Effective Schedules of Exposure of Medulloblastoma and Rhabdomyosarcoma Xenografts to Topotecan Correlate with in Vitro Assays

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ABSTRACT

The camptothecin derivative topotecan has been postulated to mediate its antitumor effect through a drug-induced increase in covalent topoisomerase I-DNA complexes. If this hypothesis is correct, then schedules of exposure to topotecan that maximize the number of topoisomerase I-DNA complexes should produce the greatest cytotoxicity. We identified schedules of exposure to topotecan that maximize levels of complexes in vitro and used these schedules to postulate effective schedules of exposure in vivo in a mouse xenograft model.

Unexpectedly, K+ SDS precipitation assays quantitating covalent topoisomerase I-DNA complexes showed that Daoy medulloblastoma and Rh30 rhabdomyosarcoma cells became refractory to drug-induced increases in complexes after an 8-h exposure to 2.5 μM topotecan. In contrast, assays using 10–50 nM topotecan showed that the cells did not become refractory, and more importantly, intermittent exposure to drug increased the level of complexes ~2-fold above the maximum level observed after a single drug exposure. The data indicate that continuous exposure to topotecan does not maximize topoisomerase I-DNA complexes and suggest that effective intermittent schedules of exposure to topotecan might be identified. Growth inhibition assays confirmed this hypothesis and showed that growth inhibition by topotecan was extremely schedule dependent in Rh30 cells but not in Daoy cells. Xenograft studies showed that schedules modeled after the in vitro experiments produced complete tumor regressions in mice. Topotecan given daily (0.6–2.2 mg/kg) or every other day (1–3.3 mg/kg) for 2 weeks, repeated every 21 days for three cycles, produced complete regressions of Daoy xenografts; however, daily exposure was required to achieve complete regressions of Rh30 xenografts. We conclude that effective intermittent schedules of exposure to topotecan, based on biochemical parameters, can be identified. The clinical utility of each schedule will depend on the relative antitumor effect compared to the toxic effect on the bone marrow, which usually limits administration of topotecan to patients.

INTRODUCTION

The camptothecin derivative topotecan has demonstrated antitumor activity against a variety of refractory solid tumors in preclinical models (1–4) and is currently in Phase I–II clinical trials. In these trials, topotecan has been administered as follows: as a 30-min infusion daily times five, repeated every 3–4 weeks; as a 30-min or 24-, 72-, 96-, or 120-h infusion every 3–4 weeks; and as a 21-day infusion every 4 weeks. Topotecan has also been given by oral or i.p. administration (5–8). In preclinical xenograft models, low-dose, protracted schedules of daily administration produced as many tumor regressions as intense, shorter schedules of exposure (4). Thus far, the most effective schedule of exposure in vivo has not been determined.

Topotecan is an inhibitor of topoisomerase I, and its cytotoxic effect has been postulated to be mediated by a dose-dependent increase in covalent topoisomerase I-DNA complexes. The interaction of replication forks with topoisomerase I-DNA complexes results in DNA double-strand breaks, which may ultimately lead to apoptosis (9–13). Cell lines resistant to the cytotoxicity of the camptothecins frequently form fewer DNA–protein complexes when exposed to drug than do the corresponding drug-sensitive cell lines (14–16). If levels of covalent complexes are, in fact, a primary determinant of the cytotoxicity of topotecan, then schedules of exposure that maximize the number of covalent topoisomerase I-DNA complexes should produce the greatest tumor cell kill.

We have shown previously that topoisomerase I-DNA complexes reach a maximum 15 min after topotecan lactone is added to tissue culture medium and decline thereafter, regardless of the concentration of drug added (10 nM–25 μM). This biphasic increase/decrease was observed in cell lines derived from several types of solid tumors (17, 18) and reflects, in part, the pH-dependent equilibrium between topotecan lactone and hydroxyacid. Furthermore, we showed recently that intracellular biochemical events may also contribute to the biphasic increase/decrease of protein–DNA complexes, in that levels of complexes in cells exposed to topotecan for 8–48 h were approximately equal to or below those seen in control cells, although active drug was present in the medium. Thus, continuous exposure to topotecan does not result in sustained levels of topoisomerase I-DNA complexes in vitro. Moreover, we observed that contin-
uous exposure to topotecan was not essential for growth inhibition in vitro (18).

The purpose of this study was to identify schedules of exposure that maximize levels of topoisomerase I-DNA complexes in vitro and to determine whether these schedules suggested effective schedules of exposure in vitro, as well as schedules that would induce complete tumor regressions of pediatric solid tumors grown as xenografts in immune-deprived mice.

MATERIALS AND METHODS

Drugs and Chemicals. Topotecan was generously provided by SmithKline Beecham. Drug was solubilized in sterile water at a concentration of $10^{-2}$ m and stored at $-20^\circ$C without loss of potency. Stock solutions were made by serial dilution with 10 mM Tris-HCl (pH 4.0) and stored at 4°C for no more than 5 days. The drug was allowed to equilibrate overnight before use to ensure complete conversion of topotecan to the active lactone form (pH 4.0). For the xenograft studies, topotecan was dissolved in 0.9% saline for i.v. administration. All other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO) unless otherwise noted.

Cell Lines. The Daoy pediatric medulloblastoma cell line (19) was obtained from the American Tissue Type Collection (Rockville, MD). A subclone isolated from the parental line was used for experiments detailed in this paper. Daoy cells grow as a monolayer in RPMI (BioWhittaker, Inc., Walkersville, MD) supplemented with 15% fetal bovine serum (Hyclone, Logan, UT) and 2 mM glutamine. The Rh30 pediatric rhabdomyosarcoma cell line (20) grows as a monolayer in RPMI 1640 (Life Technologies, Inc., Gaithersburg, MD) supplemented with 10% fetal bovine serum and 2 mM glutamine. All experiments were performed with cells in logarithmic growth.

Quantitation of Covalent Topoisomerase I-DNA Complexes in Intact Cells. The details of this assay have been published elsewhere (17, 18). Briefly, cells were incubated overnight with $[^3]H\text{h}thymidine (0.9 \muCi/ml, 81 Ci/mm; Amer sham, Arlington Heights, IL) and $[^14]C\text{]leucine (0.2 \muCi/ml, 300 mCi/mm; DuPont NEN, Wilmington, DE). At the indicated times, supernatants were aspirated, and SDS (37°C) was added to each plate to denature proteins. DNA was sheared by passing the lysed cells through a 22-gauge needle 20 times, and proteins were precipitated with KCl. Precipitates were washed three times, and radioactivity was measured by liquid scintillation counting. Results are expressed as cpm of $[^3]H\text{DNA}$ precipitated after normalizing to the internal, $[^14]C\text{]}\text{protein control.}$

Pharmacokinetic Profile of Topotecan in Mice. The disposition of topotecan in mice was determined after a single 1.25 mg/kg dose. Heparinized blood samples (~1 ml) were collected (three mice per time point) 0, 0.25, 1, 2, 4, and 6 h after administration. All plasma samples were handled and processed as described previously (21). Briefly, to reliably quantitate topotecan lactone, plasma was separated from whole blood immediately, and 200 µl of plasma were placed in 800 µl of cold (~30°C) methanol. The mixture was vortexed for 10 s, centrifuged for 2 min at 12,000 $\times$ g in a table-top centrifuge at 4°C, and the supernatant was decanted into a plastic screw-top tube.

A sensitive and specific isocratic high-performance liquid chromatography assay with fluorescence detection (model RF535; Shimadzu, Columbia, MD) was used to determine topotecan lactone plasma concentrations (7, 21–23). Topotecan was detected using a fluorescence detector with excitation at 380 nm and emission at 520 nm. Retention times and peak heights were calculated using a data integration system (Shimadzu model CR501). Calibration curves were constructed using spiked pooled murine plasma (Hilltop Animal Laboratories, Scottsdale, PA) over a range of 0.25–300 ng/ml. The lower limit of sensitivity for the assay was 0.25 ng/ml.

A two-compartment model using maximum likelihood estimation was fit to topotecan lactone plasma concentration data (ADAPT II; Ref. 24). Model parameters estimated included the volume of the central compartment ($V_c$), elimination rate constant ($k_e$), and the intercompartment rate constants ($k_{ep}$ and $k_{pe}$). Using standard equations, systemic clearance ($CL$) and volume of distribution at steady state ($V_{dss}$) were calculated from parameter estimates (25).

We have previously shown that topotecan disposition is linear from 0.5 to 2.0 mg/kg in the xenograft model. Thus, after quantitating the disposition at 1.25 mg/kg, we used that data to extrapolate the topotecan systemic exposure associated with the 0.6 and 1.0 mg/kg dose. In that study, we measured the lactone form of topotecan, and to compare this systemic exposure with in vitro exposures, we used a factor of 0.33 to convert lactone to total topotecan (26).

Xenografts. The details of the methods used for xenograft studies have been reported (20, 27). Each tumor grows routinely in over 90% of recipient mice; all are of human origin, as determined by karyotype and species-specific isoenzyme patterns. In this study, mice bearing either Rh30 or Daoy cells as xenografts received topotecan 0.6 mg/kg i.v. [$^{[d\times5]}$]2$^3$ or 1 mg/kg ($^{[d\times5]}$]2$^3$. Each group, therefore, received the same total weekly dose of 3 mg/kg, given in increments either daily or every other day. A second group of mice bearing Daoy cells as xenografts received 2 mg/kg topotecan [$^{[d\times5]}$]2$^3$ or 3.3 mg/kg ($^{[d\times5]}$]2$^3$ i.v., for a total weekly dose of 10 mg/kg for each schedule of administration.

RESULTS

Daoy and Rh30 Cells Preincubated with 2.5 µM Topotecan for 8 h Are Refractory to a Drug-induced Increase in Covalent Topoisomerase I-DNA Complexes. We showed previously that the biphasic increase/decrease in topoisomerase I-DNA complexes in Daoy cells exposed continuously to topotecan for 2–8 h was not attributable to chemical or metabolic inactivation of topotecan (18), to decreases in the amount of nuclear topoisomerase I (18), or to a decrease in cpm of nuclear $[^3]H\text{DNA}$ available for topoisomerase I binding (data not shown). That study, however, did not rule out the possibility that, with time, drug was sequestered within the cell, preventing its interaction with nuclear topoisomerase I-DNA complexes. If
the latter hypothesis is correct, then simply adding a second dose of topotecan to cultures preincubated with drug should produce levels of complexes equal to those seen after a 15-min exposure.

To test the hypothesis, we incubated Daoy or Rh30 cells with 2.5 \( \mu \)M topotecan for 8 h, replaced the medium with drug-free medium, and rechallenged the cells with 2.5 \( \mu \)M topotecan for 15 min at the times (in h) indicated in Fig. 1, top. Drug-free intervals of 0, 2, 4, 8, and 24 h are indicated as +0, +2, +4, +8, and +24, respectively. As anticipated, the number of complexes detectable in Daoy cells after an 8-h incubation with drug was approximately equal to that of the untreated controls (Fig. 1, top). Surprisingly, however, Daoy cells incubated for 8 h and then resuspended in fresh medium and rechallenged immediately with 2.5 \( \mu \)M topotecan failed to show the expected 18-fold increase in topoisomerase I-DNA complexes that was seen when control cells were incubated for 15 min with topotecan. Daoy cells remained relatively refractory to the formation of drug-induced topoisomerase I-DNA complexes for 8–24 h following removal of drug from the first exposure.

The above experiment was then repeated with Rh30 cells (Fig. 1, bottom). Unlike Daoy cells, the level of complexes in Rh30 cells exposed to topotecan for 8 h was slightly higher than in control cells (8-fold for Rh30 versus 2-fold for Daoy). However, similar to Daoy cells, Rh30 cells were refractory to a drug-induced increase in covalent topoisomerase I-DNA complexes for 8–24 h. Thus, intermittent exposure to 2.5 \( \mu \)M topotecan produced more topoisomerase I-DNA complexes than did continuous exposure to drug.

**Effect of Nanomolar Concentrations of Topotecan on Covalent Topoisomerase I-DNA Complexes.** Although the studies with micromolar concentrations of topotecan were of interest from a mechanistic viewpoint, it was not known whether they reflected intracellular events following exposure to more clinically relevant concentrations of topotecan (10–200 nM). We, therefore, repeated the experiment with Daoy and Rh30 cells using 50 nM topotecan. As expected, we could detect few, if any, topoisomerase I-DNA complexes in Daoy and Rh30 cells after an 8-h exposure to 50 nM topotecan (Fig. 2, top and bottom, respectively). However, the cells were not refractory to a drug-induced increase in complexes when fresh medium and 50 nM drug were added. At the 8-h time point, when the cells were rechallenged with 50 nM topotecan, the number of topoisomerase I-DNA complexes induced was approximately equal to that of a 15-min exposure to drug. Results similar to those in Fig. 2 following an 8-h exposure to 50 nM topotecan were also obtained with Daoy and Rh30 cells exposed to 10 nM topotecan (data not shown). Importantly, results with 2.5 \( \mu \)M topotecan contrasted with results with the more clinically relevant nanomolar concentrations. These experiments suggest that observa-
Efficacy of Intermittent Exposure to Topotecan

Fig. 3 Quantitation of covalent topoisomerase I-DNA complexes in Daoy (top) and Rh30 (bottom) cells incubated with 50 nM topotecan for 0, 0.25, or 24 h or for 24 h followed by drug-free periods and then rechallenged with 50 nM drug, as described in the legend to Fig. 1 and in "Materials and Methods."

Intermittent Schedules of Exposure to Topotecan. The observations made when pharmacological doses of topotecan were used do not necessarily reflect cellular effects or events that occur when lower concentrations of this drug are used. Additionally and, perhaps, more importantly, after Daoy and Rh30 cells were exposed to topotecan for 8 h, allowed to remain drug free for 24 h, and then rechallenged with 50 nM topotecan, the level of topoisomerase I-DNA complexes detected was ~2-fold greater than the level of complexes detected after an initial 15-min exposure to topotecan (Fig. 2). Similarly, when Daoy and Rh30 cells were exposed to 50 nM topotecan for 24 h and rechallenged with 50 nM topotecan for 15 min after 24 h in drug-free medium, the level of complexes detected was 1.4–1.8-fold greater than that following a single exposure (Fig. 3).

Growth Inhibition of Daoy and Rh30 Cells following Intermittent Schedules of Exposure to Topotecan. The observations above, as well as data published earlier, suggested that schedules of effective intermittent exposure to topotecan might be identified and led to two questions. What length of drug-free period between 8-h exposures produces the greatest inhibition of tumor cell growth? Do in vitro assays reflect in vivo results?

To approach the first question, we compared the growth-inhibitory effect of topotecan in Daoy and Rh30 cells exposed to topotecan continuously for 6 days with fresh medium and drug added each day, with cells exposed to drug for 8 h daily for 6 days, or with cells exposed to drug for 8 h every 48 or 72 h. IC50s for each cell line with each schedule of exposure to topotecan are shown in Table 1. The IC50s for Daoy cells exposed to topotecan continuously, daily, or every other day were the same: ∼2 nM. When the interval between drug exposures was lengthened to 72 h (8 h of topotecan exposure, followed by 64 drug-free hours), the IC50 increased to 39 nM. In contrast, in Rh30 cells, the IC50 of topotecan for continuous exposure (3.9 nM), for 8 h a day (8.7 nM), or for 8 h every other day (12.4 nM) increased incrementally as the time between exposures increased. It is unlikely that the differences between the two cell lines were due to differences in time required to traverse the cell cycle because the doubling times of both Daoy and Rh30 cells are 24–26 h. It should be noted that the total area under the concentration curve [concentration of drug × time (in h)] for each schedule of exposure was different because the total numbers of hours to which cells were exposed to topotecan with the continuous, intermittent daily, every other day, and every third day schedules were 144, 48, 24, and 16 h, respectively (Table 1).

Because Phase I trials have demonstrated that the sustainable concentration of topotecan achievable in the plasma is in the nanomolar range, we considered it most relevant to design subsequent experiments in xenograft models to evaluate schedules of exposure to topotecan that would be predicted to give growth inhibition comparable to continuous exposure at low nanomolar concentrations. The hypothesis generated from the data in Table 1, therefore, was that Daoy cells, when grown as xenografts in immune-deprived mice, would require less frequent exposure to repetitive 8-h exposures to topotecan to achieve tumor regressions than would Rh30 cells grown as xenografts. A second hypothesis was that 2 nM topotecan maintained in the plasma for 8 h would produce tumor regressions in the xenograft model.

Pharmacokinetic Profile of Topotecan in Plasma of Mice Given i.v. Injections of Topotecan. Prior to comparing the antitumor effect of different schedules of topotecan systemic exposure in mice bearing human tumor xenografts, we used pharmacokinetic modeling to verify the duration of time for which the topotecan plasma concentrations were above the “effective” plasma level defined in the in vitro studies (i.e., 2 nM). Because topotecan disposition in the mouse is linear over the dosage range studied, we took data from a single dose (1.25 mg/kg) and simulated the topotecan concentration versus time curve expected from 0.6 and 1.0 mg/kg doses. As seen in Fig. 4, the plasma concentration of total topotecan in mice after a single i.v. injection of either 0.6 or 1.0 mg/kg remained above 2 nM for ∼6–7 h per day.

Antitumor Effect of Topotecan in Mice Bearing Daoy or Rh30 Xenografts. The pharmacokinetic profile of topotecan in mouse serum (Fig. 4) shows that both daily and every other day exposure to topotecan constitute intermittent exposures to drug. In vitro experiments (Table 1) predicted that daily intermittent exposure would produce an inhibition of tumor cell growth in both Daoy and Rh30 xenografts but that every other day exposure to topotecan would be effective only for Daoy xenografts. Thus, our objective in the xenograft experiments was to compare the antitumor effect of daily versus every other day exposure to topotecan in mice bearing Daoy and Rh30 xenografts.
The concentration versus exposure of Daoy xenografts to topotecan produced equivalent antitumor effect. The goal of this study was to determine whether a schedule of exposure to topotecan that maximized levels of topoisomerase I-DNA complexes in vitro could provide information about effective schedules of exposure to this drug both in vitro and in xenograft models. This work presents the novel observations that intermittent schedules of exposure to topotecan that inhibit tumor cell growth in vitro can be identified based on the length of time for which covalent topoisomerase I-DNA complexes are detectable. Data presented here also show that schedules of exposure to topotecan that produce inhibition of tumor cell growth in vitro correlated with schedules of exposure that induced regression of human tumor xenografts in mice. That is, biochemical events suggested effective in vitro exposures to drug, which, in turn, correlated with effective schedules in xenograft models.

**DISCUSSION**

The antitumor effect of topotecan was also shown to be extremely schedule dependent in Rh30 cells and xenografts but less so in the Daoy cells and xenografts. Topotecan had a steep dose-response curve, in that a 3-fold difference in dose administered produced either no or complete tumor regressions (2–3.3 mg/kg). The biochemical or pharmacokinetic basis for Rh30 being more sensitive to topotecan in the xenograft model and less sensitive in growth inhibition assays compared to the Daoy cell line is unknown.

**Table 1 Growth-inhibitory effect of different schedules of topotecan on Daoy and Rh30 cells**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>IC₅₀ of topotecan (nm)ᵃ 6-day exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>Daoy</td>
<td>2.2 ± 0.84</td>
</tr>
<tr>
<td>Rh30</td>
<td>3.9 ± 0.43</td>
</tr>
</tbody>
</table>

ᵃ Mean ± SD of three to six replicate experiments; in the cells treated continuously for 6 days, drug and medium were replaced every 24 h. IC₅₀ is the drug concentration required to inhibit cell growth by 50%, relative to no-drug.

ᵇ AUC = 33% that of continuous exposure.
ᶜ AUC = 17% that of continuous exposure.
ᵈ AUC = 8% that of continuous exposure.
⁴ ND, not determined.
Fig. 5  Responses of Rh30 rhabdomyosarcoma xenografts to topotecan (0.6–1.0 mg/kg). Mice bearing advanced s.c. tumors were treated i.v. with three cycles of topotecan. A, tumor volume in controls. B, mice treated with 0.6 mg/kg topotecan [(d×5)2]3. C, mice treated with 1 mg/kg topotecan [(MWF)2]3. Lines, growths of individual tumors.

Fig. 6  Responses of Daoy medulloblastoma xenografts to topotecan (0.6–1.0 mg/kg). Mice bearing advanced s.c. tumors were treated i.v. with three cycles of topotecan. A, tumor volume in controls. B, mice treated with 0.6 mg/kg topotecan [(d×5)2]3. C, mice treated with 1 mg/kg topotecan [(MWF)2]3. Lines, growths of individual tumors.

Fig. 7  Responses of Daoy medulloblastoma xenografts to topotecan (2–3.3 mg/kg). Mice bearing advanced s.c. tumors were treated i.v. with three cycles of topotecan. A, tumor volume in controls. B, mice treated with 2 mg/kg topotecan [(d×5)2]3. C, mice treated with 3.3 mg/kg topotecan [(MWF)2]3. Lines, growths of individual tumors.

demonstrated a greater antitumor effect, although the total drug administered on the daily schedule (22.5 mg/kg) was less than half the total amount given on the every 4 days schedule (50 mg/kg). However, because host toxicity limits the amount of drug and the duration for which drug can be given to patients, the most effective, tolerated schedule of exposure has yet to be determined. If, as our study suggests, *in vitro* studies are relevant to or can be predictive of antitumor activity of topotecan, it may be of interest to note that 8-h repetitive exposures to topotecan are more effective than shorter repetitive exposures (18). We have measured the topotecan systemic exposure in mice receiving topotecan at doses associated with antitumor effects (Fig. 4). By comparing these data with results of pharmacokinetic studies in pediatric patients receiving topotecan as a 30-min infusion (7, 28), we estimate that a dose of ~3 mg/m² topotecan would produce a similar plasma concentration-time profile.
Biochemical studies also suggest that several factors, in addition to levels of covalent topoisomerase I-DNA complexes and length of exposure to topotecan, are involved in camptothecin cytotoxicity. For example, there is evidence to support both a DNA synthesis-dependent and -independent component to the cytotoxicity of the camptothecins (29-32). Other factors such as the p53 status of the cell (33-35), cellular localization of topoisomerase I (17, 36), binding of this enzyme to other cellular proteins (37), the phosphorylation state of replication protein A (38), and the DNA repair capacity of the cell (39) may also contribute to the cellular response to the camptothecins.

Additionally, it may be important to note that, although data presented here show a correlation between schedules of exposure to topotecan in vitro and in vivo, our analysis showed no correlation between the sensitivity of Rh30 or Daoy cells grown in tissue culture compared to grown as a xenograft. As pointed out above, the biochemical or pharmacokinetic basis for Rh30 cells being more sensitive to topotecan than Daoy cells in the xenograft model but less sensitive in in vitro growth inhibition assays is unknown. This lack of a predictable relationship between tumor cell sensitivity in vitro and in vivo may be due to factors present in whole-animal systems that are not present in tissue culture and is consistent with previously published observations. For example, Zamboni et al. (40) reported that tumor burden and route of administration each influenced pharmacokinetics and, therefore, effective dose, of CPT-11 in mice bearing neuroblastoma xenografts. Also, Frei et al. (41) showed that apparent differences in potency of cyclophosphamide and other alkylating agents in vitro compared to in vivo could be explained by differences in drug metabolism in the two systems.

In summary, in vitro data showed that repetitive 8-h exposures to topotecan produced maximum levels of covalent topoisomerase I-DNA complexes and that schedules of exposure that were growth inhibitory in vitro correlated with schedules of exposure that produced complete regressions of human tumors in xenograft models. Ongoing studies in our laboratory are focused on determining the effect of intermittent repetitive exposures to topotecan on human bone marrow progenitor cells to try to assess in an in vitro system the therapeutic index of different schedules of intermittent exposure to this drug.

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