (1.5-2.00)	2.03 (1.00-4.08)	1.50

NOTE: Data are presented as mean ± SD.

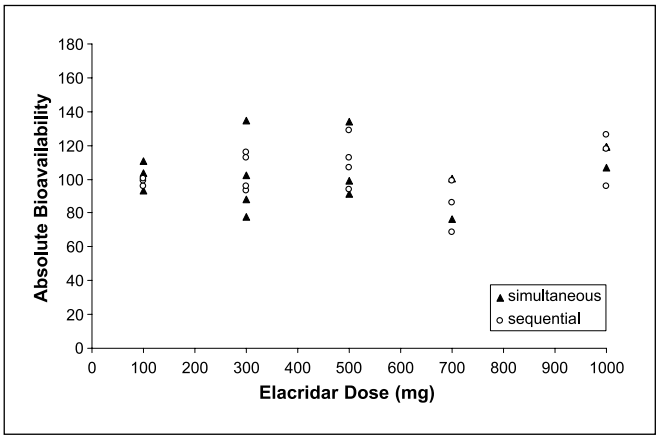

Fig. 2. Part I absolute apparent bioavailability of total topotecan versus dose elacridar simultaneously and sequentially administered.

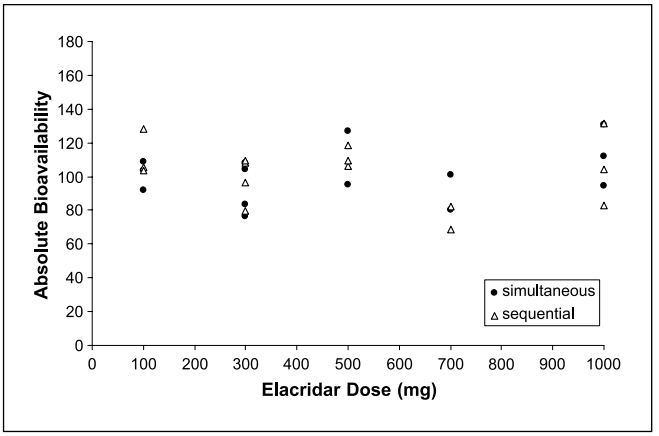

Fig. 3. Part I absolute apparent bioavailability of topotecan lactone versus dose elacridar simultaneously and sequentially administered.

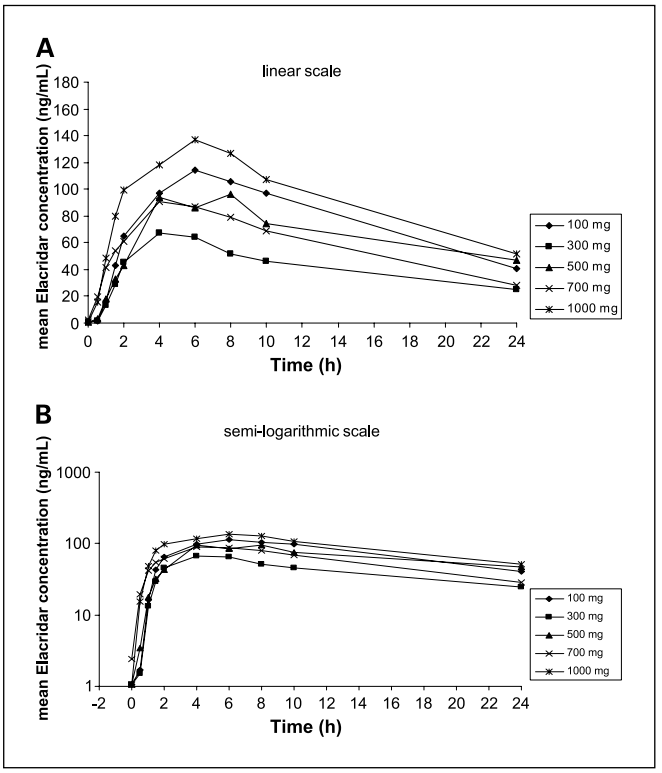

Fig. 4. *A,* part I linear and semilogarithmic plots of mean plasma elacridar concentration-time curve of simultaneous administration with topotecan. *B,* part I linear and semilogarithmic plots of mean plasma elacridar concentration-time curve of sequential administration with topotecan.

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