Anti-Cancer Drugs 1994, **5**, pp. 394–402

Phase I and pharmacokinetic studies of topotecan administered as a 72 or 120 h continuous infusion

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Topotecan (SK&F 104864-A, NSC 609699) is a water-soluble, semi-synthetic analog of camptothecin which is an inhibitor of topoisomerase I. Since topoisomerase I is cell specific for S phase, we undertook a phase I study to determine the maximum tolerated dose and toxicities of continuous infusion (CI) topotecan. This phase I trial first explored a 5 day CI every 21 day schedule. Doses of topotecan included 0.17, 0.34 and 0.68 mg/m^2/day. Fourteen patients [median age 60; median performance status (PS) of 1] with refractory malignancies received 59 courses of drug. Hematologic toxicities occurred only at the highest dose level; NCI grade 3–4 granulocytopenia and thrombocytopenia occurred in 4/8 and 3/8 patients, respectively. The protocol was amended to a 3 day infusion in an effort to ameliorate toxicity and obtain greater dose intensity (DI). Doses of 0.68, 0.85, 1.05, 1.3 and 1.6 mg/m^2/day were evaluated. Thirty-two patients (median age 60; median PS of 1) received a total of 115 courses. The major toxicity seen was hematologic with 9/32 and 5/32 patients demonstrating grade 3–4 granulocytopenia and thrombocytopenia, respectively. Non-hematologic toxicities were mild (grade 1–2) in the two schedules and included nausea, vomiting, fatigue and alopecia. At the maximum tolerated dose (MTD) on the 5 day schedule, patients received 0.87 mg/m^2/week, whereas they received 1.08 mg/m^2/week at the MTD on the 3 day schedule (24% increase in relative dose intensity). A steady-state plasma lactone concentration of 5.5 ng/ml of topotecan was achieved at the phase II recommended dose of 1.6 ng/m^2/day as a 3 day continuous infusion. Minor responses were seen in two patients with non-small cell lung cancer and three patients with ovarian cancer. In summary, a greater DI can be achieved with topotecan given on a 3 day schedule than on a 5 day schedule.

Key words: Phase I trial, pharmacokinetics, solid tumors, topotecan.

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Introduction

Topotecan (SKF 104864A; NSC 609699; (*S*)-9-dimethylaminomethyl-10-hydroxy-camptothecin hydrochloride) is a semisynthetic analog of camptothecin (agent derived from *Camptotheca acuminata*) which incorporates a stable basic side chain at the 9-position of the A-ring of 10-hydroxycamptothecin (Figure 1). The basic side-chain of topotecan affords water solubility of the compound without requiring hydrolysis of the E-ring lactone.

Topotecan was synthesized because clinical trials with sodium camptothecin in the late 1960s showed clinical activity but unpredictable and severe myelosuppression, gastrointestinal toxicity and hemorrhagic cystitis.[1–4] Compared with sodium camptothecin, topotecan has increased hydrophilicity[5,6] and therefore is expected to have decreased potential for bladder toxicity. Topotecan has also greatly reduced binding to plasma proteins.[7] Cellular pharmacology studies have shown the compound is a more selective inhibitor of topoisomerase I than is sodium camptothecin. Finally, topotecan has unequivocal systemic activity in mice bearing a broad spectrum of tumor models. It is highly effective against murine leukemias and colon carcinomas 38 and 51, Lewis lung carcinoma, and B16 melanoma, all of which are relatively refractory to sodium camptothecin.[8,9] Also, testing of topotecan in a human tumor cloning system revealed a broad spectrum of *in vitro* cytotoxic activity.[10]

Topotecan is known to undergo a reversible pH-dependent hydrolysis of the E-ring lactone (Figure 2); only the closed lactone form of the drug is active.[5,6] At pH levels below 7.0, the closed form of topotecan predominates. At pH 6.0, for example, the lactone accounts for more than 80% of the total compound.

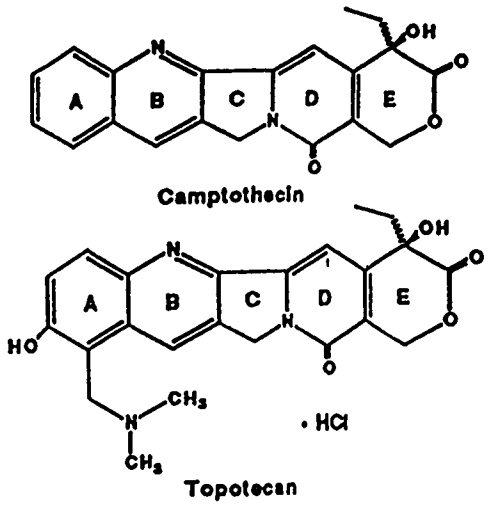

Figure 1. Structures of camptothecin and topotecan (SK&F 104864).

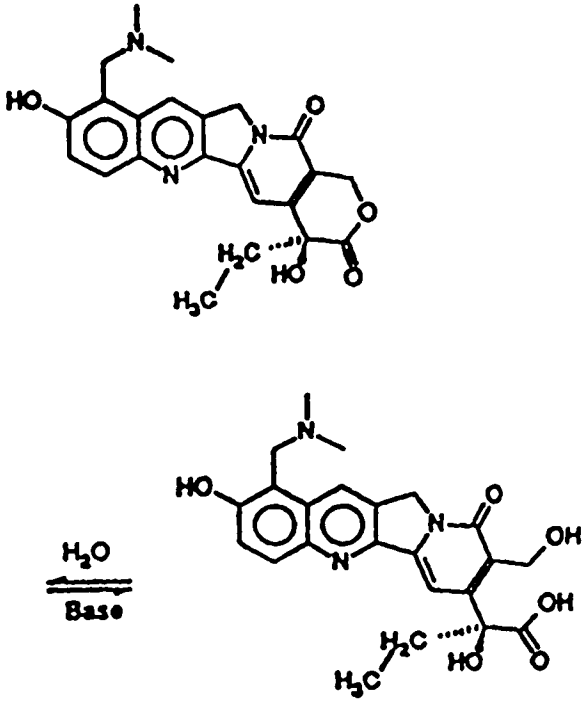

Figure 2. Hydrolysis reaction of topotecan from the lactone (closed) form of the molecule to the carboxylate (open) form of the molecule.

The mechanism of action of topotecan has been definitively shown to involve binding to topoisomerase I, stabilizing a covalent DNA–topoisomerase I complex, which results in DNA single-strand breaks.[11] After toxicology studies demonstrated acceptable toxicity in animals (reversible, dose-related toxicity to proliferating tissues such as bone marrow and gastrointestinal epithelium), topotecan advanced to phase I clinical trials.[12]

The purposes of these studies were (i) to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs) and recommended dose for efficacy trials of topotecan, when administered on a 5 or 3 day continuous infusion schedule; (ii) to characterize the pharmacokinetics/pharmacodynamics of topotecan; and (iii) to observe patients for antitumor activity.

The rationale for using a more prolonged clinical schedule of administration of topotecan is 3-fold in nature. Topotecan is a cell-cycle-specific cytotoxic drug[13,14] so brief exposure to this agent produces little or no cell kill and quiescent cells are refractory. Moreover, based on preclinical studies using human tumor colony-forming units *in vitro*, a more prolonged clinical schedule of administration of topotecan could improve the chances that the agent will have antitumor activity in patients.[10] Finally, when given by continuous infusion (CI), topotecan may have greater potency due to the presence of increased amounts of the active lactone form.

Materials and methods

Patient selection

All patients had a pathologically confirmed diagnosis of metastatic solid tumors refractory to all known forms of effective therapy as well as other investigational agents of higher potential efficacy. They also had a Southwest Oncology Group (SWOG) performance status of $\geqslant 2$ and an anticipated life expectancy of at least 12 weeks. Additional eligibility criteria included: white blood cell count of $\geqslant 3000$ cells/μl (granulocytes $\geqslant 1500$ cells/μl), platelets 100 000/μl, hemoglobin 10 g/dl, serum creatinine $\leqslant 1.5$ mg/dl and bilirubin $\leqslant 1.5$ mg/dl. Patients with a prior history of hemorrhagic cystitis, prior pelvic irradiation or urinalysis indicating greater than five red blood cells per high power field on microscopic examination were excluded. Patients must have been off previous anticancer therapy for at least 3 weeks (6 weeks if a nitrosourea or mitomycin C were used). All patients signed informed consent documents approved by the Institutional Review Board of the treating institution.

Study design

In this phase I trial, topotecan was first administered as a 5 day CI schedule but the protocol was amended to a 3 day infusion in an effort to ameliorate toxicity and obtain greater dose intensity (see below). A minimum of three patients were treated at each dose level of topotecan. Once NCI Common Toxicity Criteria grade ≥ 2 non-hematologic and/or grade ≥ 3 hematologic toxicity was observed, additional patients were treated to define the qualitative and quantitative toxicity of topotecan. Patients who tolerated topotecan without serious toxicity continued to receive the drug as long as their tumor remained stable or decreased in size. Patients with evidence of tumor progression were removed from the study. Patients were also removed from the study when they experienced life-threatening toxicity (defined by NCI Common Toxicity Criteria as grade 4 hematologic or grade 3 for any other organ system). Complete response was defined as a complete regression of all measurable disease. Partial response was defined as a > 50% reduction of the product of the two longest perpendicular diameters of the measurable lesions.

Drug administration

The lyophilized formulation of topotecan was supplied by the NCI as an injection, 5 mg vial (as the base) with 100 mg of mannitol. The pH was adjusted to 3.0 with HCl/NaOH. The drug, diluted in 500 ml of D5W (pH 4.3, range 3.5–6.5), was administered as a continuous infusion for five or three consecutive days and repeated every 21 days. Chemotherapy bags were changed every 24 h throughout the infusion period. In dogs receiving the daily × 5 schedule, a dose of 0.2 mg/m^2 caused some mild toxic effects. The daily × 5 bolus dose in patients ranged from 1.5 to 2.0 mg/m^2 and the total dose was 7.5–10 mg/m^2 over 5 days (median of 8.7 mg/m^2). Therefore, the starting dose for the 5 day CI schedule was 0.17 mg/m^2/day (8.7 mg/m^2 divided by 5 days = 1.7, divided by 10 or 1/50th of the current safe dose level in man). After 14 patients were treated, this daily × 5 protocol was amended to a 72 h (3 day) CI schedule due to dose-limiting myelosuppression with the daily × 5 schedule and in an effort to obtain greater dose intensity and ameliorate toxicity. The starting dose for the study with a 3 day CI schedule was 0.68 mg/m^2/day as this was the MTD on the 5 day CI schedule of topotecan. Subsequent doses were escalated using a modified Fibonacci scheme for the study with the 5 day CI schedule and using a 25% increase in dose on the 3 day CI schedule. For the first course of topotecan administration, all patients were hospitalized. Subsequent courses were administered to the patient, if possible, as an outpatient by an ambulatory infusion device. Patients returned weekly for physician visits to record history and physical examinations. Chemistry profiles, hemograms, urinalyses and stool specimens for occult bleeding were checked weekly. Chest X-rays were repeated prior to each cycle only if this area was a site of measurable disease; otherwise, they were done every other course of therapy. Tumor measurements were performed every two cycles.

Pharmacokinetics

Blood samples were obtained from selected patients at or close to the MTD during the 3 or 5 day infusion of topotecan at the end of infusion and 5, 15, 30, 60 and 120 min post-infusion. Each plasma sample was analyzed for the amount of topotecan existing in the lactone form and for total (lactone + carboxylate) by the previously described HPLC method.[15]

Results

Patient characteristics

A total of 46 patients were enrolled on the two schedules. The patient characteristics are outlined in Table 1. The majority of patients had received some form of prior therapy. Forty-three patients had a SWOG performance status of 0 or 1. All patients were evaluable for toxicity. A total of 174 courses of therapy were given on the two schedules; the median number of courses per patient was three (range 1–11) with the 5 day CI schedule and two (range 1–13) with the 3 day CI schedule. Table 2 indicates the number of patients entered at each dose level, the number of courses, the cumulative dose administered per patient (CD), the dose intensity (DI; CD divided by time in weeks) and finally the relative DI.

Toxicity

The MTD of topotecan given as an intravenous CI over 120 h every 21 days was 0.68 mg/m^2/day.

Table 1. Patient characteristics

Schedule	5 day CI	3 day CI
Patients entered	14	32
Male/female	6/8	19/13
Median age in years (range)	60 (48–74)	60 (35–76)
Performance status		
0	5	7
1	8	23
2	1	2
Prior therapy		
none	1	6
radiotherapy	2	0
chemotherapy	8	11
chemotherapy and radiotherapy	3	15
Primary tumors		
colorectal	5	4
lung (non-small cell)	3	15[a]
ovarian	4	4
carcinoid	1	0
unknown primary	1	0
pancreas	0	1
renal cell	0	2
prostate	0	2
breast	0	1
gastric	0	1
esophageal	0	1
skin	0	1

[a] One patient with small cell lung cancer.

Table 2. Courses and doses administered

Dose level (mg/m²/day)	No. of patients	Total no. of courses	Theoretical total dose per course (mg/m²)	Cumulative dose administered per patient (mg/m²) median (range)	DI (mg/m²/week) median (range)	Relative DI
5 Day CI						
0.17	3	16	0.85	4.25 (3.4–6.8)	0.27 (0.26–0.28)	—
0.34	3	5	1.7	3.4 (1.7–3.4)	0.48 (0.48–0.56)	—
0.68[a]	8	38	3.4	13.6 (5.9–37)	0.87 (0.72–1.13)	1
3 Day CI						
0.68	7	16	2.04	4.08 (2.04–8.16)	0.68 (0.51–0.68)	0.78
0.85	6[b]	16	2.55	7.65 (2.5–28.8)	0.81 (0.51–0.93)	0.93
1.05	5[c]	34	3.15	6.3 (3.1–47)	1.05 (1.05–1.12)	1.20
1.30	9[d]	43	3.9	11.7 (3.9–41)	1.06 (0.78–1.3)	1.22
1.60	5[e]	6	4.8	9.6 (4.8–16.5)	1.08 (0.91–1.37)	1.24

[a] Three patients received five courses with a dose reduction of 25% (dose = 0.51 mg/m²/day).
[b] One patient was dose escalated to 1.05 mg/m²/day (three courses) and to 1.3 mg/m²/day (three courses).
[c] Two patients were dose escalated to 1.3 mg/m²/day (10 courses).
[d] Five patients received 16 courses at dose level 1.05 mg/m²/day.
[e] Three patients received six courses at dose level 1.3 mg/m²/day.

Three dose levels were evaluated to reach this dose. Thrombocytopenia was the major DLT (granulocytopenia was also noted). Hematologic toxicities occurred only at the highest dose level (Table 3). NCI Common Toxicity Criteria grades 3 or 4 granulocytopenia occurred in four of eight patients treated with 0.68 mg/m²/day. An additional patient treated with 0.68 mg/m²/day experienced NCI grade 2 granulocytopenia. Thrombocytopenia was also frequent at the highest dose level. At 0.68 mg/m²/day, two patients had NCI grade 2 and three experienced NCI grade 4 thrombocytopenia. Three out of four patients with grade 4 hematological toxicity were dose reduced 25% to 0.5 mg/m²/day for course 2

Table 3. Topotecan: hematologic toxicities

	Dose level (mg/ml) at 5 day CI			Dose level (mg/ml) at 3 day CI				
	0.17	0.34	0.68	0.68	0.85	1.05	1.30	1.60
No. of patients	3	3	8	7	6	5	9	5
Neutrophil nadir[a]								
0 = ≤ 2.0	3	3	3	7	6	4	4	1
1 = 1.5–1.9	—	—	—	—	—	—	—	—
2 = 1.0–1.4	—	—	1	—	—	—	—	1
3 = 0.5–0.9	—	—	2	—	—	1	1	—
4 = < 0.5	—	—	2	—	—	—	4	3
Platelet nadir[a]								
0 = NL	3	3	3	7	6	5	5	2
1 = 75.0–NL	—	—	—	—	—	—	—	1
2 = 50.0–74.9	—	—	2	—	—	—	1	—
3 = 25.0–49.9	—	—	—	—	—	—	—	—
4 = < 25.0	—	—	3	—	—	—	3	2
Hemoglobin nadir[a] (g/dl)								
0 = NL	3	3	5	6	5	4	7	3
1 = 10.0–NL	—	—	—	—	—	—	—	1
2 = 8.0–10.0	—	—	1	1	1	1	1	1
3 = 6.5–7.9	—	—	1	—	—	—	1	—
4 = < 6.5	—	—	1	—	—	—	—	—

[a] Nadir value during any course of therapy.

and two of them experienced grade 2–3 hematologic toxicity.

When the protocol was amended to a 3 day infusion in an effort to ameliorate toxicity and obtain greater DI, doses of 0.68, 0.85, 1.05, 1.3 and 1.6 mg/m^2/day were evaluated. As in the 5 day schedule, the major toxicity seen was hematologic (Table 3) and 9/32 and 5/32 patients demonstrating NCI grades 3–4 granulocytopenia and thrombocytopenia, respectively. NCI grades 3–4 granulocytopenia occurred in five of nine patients treated with 1.3 mg/m^2/day and three of five treated with 1.6 mg/m^2/day. NCI grade 4 thrombocytopenia occurred in three of nine patients treated with 1.3 mg/m^2/day and two of five treated with 1.6 mg/m^2/day. Anemia was less severe and generally not dose related.

Seventeen of 46 patients received four or more courses of topotecan on the two schedules. In these patients, there was no evidence of cumulative hematologic toxicity during the course of this trial. The granulocyte nadirs typically occurred on days 10–14 and were of brief duration. There were no episodes of documented bacteremia during the neutropenic episodes. The eight patients who developed grade 4 thrombocytopenia required platelet transfusions of a total of 10 units of platelets during the nadir period.

The assessment of prior treatment on the incidence of hematologic toxicity was analyzed in 22 patients (eight in the 5 day schedule at 0.68 mg/m^2/day, and 14 in the 3 day schedule at 1.3 and 1.6 mg/m^2/day) by dividing patients into two groups: (i) patients with no prior treatment or two or fewer prior chemotherapy regimens or one regimen plus radiotherapy and (ii) patients with more than two prior chemotherapy regimens or two regimens plus radiotherapy. The extent of prior treatment did not predict the severity of myelosuppression resulting from topotecan ($p = 0.2$, Fisher exact test). Nonhematologic toxicities were mild (grade 1 or 2) and generally not dose related (Table 4). Mild nausea occurred in the majority of patients. Other toxicities were vomiting, diarrhea, fatigue/malaise and alopecia. Of note, macroscopic hematuria was not observed, but four out of 46 patients (9%) experienced microscopic hematuria. This event was not dose related and was felt to be unrelated to topotecan administration.

Pharmacokinetic results

We found that for those patients receiving 0.68 mg/m^2 of topotecan by 120 h CI, steady-state plasma lactone concentrations were below the limit of assay detection (2 ng/ml). However, when topotecan was administered by CI over 3 days at doses of 1.3 and 1.6 mg/m^2/day, steady-state lactone levels of 3.7 and 5.5 ng/ml were obtained, respectively. The lac-

Table 4. Topotecan: non-hemtologic toxicities

Type	No. of patients[a] (n = 46)	Percentage of patients
Gastrointestinal toxicities (grade 1–2)		
nausea	40	87
vomiting	24	52
diarrhea	7	15
Miscellaneous toxicities (grade 1–2)		
fatigue	12	26
fevers (low grade)	8	17
alopecia	8	17
malaise	5	11

[a] Toxicities in the two schedules (3 and 5 day).

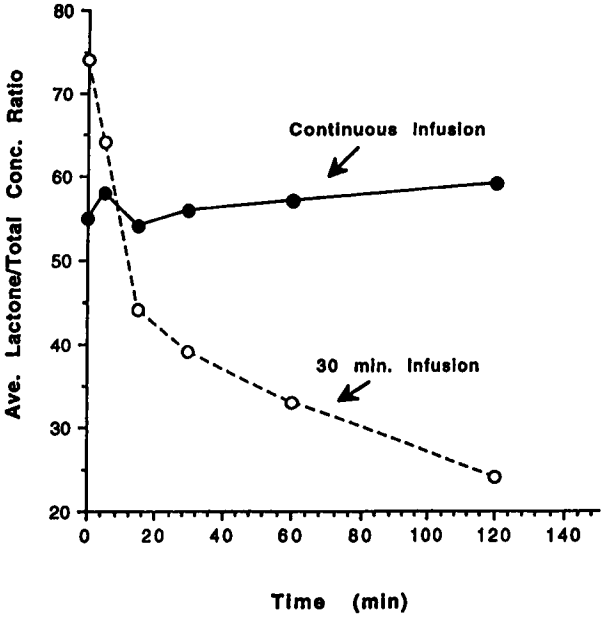

Figure 3. Representative curves of average lactone to total concentration ratios of 30 min and CI schedules versus time.

tone-to-total concentration ratio at steady-state averaged 59 ± 8%, indicating that the lactone was the predominant form during infusion. An additional observation was made by visual inspection of the plasma concentration versus time curves. From the end of infusion out to 120 min past infusion, the rate of decline of the lactone appeared to be slower by the continuous route infusion schedule, compared to our previous 30 min infusion schedule.[16] We, therefore, randomly selected two patients who previously received topotecan on the 30 min infusion schedule at doses of 17.5 and 22.5 mg/m^2, and compared the average lactone to total concentration ratios versus time to two patients treated with 1.3 and 1.6 mg/m^2/day of topotecan on the 3 day CI schedule. Figure 3 depicts the results of this comparison.

Responses

No patients met the standard criteria for partial or complete response. Some suggestion of anticancer activity was observed in five patients. Disease stabilization was noted in two patients with non-small cell lung cancer (duration: 9 and 16 months) and three patients with ovarian cancer (duration: 3, 5 and 6 months). All patients had failed platinum-containing regimens. Periods of disease stabilization were seen in other patients as well.

Discussion

Topotecan is a specific inhibitor of DNA topoisomerase I. In this phase I trial, topotecan was administered by CI, with a 5 day CI every 21 day schedule evaluated first. Doses of topotecan included 0.17, 0.34 and 0.68 mg/m^2/day. The most DLT was thrombocytopenia (granulocytopenia was also noted). Anemia and non-hematologic toxicities were mild and easily managed. The MTD was 0.68 mg/m^2/day in moderately pretreated patients. The median period between courses was 23 days (range: 20–42). The protocol was amended to a 3 day infusion in an effort to ameliorate toxicity and obtain greater dose intensity. Doses of 0.68, 0.85, 1.05, 1.3 and 1.6 mg/m^2/day were evaluated. The major DLTs were thrombocytopenia and granulocytopenia, especially at the two highest dose levels. The median period between treatment courses was 21 days (range: 19–42).

Table 2 shows that a greater DI can be achieved with topotecan given on a 3 day schedule than on a 5 day schedule. In fact, at the MTD on the 5 day schedule, patients only received 0.87 mg/m^2/week (range: 0.72– 1.13; 92% of projected DI), whereas they received 1.08 mg/m^2/week (90% of projected DI) at the MTD on the 3 day schedule (increase in relative DI of 24%). Compared with the 5 day CI, patients on the 3 day CI received fewer cycles, possibly due to early withdrawal resulting from disease progression, death or toxicity.

Table 5 summarizes the published pharmacokinetic parameters for topotecan given as a CI schedule in other studies.[17-23] A steady-state plasma lactone concentration of 5.5 ng/ml of topotecan was achieved at the phase II recommended dose of 1.6 mg/m^2/day as a 72 h infusion. The interesting

Table 5. Topotecan: pharmacokinetic parameters (continuous infusion schedule)

Schedule	$t_{1/2}$ β (h)	Clearance (l/h/m^2)	C_p, ng/ml (dose, mg/m^2/day)	Reference
24 h CI q 21 days	8.0	—	20	17
24 h CI weekly[a]	4.9	10.8	7 ± 1.8 (1.5)	18
24 h CI q 21 days[b,c]	2.4	26.5	30.7[d] (7.5)	19
72 h CI[c]	3 ± 0.8	20.9 ± 10.6	3.6 (1.9)	20
24 h CI q 21 days	5.2	27.9	4–10[b]	21
24 h CI q 21 days[b,e]	4.3	29	—	22
21 d CI q 28 days[b]	—	—	4.4 ± 0.09 (0.53)	23

[a] Topotecan (lactone + open forms).
[b] Topotecan lactone.
[c] Pediatric patients.
[d] nM.
[e] Granulocyte colony stimulating factor given 24 h after the completion of the topotecan infusion.

observation of the slower rate of conversion of the lactone ring to the open carboxylate form of topotecan post the 72 h infusion compared with the 30 min infusion schedule is intriguing. Further examination of this phenomenon is necessary to determine whether this could represent some type of equilibrium between the closed (lactone) and open (carboxylate) forms of topotecan.

Table 6 summarizes the additional phase I trials, utilizing different CI schedules.[17–28] Beran *et al.*[25] gave topotecan as a 5 day CI in patients with refractory acute leukemia. Mucositis was the DLT at the MTD of 2.0 mg/m^2/day. Five responses were observed in 27 patients. Saviers *et al.*[26] described their experience administering topotecan as a 3 day CI on a weekly or every 2 week schedule in patients with solid tumors. The DLT was myelosuppression. Pratt's group[27] treated 21 pediatric patients using a 3 day CI schedule and observed one complete remission (neuroblastoma). Hochster *et al.*[23] enrolled 33 patients, using topotecan administered as a 21 day CI repeated every 28 days. They observed one partial response in a patient with non-small cell lung cancer and one minor response in a patient with breast cancer. Eleven patients had stabilization of their disease. Finally, Plaxe, *et al.*[28] gave topotecan as a 24 h intraperitoneal CI to patients with a variety of tumor types including refractory ovarian cancer. The MTD was 4 mg/m^2. Interestingly, they observed reduction of ascites in five patients. Overall, myelosuppression was the DLT in all CI schedules with the exception of the study in acute leukemia,[25], where mucositis was the DLT.

In the present study, thrombocytopenia was the main DLT. In the 3 day schedule, 1.6 mg/m^2/day was considered the MTD. The recommended dose for phase II studies is 1.6 mg/m^2/day. This schedule and dose gave the greatest DI.

To date, four phase II studies of topotecan utilizing different schedules of administration are published in abstract form. Interestingly, there were four partial responses and 17 stable diseases in 28 patients with ovarian cancer who had failed platinum-containing regimens.[29] In hormonal-resistant prostate cancer, Giantonio *et al.* observed one partial response in 28 patients.[30] In advanced renal cell carcinoma, Ilson reported only two minor responses in 15 patients without prior chemotherapy.[31]. Finally, Janik *et al.* reported preliminary data from a randomized study in previously untreated renal cell carcinoma and melanoma using topotecan and granulocyte macrophage colony stimulating factor. In 24 evaluable patients, they observed a complete resolution of pulmonary nodules in one patient but no response in his primary renal tumor. However, the primary tumor was surgically resected and the patient was rendered disease free for 6 months.[32]

Combinations containing topotecan (i.e. topotecan + VP-16 or cisplatin) are under investigation.[33–35] The rationale for combining topoisomerase I and II inhibitors is the synergism observed *in vitro* and *in vivo* when the drugs are given sequentially. This is probably due to upregulation of cellular topoisomerase II levels which have been found to increase 24–48 h after exposure to a topisomerase I inhibitor. The combination of topotecan and cisplatin is promising due to non-overlapping toxicities and the potential for topotecan to interfere with DNA repair, the major cause for cisplatin resistance.

Table 6. Topotecan: phase I studies (CI schedule)

Reference	Schedule	No. of patients	Dose (mg/m^2/day)				DLT (other toxicities)	Anti-neoplastic activity (tumor type)
			lowest	highest	MTD	RDPII		
17	24 h CI q 21 day	22	2.5	10.5	8.4	—	neutropenia and thrombocytopenia (alopecia, N/V, anemia)	none
24	24 h CI q 21 days	15	1.9	5.0	4 (HP)	—	neutropenia and thrombocytopenia (N/V)	none
22[a]	24 h CI q 21 days	13	10	15	15	—	thrombocytopenia	none
19[b]	24 h CI q 21 days	29	2.0	7.5	5.5	—	neutropenia and thrombocytopenia	none
18	24 h CI weekly	26	1.0	2.0	1.75	1.5[c]	neutropenia	1 PR (colon)
25[d]	120 h CI q 21–28 days	27	0.6	3.6	2.0	—	mucositis (myelosuppression, N/V, diarrhea)	3 CR + 2 PR[d]
26	72 h CI weekly	12	—	—	2.0[e]	2.0[e]	myelosuppression (alopecia, fatigue, nausea	
26	72 h CI q 14 days	7	—	—	> 2.6	—	myelsuppression	—
21	24 h CI q 21 days	13	2.5	5.0	5.0	—	neutropenia (alopecia)	none
27[b]	72 h CI	21	0.75	1.9	1.0	—	myelsuppression	1 CR (neuroblastoma)
23	21 days CI q 28 days	33	0.2	0.53	NR	—	NR	1 PR (NSCLC) 1 MR (breast); 11 SD
28	24 h CI i.p. q 28 days	12	3.0	4.0	4.0	3.0	myelsuppression	reduction of ascites (5 patients)

[a] Granulocyte colony stimulating factor (5 μg/kg/day) 24 h after the completion of the topotecan infusion.
[b] Pediatric patients.
[c] mg/m^2/week.
[d] Patients with refractory and relapsed acute leukemia.
[e] 2.0 mg/m^2/72 h.
RDPII, recommended dose for phase II; N/V, nausea/vomiting; HP, heavily pretreated; PR, partial response; CR, complete response; NR, not yet reached; NSCLC, non-small cell lung cancer; MR, mixed response; SD, stable disease.

Based on all the data described above, we recommend the phase II clinical evaluation of topotecan administered as a 3 day CI, especially for patients with leukemia, neuroblastoma, and in lung (non-small cell), ovary, colon, breast, and renal carcinoma. A prolonged infusion schedule (e.g. 21 day CI) is also an interesting possible schedule that needs further evaluation.

Acknowledgments

The authors gratefully acknowledge the expert assistance of Laida Garcia and Alice Louise Goodwin in preparing the manuscript for publication.

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(Received 7 March 1994; accepted 7 April 1994)