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Camptothecin analogues: studies from The Johns Hopkins Oncology Center

William J. Slichenmyer, Eric K. Rowinsky, Louise B. Grochow, Scott H. Kaufmann, Ross C. Donehower

The Johns Hopkins Oncology Center, 600 North Wolfe Street, Baltimore, MD 21287, USA

Abstract. The camptothecin analogues topotecan and irinotecan (CPT-11) are active anticancer drugs. This article reviews the accumulated results of clinical and laboratory studies performed with these agents at The Johns Hopkins Oncology Center. In a phase I clinical and pharmacology trial of topotecan given as a 30-min infusion daily for 5 days every 3 weeks, profound neutropenia precluded dose escalation above 1.5–2.0 mg/m^2 per day, the maximum tolerated dose (MTD). The daily $\times 5$ schedule has been developed further with dose escalation using granulocyte-colony-stimulating factor support in patients who have kidney or liver dysfunction and given in combination with cisplatin. In addition, a phase I trial of topotecan given as a 5-day continuous intravenous infusion to patients with refractory leukemia has had promising antileukemic responses. A separate series of in vitro studies indicates that a modest degree of resistance to the cytotoxicity of topotecan can be mediated by P-glycoprotein. A phase I and pharmacology study of irinotecan given as a 90-min infusion every 3 weeks has defined an MTD of 240 mg/m^2, with dose escalation being limited by several toxicities. These included an acute treatment-related syndrome of flushing, warmth, nausea, vomiting, and diarrhea; a subacute combination of nausea, diarrhea, anorexia, and weight loss; and/or neutropenia. Antitumor activity has been observed with topotecan and irinotecan in patients with a variety of solid tumors and refractory leukemia in our studies, which supports the widespread enthusiasm for this group of compounds.

Key words: Topoisomerase I – Camptothecin – Cancer chemotherapy

Introduction

Camptothecin (CPT) is an antitumor drug derived from an extract of the Chinese tree *Camptotheca acuminata* [28]. After early clinical trials in the 1970s met with unpredictable and severe toxicity, further development of CPT was abandoned until identification of the nuclear enzyme topoisomerase I as the target of camptothecin [8]. This finding, coupled with the development of the water-soluble CPT analogues topotecan [12] and irinotecan (CPT-11) [14], has led to renewed interest in the clinical development of this class of agents. Some clinical and preclinical features of these drugs have been reviewed elsewhere [1, 26].

This article reviews the experience at The Johns Hopkins Oncology Center with topotecan and irinotecan. In addition to pharmacology and clinical phase I studies of topotecan in patients with solid tumors and leukemia, the development of the combination of topotecan with cisplatin is described, as are a series of in vitro experiments that examine the role of P-glycoprotein in mediating resistance to topotecan. Studies with irinotecan have been limited to a single phase I trial of the drug given as a single dose on an every-3-week schedule. These studies have revealed a rich pharmacology for these compounds. Topotecan exists in a dynamic equilibrium between a less potent hydroxy-acid and an active lactone form. Irinotecan is a prodrug that is metabolized to the active agent SN-38. Both irinotecan and SN-38 exist in the forms of a less potent hydroxy-acid and an active lactone species. In defining the pharmacokinetic and pharmacodynamic relationships of these drugs, all species need to be considered.

Topotecan

Initial phase I clinical trial with the daily $\times 5$ schedule

Topotecan was given to patients bearing refractory solid tumors as a daily 30-min infusion for 5 consecutive days repeated in a cycle of 3 weeks. Patients enrolled in the study had an Eastern Cooperative Oncology Group

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Correspondence to: William J. Slichenmyer

(ECOG) performance status of ≤2, an absence of serious comorbid conditions, and normal bilirubin and creatinine levels [21]. The starting dose was 0.5 mg/m² per day, which is equivalent to 1/30 of the dose inducing 10% lethality (LD_{10}) in mice. Plasma samples for pharmacokinetic analysis were obtained from each patient on day 1 and day 5 during the first cycle of treatment. Total and lactone species of topotecan were measured by high-performance liquid chromatography (HPLC). Patients received treatment until disease progression or intolerance of side effects.

A total of 29 patients received 161 courses of therapy (median, 3 courses/patient). The dose levels studied were 0.5, 1.0, 1.5, 2.0 and 2.5 mg/m² per day. The dose-limiting toxicity was neutropenia, which was frequent, brief, well tolerated, and noncumulative. Occasional thrombocytopenia was observed. In all, 22 treatment cycles were complicated by anemia of sufficient severity to require transfusion. This anemia began 5–8 days after the start of treatment, raising the possibility that topotecan induced hemolysis. However, laboratory evidence of hemolysis was not observed, and the etiology of this phenomenon remains unknown. Mild diarrhea occurred in ten patients, and mild treatment-associated nausea and vomiting were also occasionally seen. Alopecia that was dose-related and cumulative affected most of the patients. The maximum tolerated dose (MTD) was 1.5 mg/m² per day, but several patients tolerated 2.0 mg/m² per day without developing dose-limiting toxicity. The recommended dose for phase II studies was 1.5 mg/m² per day, with escalation to 2.0 mg/m² per day being carried out in patients who tolerated the lower dose. Other phase I studies of topotecan using this schedule have reached similar conclusions regarding the MTD and dose-limiting toxicity [25, 27]. Antitumor activity was observed in one patient with ovarian carcinoma [partial response (PR)] and in four of seven patients with non-small-cell lung cancer [one complete response (CR), two PRs, and one minor response (MR)].

Pharmacokinetic data for total topotecan and the lactone species are shown in Table 1 [5]. For the lactone form, the mean alpha and beta half-lives were 5.7 and 110 min, respectively. The mean volume of distribution was 26 l/m², and the mean clearance rate was 1220 ml min⁻¹ m⁻². For total topotecan, the mean alpha and beta half-lives were 4.1 and 173 min, respectively. The mean volume of distribution was 25 l/m², and the mean clearance rate was 493 ml min⁻¹ m⁻². A mean of 39% of the total dose was excreted in the urine over 24 h. These parameters appeared to be linear over the dose ranges studied. Topotecan lactone and hydroxy-acid are in dynamic chemical equilibrium favoring the less potent hydroxy-acid form at physiologic pH; as expected, the proportion of total drug existing in the lactone form decreased over time from approximately 50% at the end of the infusion to <20% at 18 h. When prepared in D5 W at pH 4.7 in the clinical formulation, 6%–16% of the dose was delivered as the hydroxy-acid. A wide interindividual variation existed in clearance rates, but there was no consistent change in pharmacokinetic parameters from day 1 to day 5. The relationship between the percentage of fall in the absolute neutrophil count (ANC) and either the delivered dose or the total topotecan area under the concentration-time curve (AUC) was described by a sigmoidal

Table 1. Pharmacokinetic parameters for topoisomerase I inhibitors

Parameter	Topotecan (lactone)	Topotecan (total)	Irinotecan (total)
Clearance (ml min⁻¹ m⁻²)	1220	493	352
Elimination $t_{1/2}$ (h)	1.8	2.9	5.2
VD (l/m²)	26	25	148
Urinary excretion (%)	–	39	37

VD, Volume of distribution

Table 2. Effect of G-CSF schedule on myelosuppression in patients treated with topotecan[a]

G-CSF schedule	Courses given (*n*)	Mean ANC nadir (mm³)	Mean platelet nadir (mm³)
None	46	735	153
Day 1	10	375	72
Day 6	6	2331	149

ANC, Absolute neutrophil count
[a] Topotecan 2.0 mg/m² daily ×5 [22]

E_{max} function. This pharmacodynamic correlation with the topotecan dose or the total drug AUC, but not with the lactone AUC, suggests that both the lactone and the hydroxy-acid species contribute to myelosuppression, probably due to conversion of the latter species to active lactone. Similar results have been reported from other centers [25, 27].

Dose escalation with granulocyte-colony-stimulating factor

Given the encouraging clinical antitumor activity as well as a preclinical dose-response relationship and lack of serious nonhematologic side effects, doses were escalated with granulocyte-colony-stimulating factor (G-CSF) as support [22]. The initial results obtained with this strategy are shown in Table 2. In addition to determining the MTD and dose-limiting toxicities (DLTs) for topotecan on this administration schedule, a secondary aim of the study was to evaluate the optimal schedule of G-CSF administration. At this studys first dose level, G-CSF was given in a subcutaneous dose of 5.0 μg/kg daily starting concurrently with topotecan (beginning on day 1). At the 2.0-mg/m² daily dose level, patients treated with concurrent G-CSF had significantly worse neutropenia and thrombocytopenia than patients who did not receive G-CSF. However, when G-CSF was begun after the completion of topotecan administration (starting on day 6), the depth and duration of neutropenia were diminished. Therefore, further dose escalations of topotecan have continued with G-CSF beginning on day 6. To date we have observed only sporadic nonhematologic toxicity and thrombocytopenia that has not been dose-limiting. The study continues to accrue patients at topotecan doses of 4.2 mg/m² per day. The G-CSF schedule has had no effect on topotecan pharmacokinetics. For unexplained reasons, these results are dissimilar from those reported from a comparable trial performed at Memorial Sloan-Kettering Cancer Center, where dose-limiting fatigue and severe thrombocytopenia requiring platelet

transfusion occurred in three of four patients treated at the 2.0-mg/m^2 daily dose level [25].

Pharmacokinetics in patients with renal or hepatic dysfunction

Previous studies had shown that a mean of 39% of a dose of topotecan was recovered from the urine. Significant quantities of the drug have also been identified in bile [13], suggesting that both renal and hepatic mechanisms play a role in the clearance of topotecan. To gain a better understanding of topotecan clearance and to provide guidance for the dosing of topotecan in patients with impaired liver or kidney function, a phase I and pharmacology study of topotecan given on the daily $\times 5$ schedule has been initiated in patients with hepatic or renal dysfunction [6]. Eligibility criteria include diagnosis of a refractory solid tumor, adequate hematopoietic function, and renal insufficiency (creatinine clearance, <60 ml/min) or hyperbilirubinemia (serum total bilirubin, >1.5 mg/dl), but not both. A control group of patients with normal hepatic and renal function has also been included. The patients with renal insufficiency have been stratified on the basis of the creatinine clearance (≤ 20, 21–40, or 41–60 ml/min), and these five different groups (three with renal dysfunction, one with hepatic dysfunction, and one control) have been treated separately for dose escalation and toxicity evaluation.

Toxicity data for the first 20 patients are shown in Table 3. As expected, the control patients experienced significant neutropenia at the recommended phase II dose level, 1.5 mg/m^2 per day. The patients with abnormal hepatic function have experienced only very mild myelosuppression at the 0.5- and 1.0-mg/m^2 daily dose levels. In contrast, unexpectedly severe neutropenia has been observed in the patients with moderate to severe renal insufficiency at the 0.5-mg/m^2 daily dose level. For patients with creatinine clearance of <40 ml/min, the MTD appears to be 0.5 mg/m^2 per day. Extreme caution must be used in treating patients with more profound renal insufficiency. Thrombocytopenia has been significant for some of these patients but has not been seen in the absence of neutropenia. Nonhematologic toxicity has been mild and similar to that described for patients with normal renal and hepatic function.

Table 3. Neutropenia induced by topotecan in patients with hepatic or renal dysfunction

Patient dysfunction group	Topotecan dose (mg/m^2 per day)	Incidence per total treated: Cycles associated with grade 3–4 neutropenia (*n*)	Incidence per total treated: Patients with dose-limiting neutropenia (*n*)
Renal:			
Mild	0.5	2/12	0/2
Moderate	0.5	3/8	2/3[a]
Severe	0.5	2/4	1/2[a]
Hepatic	0.5	5/11	0/5
	1.0	3/5	1/3
Control	1.5	19/23	2/4

[a] MTD

Preliminary pharmacokinetic analysis suggests that the clearance of total topotecan is proportional to the creatinine clearance. The elimination half-life is inversely proportional to the creatinine clearance. Hyperbilirubinemia does not significantly affect the toxicity or disposition of topotecan at these doses. This study continues to accrue patients.

Combined topotecan and cisplatin

Preclinical studies had suggested a schedule-dependent synergistic cytotoxicity for the combination of topotecan with cisplatin ([9–11]; D. Peereboom, personal communication). A phase I and pharmacokinetics trial at Johns Hopkins has been testing these agents in combination and the hypothesis that the toxicity induced by this combination is schedule-dependent. Patients have been receiving topotecan on the daily $\times 5$ schedule along with a single dose of cisplatin on day 1 or day 5. The sequence of drug administration (cisplatin on day 1 or cisplatin on day 5) is alternated with each new patient at each dose level and with each successive course in individual patients. Preliminary results suggest that treatment with cisplatin before topotecan produces more myelosuppression than treatment with cisplatin following topotecan. Coadministration of cisplatin has not affected topotecan clearance in the patients studied to date [24]. Studies from other institutions [17, 20] have also observed severe neutropenia when topotecan is given on a daily $\times 5$ regimen in combination with cisplatin on day 1.

Continuous infusion for 5 days in patients with leukemia

A total of 17 adults with refractory or relapsed acute leukemia have been treated with topotecan by continuous intravenous infusion for 120 h (Rowinsky et al., manuscript in preparation). On this schedule, the MTD is 2.1 mg/m^2 per day and mucositis is the dose-limiting toxicity. Other toxicities have included mild nausea, vomiting, and skin rash. Thus far, all of the patients have had substantial reductions in the number of circulating blasts after treatment. One CR and one PR response have been observed in heavily pretreated patients with chronic myelocytic leukemia (CML) in blast crisis and acute myeloblastic leukemia (AML), respectively.

Several laboratory studies were performed in conjunction with this leukemia study. The topotecan dose lethal to 90% (LD_{90}) of leukemic colony-forming units (CFU-L) over a 5-day period of exposure ex vivo (6–22 n*M*) overlapped with the steady-state concentrations of topotecan (8.5–38 n*M*) observed. The content of topoisomerase I protein in blasts obtained from different patients varied widely and did not correlate with the antileukemic response.

In vitro study of resistance to topotecan mediated by P-glycoprotein

Resistance to the cytotoxic effects of anticancer drugs is often mediated by P-glycoprotein, a plasma-membrane efflux pump. The susceptibility of topotecan to P-glyco-

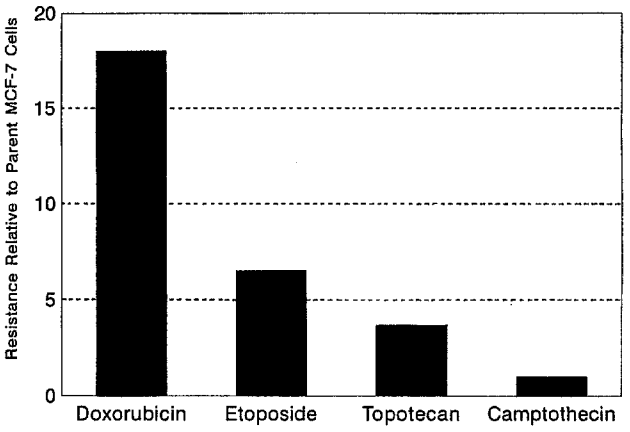

Fig. 1. Reversal of drug resistance in MCF-7/Adria cells, which express P-glycoprotein (after [7])

protein-mediated resistance has been examined in a variety of cell lines [7]. Results obtained in human breast-cancer cell lines are summarized below to illustrate the role of this resistance mechanism.

The MCF-7/Adria breast-carcinoma line expresses P-glycoprotein and is resistant to doxorubicin as compared with the parental MCF-7 line, which does not express P-glycoprotein. Modulators of P-glycoprotein function increased the accumulation of topotecan 3-fold in MCF-7/Adria cells but had no effect on topotecan accumulation in MCF-7 cells. Cytotoxicity studies revealed that these modulators decreased the 50% inhibitory concentration (IC_{50}) for topotecan by a factor of 3.6, that for etoposide by a factor of 6.5, and that for doxorubicin by a factor of 18 but had no effect on the IC_{50} for camptothecin in the MCF-7/Adria cell line, a drug to which the cells had maintained sensitivity (Fig. 1).

Similar results have been observed in other cell lines that overexpress P-glycoprotein, including $CH^{R}C5$ Chinese hamster ovary cells [7, 16], KG1a human leukemia cells [7], and HeLa-derived KB-V1 cells [2]. In each case, topotecan was observed to be modestly susceptible to P-glycoprotein-mediated efflux. The magnitude of these effects was much smaller than that obsrved for doxorubicin or etoposide but greater than that noted for camptothecin, which is unaffected by P-glycoprotein [2, 7, 18].

Irinotecan

A phase I and pharmacology study of irinotecan has recently been completed at Johns Hopkins [23]. A 90-min infusion of the drug was given every 21 days to patients with refractory solid tumors. The starting dose was 100 mg/m^2, a dose shown to be well tolerated in prior studies in Japan. Plasma samples for pharmacokinetic analysis were obtained from each patient with the initial course of treatment. Total irinotecan, its potent metabolite SN-38, and lactone forms of the parent drug and SN-38 were quantitated by HPLC. Treatment continued until progression of disease or development of intolerable side effects.

A total of 144 cycles of irinotecan were given to 32 patients (median, 3 cycles/patient). The dose levels studied were 100, 150, 200, 240, 290 and 345 mg/m^2. Both, the MTD and the recommended phase II dose were 240 mg/m^2. A variety of toxicities were considered dose-limiting, including diarrhea, nausea and vomiting, and neutropenia. The diarrhea in some patients became progressively more severe with repeated doses of irinotecan; in one patient the severity decreased after treatment with octreotide. A syndrome of flushing, diarrhea, and vomiting had onset during the infusion of irinotecan. This responded well to treatment with diphenhydramine, which was added to ondansetron as a premedication regimen for patients treated at higher doses. At the two highest dose levels, premedication did not prevent the flushing and vomiting syndrome. Neutropenia was generally brief, with the ANC nadir occurring around days 8–12. It was the dose-limiting toxicity in 3 of 13 patients treated at a dose of 240 mg/m^2. One patient treated at 240 mg/m^2 developed dose-limiting thrombocytopenia. Other toxicities observed in this study included complete alopecia and mild mucositis. Brief partial responses were observed in three patients with colorectal, cervical, and renal cell carcinoma, respectively. Three other patients with colorectal carcinoma had minimal responses. Combined marrow and gastrointestinal toxicity has been reported in other trials with irinotecan [3, 4, 19].

The pharmacokinetic parameters for total irinotecan derived from this study are depicted in Table 1. The data were fit to a two-compartment model with a mean alpha half-life of 5 min and a mean beta half-life of 3.9 h. The mean clearance rate was 352 ml min^{-1} m^{-2} and appeared linear over the dose range studied. The mean steady-state volume of distribution was 148 l/m^2. On average, 37% of each dose was recovered in the urine as irinotecan or SN-38. The extent of conversion of irinotecan to its active metabolite SN-38 varied widely among individuals, and the AUCs for SN-38 were between 2% and 8% of the AUCs for irinotecan. Approximately 50% of the SN-38 existed in the lactone form. Correlations were evaluated between measures of irinotecan and SN-38 exposure [peak plasma concentration (C_{max}), concentration at 24 h (C_{24}) and area under curve (AUC)] and measures of toxicity. The best relationship fit the percentage of fall in ANC against a sigmoidal E_{max} function of AUC for total SN-38. No relationship was apparent between gastrointestinal toxicity and pharmacokinetic parameters.

Future directions

These phase I trials have demonstrated encouraging signs of antitumor activity for both topotecan and irinotecan. The results of current phase II trials with topotecan at the Johns Hopkins Oncology Center (cancers of the ovary and pancreas) and in several other centers will be eagerly awaited. Phase II testing of combined topotecan and cisplatin may be worthwhile, especially in lung, ovary and other tumor types. The 120-h continuous infusion of topotecan should be further tested in the acute leukemias and considered for solid-tumor patients as well. Ongoing studies of topotecan with G-CSF and in patients with organ dysfunction may provide other insights for future exploration. Combination of topotecan with other cytotoxic drugs or biologic response modifiers may also prove beneficial.

Phase II testing of irinotecan in Japan has also shown encouraging activity in a variety of malignancies (reviewed in [1, 26]). These results should be confirmed and further explored around the world. Combinations of irinotecan with other drugs may also improve the efficacy and lead to improved survival for patients with cancer. These studies have initially focused on cisplatin and topoisomerase II inhibitors such as etoposide.

This class of compounds remains one of considerable interest to clinical investigators around the world. Several new agents have also recently entered the clinic and may add to the potential for these drugs if they have unique characteristics. Further studies conducted during the next few years should define the role of these agents in cancer therapy.

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