A Comparison of Clinical Pharmacodynamics of Different Administration Schedules of Oral Topotecan (Hycamtin)


ABSTRACT

Prolonged exposure to topotecan in in vitro and in vivo experiments has yielded the highest antitumor efficacy. An oral formulation of topotecan with a bioavailability of 32–44% in humans enables convenient prolonged administration. Pharmacokinetic/pharmacodynamic relationships from four Phase I studies with different schedules of administration of oral topotecan in 99 adult patients with malignant solid tumors refractory to standard forms of chemotherapy were compared. Topotecan was administered as follows: (a) once daily (o.d.) for 5 days every 21 days (29 patients); (b) o.d. for 10 days every 21 days (19 patients); (c) twice daily (b.i.d.) for 10 days every 21 days (20 patients); and (d) b.i.d. for 21 days every 28 days (31 patients). Pharmacokinetic analysis was performed in 55 patients using a validated high-performance liquid chromatographic assay and noncompartmental pharmacokinetic methods. Totals of 109, 48, 64, and 59 courses were given, respectively. Dose-limiting toxicity consisted of granulocytopenia for the o.d. and 109, 48, 64, and 59 courses were given, respectively. Dose-limiting toxicity consisted of granulocytopenia for the o.d. 5-day dosage, a combination of myelosuppression and diarrhea in both of the 10-day schedules, and only diarrhea in the 21-day schedule. Pharmacokinetics revealed a substantial variation of the area under curve (AUC) of topotecan lactone in all of the dose schedules with a mean intrapatient variation of 25.4 ± 31.0% (o.d. × 5), 34.5 ± 25.0% (o.d. × 10), 96.5 ± 70.1% (b.i.d. × 10), and 59.5 ± 51.0% (b.i.d. × 21). Significant correlations were observed between myelotoxicity parameters and AUC(t) day 1 and AUC(t) per course of topotecan lactone. In all of the studies, similar sigmoidal relationships could be established between AUC(t) per course and the percentage decrease of WBCs. At maximum-tolerated dose level, no significant difference in AUC(t) per course was found [AUC(t) per course was 107.4 ± 33.7 ng·h/ml (o.d. × 5), 145.3 ± 23.8 ng·h/ml (o.d. × 10), 100.0 ± 41.5 ng·h/ml (b.i.d. × 10), and 164.9 ± 92.2 ng·h/ml (b.i.d. × 21), respectively.] For oral topotecan, the schedule rather than the AUC(t)-per-course seemed to be related to the type of toxicity. Prolonged oral administration resulted in intestinal side effects as a dose-limiting toxicity, and short-term administration resulted in granulocytopenia. On the basis of this pharmacokinetic study, no schedule preference could be expressed, but based on patient convenience, administration once daily for 5 days could be favored.

INTRODUCTION

Topotecan, 9-dimethylaminomethyl-10-hydroxycamptothecin, is a water-soluble semisynthetic analogue of camptothecin (1). Like camptotecin, topotecan is a specific inhibitor of topoisomerase I. Topotecan administered daily by 30-min infusion on 5 subsequent days every 3 weeks results in brief myelosuppression as the most important side effect (2–5). Antitumor activity was reported in patients with small cell lung cancer (6) and in pretreated patients with ovarian cancer (7–9). Recently topotecan was registered in Europe and the United States for the latter indication. Cytotoxicity of topoisomerase I inhibitors is more specific to the S-phase of the cell cycle, in which double-strand breaks occur (10–12).

Preclinical in vitro and in vivo studies indicate that prolonged exposure to low-dose topoisomerase I inhibitors is the most efficacious (13–18). The feasibility of the concept of prolonged exposure to topotecan in humans was initially reported by Hochster et al. (19) in a Phase I study using a 21-day continuous infusion. Myelosuppression was the DLT; and remarkable antitumor activity was seen. Infusion, especially continuous infusion, is relatively patient-inconvenient. Recent studies in humans reported a 32–44% bioavailability of the i.v. formulation of topotecan when given p.o. (20, 21). Oral administration would be a more simple and perhaps a more convenient method to achieve prolonged exposure.

We performed four Phase I and pharmacological studies with different schedules of oral administration of topotecan in adult patients. The present analysis was performed to see
whether, from a pharmacokinetic/pharmacodynamic point of view, there was a preference for a particular schedule to be taken forward for further development.

PATIENTS AND METHODS

Patient Selection. Patients with a histologically confirmed diagnosis of malignant solid tumor refractory to standard forms of therapy were eligible. Eligibility criteria included: (a) age ≥18 years; (b) WHO performance status ≤2; (c) an estimated life expectancy of ≥12 weeks; (d) no previous anticancer therapy ≥4 weeks (6 weeks for nitrosoureas or mitomycin C); and (e) adequate hematopoietic (WBCs ≥4 × 10^9/liter and platelets ≥100 × 10^9/liter), hepatic (bilirubin within normal limits, AST, ALT, and/or alkaline phosphatase ≤2 × normal), and renal function (serum creatinine ≤133 μmol/liter (2.0 mg/dl). Specific exclusion criteria included: (a) active peptic ulcer or any gastrointestinal condition that could alter absorption or motility; (b) the taking of H2-antagonists or proton pump inhibitors. All of the patients gave written informed consent.

Treatment and Dose Escalation. Oral administration of topotecan was studied in Phase I studies: (a) b.i.d. for 21 days every 28 days; (b) once or b.i.d. for 10 days every 21 days; and (c) o.d. for 5 days every 21 days. The 21-day administration was studied based on the 21-day continuous i.v. administration (19, 22, 23). In view of the relatively short half-life of topotecan, the twice-daily dosing was given. Dose levels studied were 0.15, 0.3, 0.4, 0.5, and 0.6 mg/m² b.i.d., which resulted in total daily doses of 0.3, 0.6, 0.8, 1.0, and 1.2 mg/m²), respectively. The 10-day schedules were studied because of severe diarrhea occurring in the third week of the 21-day administration of oral topotecan and the finding that topoisomerase I down-regulation was optimal after 10–14 days with continuous infusion of topotecan (19, 23, 24). Dose levels studied with the 10-day administration were 0.5, 0.6, 0.7, and 0.8 mg/m² b.i.d., and 1.0, 1.4, and 1.6 mg/m²/day o.d. The reduction from two to one administration/day was intended to reduce gastrointestinal toxicities. A daily × 5 dose o.d. every 21 days was based on the daily × 5 i.v. administration, with dose levels 1.2, 1.8, 2.3, and 2.7 mg/m²/day.

Dose escalations were based on the toxicity seen at the prior dose level. If no toxicity was seen in the prior dose, ≤100% dose escalation was allowed. However, if toxicity was seen, a dose escalation of 25–50% was prescribed. The MTD was defined as one dose level below the dose that induced DLTs, which were defined as CTC grade IV hematological toxicity and/or nonhematological toxicity ≥CTC grade III during the first course in more than 2 of 6 patients. Intrapatient dose escalation was not allowed.

Treatment Source and Formulation. Topotecan was supplied as capsules containing topotecan hydrochloride, equivalent to either 0.25, 0.50, or 1.0 mg of the anhydrous free base (SmithKline Beecham). Capsules had to be stored at between 2–8°C. Capsules were taken with a glass of water in the morning on an empty stomach with a 2-h period of fasting. With b.i.d. administration of topotecan, the second dose was taken with an interval of 12 h with a glass of water at least 10 min before meals, preferably on an empty stomach. Patients were treated as outpatients.

Treatment Assessment. Before therapy and weekly during therapy, evaluations were performed including history, physical examination, toxicity assessment according to the CTC criteria, and serum chemistries (25). Complete blood counts were determined twice weekly. Tumor measurements were performed after every two courses and evaluated according to the WHO criteria for response (26). Patients were taken off of the protocol in the case of disease progression.

Pharmacokinetics. For pharmacokinetic analysis, whole blood samples (2.8 ml) in heparinized tubes were collected during the first course, before dosing, and 15, 30, and 45 min and 1, 1.5, 2.5, 3.5, 4.5, 8.5, and 12 h after the administration of the drug on day 1 and on day 4 (o.d. × 5), or day 8 (× 10 and × 21 schedules). For the twice-daily dosing schedules, pharmacokinetic samples were taken after the morning dose. The samples were immediately processed and analyzed according to a method described previously (27).

AUCs of topotecan lactone and hydroxy-acid were calculated by noncompartmental analysis (linear-logarithmic trapezoidal method). Because a >20% extrapolation was needed to calculate the total AUC of topotecan lactone in most cases of the b.i.d. × 21 and b.i.d. × 10 administration, pharmacokinetic-pharmacodynamic analysis was carried out with AUC(t) in all studies. AUC(t) was calculated up to the last measured time point “t”. In all of the patients, samples were obtained up to 12 h after drug intake. The terminal half-life (T1/2) was calculated as ln2/k, where ln2 is logarithm and k is the elimination rate constant (h⁻¹). In the studies with a o.d. administration of topotecan, no steady-state situation will be reached because of the T1/2 of 3.5–4.0 h. To compare the four schedules of administration, we chose AUC per course as a reliable measure for dose intensity. The AUC(t) per course was calculated by multiplying the AUC(t) day 1 with the number of doses per course. The AUC(t) day 1 and AUC(t) per course were fitted to the observed percentage decrease in WBCs using the sigmoidal Emax model (28). For all calculations, the Siphar software package release 4.0 (Siphar SIMED, Cedex, Creteil, France) was used. Spearman rank correlation coefficients were calculated between AUC(t) day 1 and AUC(t) per course and the percentage of decrease of WBCs, granulocytes, and platelets.

Two-way ANOVA was used to compare AUC(t) per course for the different schedules at MTD dose level. ANOVA was used for analysis on difference in myelotoxicity, diarrhea, maximal concentration day 1, and intrapatient variation. Intrapatient variation was calculated as follows (day 4/8, either day 4 or day 8):

$$\frac{AUC\ day\ 1 - AUC\ day\ 4/8}{AUC\ day\ 1} \times 100\%$$

The duration of exposure to topoisomerase I inhibitors seems important for antitumor effects. In vitro experiments with continuous exposure of topotecan were performed with a minimum concentration of 100 ng/ml (16), and steady-state plasma concentrations were 0.62 and 4.4 ng/ml, respectively, in studies in humans with 21 day continuous infusion (19, 22). An arbitrary threshold plasma concentration of >1 ng/ml was chosen to study the differences in duration of exposure in the schedules used. Duration of time of topotecan >1 ng/ml per course was
calculated from the duration measured on day 1 multiplied by the number of doses per course.

RESULTS

A total of 99 eligible patients were entered into the studies, of whom 96 were evaluable for toxicity. Because of technical problems during the shipment of the blood samples from the patients from San Antonio, reliable pharmacokinetic data could not be obtained from these patients. Pharmacokinetic analysis could be performed in 55 patients treated at the Rotterdam Cancer Institute. The patient characteristics are given in Table 1. The median WHO performance status of patients was: 0 (range, 0–2). The majority of patients received prior chemotherapy; minimally or extensively pretreated patients were balanced in the four schedules studied.

Hematological Toxicity. The occurrence of CTC grade III–IV leucocytopenia and granulocytopenia with the various schedules is listed in Table 2. They were observed in 11.9% and

<table>
<thead>
<tr>
<th>Schedule and dose levels</th>
<th>No. of patients</th>
<th>No. of courses</th>
<th>Leucocytes</th>
<th>Granulocytes</th>
<th>Platelets</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td></td>
<td></td>
<td>III</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>× 5 days</td>
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<td>15</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>MTD</td>
<td>8</td>
<td>15</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>× 10 days</td>
<td></td>
<td></td>
<td>19</td>
<td>48</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>19</td>
<td>48</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MTD</td>
<td>9 (1)'</td>
<td>18 (1)'</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Twice daily</td>
<td></td>
<td></td>
<td>19</td>
<td>64</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>× 10 days</td>
<td></td>
<td></td>
<td>8</td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>All</td>
<td>18</td>
<td>64</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>MTD</td>
<td>6</td>
<td>15</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>× 21 days</td>
<td></td>
<td></td>
<td>30</td>
<td>59</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>30</td>
<td>59</td>
<td>8</td>
<td>18</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>MTD</td>
<td>8</td>
<td>18</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

a All, patients studied at all dose levels; MTD, patients studied at MTD dose level.

b CTC grades. Toxicity per course.

c In both of these patients, a relationship to topotecan is possible.

d The number in parentheses is the number of patients who were also studied at this dose level but who had been treated previously at a higher dose level.
21.1%, respectively, of courses at the daily × 5 administration, 6.2% and 4.2%, respectively, of courses with o.d. × 10, both 4.6% of courses with b.i.d. × 10, and 10.2% and 5.1% of courses for b.i.d. × 21, respectively. Granulocytopenia was significantly (P < 0.001) more frequent in the daily × 5 administration as compared with the other schedules; this was true for leucocytopenia also.

At MTD, granulocytopenia was more frequent with the 21-day schedule because of a more limited increase of AUC(t) vs. Cmax. Intrapatient variation appeared lower in the o.d. dose schedules; this was true for leucocytopenia also.

At MTD, no CTC grade III–IV diarrhea occurred with the daily × 5 administration. CTC grade IV diarrhea was seen in two of eight patients treated at MTD with the 21-day schedule. For the different schedules of administration, MTDs were 0.5 mg/m² b.i.d. × 5, 0.7 mg/m² b.i.d. × 10, 1.4 mg/m²/day × 10, and 2.3 mg/m²/day × 5.

**Pharmacokinetics and Dynamics.** The AUC(t) of topotecan lactone was consistently higher on day 4 (o.d. × 5) and day 8 (10- and 21-day schedules) compared with day 1. Significant correlations were found between AUC(t) day 1 and day 4/8 (Table 3). In the b.i.d. × 10 schedule AUC(t), day 8 was significantly higher compared with day 1 (P < 0.05). Thus, limited cumulation of topotecan occurred in this schedule.

### Table 3 Correlations coefficients (R): pharmacokinetics and dynamics

<table>
<thead>
<tr>
<th>Correlation</th>
<th>o.d. × 5 days (R)</th>
<th>o.d. × 10 days (R)</th>
<th>b.i.d. × 10 days (R)</th>
<th>b.i.d. × 21 days (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(t) day 1 vs. AUC(t) day 4/8</td>
<td>0.81</td>
<td>0.76</td>
<td>0.74</td>
<td>0.95</td>
</tr>
<tr>
<td>Cmax vs. % decrease granulocytes</td>
<td>0.55</td>
<td>0.76</td>
<td>0.99</td>
<td>Not reliable</td>
</tr>
<tr>
<td>Topotecan lactone &gt; 1 ng/ml per course</td>
<td>0.44</td>
<td>0.74</td>
<td>1.0</td>
<td>Not reliable</td>
</tr>
<tr>
<td>AUC(t) day 1 topotecan vs. % decrease leucocytes</td>
<td>0.76</td>
<td>0.61</td>
<td>0.69</td>
<td>0.66</td>
</tr>
<tr>
<td>AUC(t) day 1 vs. % decrease platelets</td>
<td>0.60</td>
<td>0.83</td>
<td>0.78</td>
<td>Not reliable</td>
</tr>
</tbody>
</table>

* N.S., not significant.

### Table 4 Pharmacokinetics after oral administration of topotecan in patients treated at MTD (Median (range))

<table>
<thead>
<tr>
<th>Schedule</th>
<th>No. of patients</th>
<th>Dose (mg/m²/day)</th>
<th>AUC(t) topotecan</th>
<th>Cmax topotecan, day 1 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o.d. × 5 days q* 3 wk</td>
<td>6</td>
<td>2.3</td>
<td>19.6</td>
<td>8.4</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>6.7</td>
<td>2.2</td>
</tr>
<tr>
<td>o.d. × 10 days q 3 wk</td>
<td>3</td>
<td>1.4</td>
<td>13.2</td>
<td>3.3</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>2.4</td>
<td>3.3</td>
</tr>
<tr>
<td>b.i.d. × 10 days q 3 wk</td>
<td>4</td>
<td>1.4</td>
<td>5.6</td>
<td>1.3</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>b.i.d. × 21 days q 4 wk</td>
<td>4</td>
<td>1.0</td>
<td>4.1</td>
<td>1.6</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>2.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* q, every.
C_{\text{max}} was correlated to the percentage of decrease of granulocytes for o.d. \times 5 and for b.i.d. \times 21 (Table 3). C_{\text{max}} did not correlate with other myelotoxicity parameters. Time-point of maximal concentration and half-life were of similar magnitude for all of the four dose schedules (N.S.).

The AUC per course at MTD was not significantly different between the four schedules of oral administration (Table 4). The resulting AUC per course at MTD was 107.4 \pm 33.7 ng\cdot h/ml for o.d. \times 5, 145.3 \pm 23.8 ng\cdot h/ml for o.d. \times 10, 100.0 \pm 41.5 ng\cdot h/ml for b.i.d. \times 10, and 164.9 \pm 92.2 ng\cdot h/ml for b.i.d. \times 21 (N.S.) (Table 4). The AUC per week at the MTD dose level, a measure for dose intensity, was not significantly different between the 4 schedules studied (Table 4).

Calculating AUC per course at MTD from AUC(t) day 4/8 resulted in an AUC per course of 124.8 \pm 50.2 ng\cdot h/ml (o.d. \times 5), 217.2 \pm 75.6 ng\cdot h/ml (o.d. \times 10), 164.1 \pm 70.0 ng\cdot h/ml (b.i.d. \times 10), and 229.4 \pm 79.5 ng\cdot h/ml (b.i.d. \times 21), respectively (N.S.).

A duration of time of topotecan lactone >1 ng/ml per course was lowest in the o.d. \times 5 administration with a mean duration of 20.1 \pm 7.9 h/course. Duration of topotecan >1 ng/ml per course was 26.5 \pm 13.6 h (o.d. \times 10), 47.9 \pm 49.2 h (b.i.d. \times 10), and 44.6 \pm 12.2 h (b.i.d. \times 21), respectively. Duration of time of topotecan lactone >1 ng/ml per course was significantly lower (P = 0.006) for the 5 day o.d. schedule compared with the 10-day and 21-day b.i.d. schedules.

The correlation between topotecan lactone >1 ng/ml per course with the percentage of decrease of leukocytes was low for o.d. \times 5 but higher in the 10-day schedules (Table 3). The correlation for the 21-day schedule could not be calculated reliably.

The correlation between the AUC(t) day 1 of topotecan and the percentage of decrease of leukocytes is significant in the o.d. \times 5, b.i.d. \times 10, and b.i.d. \times 21 schedules of administration. The correlation between AUC(t) day 1 topotecan and percentage decrease of leukocytes showed a same trend for the o.d. \times 10 administration. The relationship between the AUC(t) day 1 of topotecan lactone and the percentage decrease of leukocytes could be fitted best using a sigmoidal E_{\text{max}} model (Fig. 1).

A significant correlation between the AUC(t) of topotecan lactone and the percentage decrease of platelets was observed in the 10-day dose schedules and in the 5-day schedule (Table 3). Thus, significant correlations with myelotoxicity parameters are found with all schedules. When plotting AUC day 1 and day 4/8 per course against the percentage decrease of leukocytes, all of the sigmoidal curves showed a similar pattern (Fig. 2, a and b).

**DISCUSSION**

A 21-day continuous infusion of topotecan in patients with solid tumors was well tolerated, and antitumor effects were seen (19, 22). Continuous infusion is inconvenient and sometimes leads to complications of the central venous catheters (19, 22). Oral administration of topotecan may perhaps be more convenient in patients and was considered worthwhile testing in view of a bioavailability of 32–44% of the i.v. formulation when given p.o. (20, 21).

For both oral and i.v. topotecan administered on 5 consecutive days every 3 weeks, myelosuppression was dose limiting. No clinically important diarrhea was seen in the daily \times 5-day administration. In contrast, for the b.i.d. \times 21-day administration of oral topotecan, uncontrollable diarrhea was the single
dose-limiting side effect, whereas the dose-limiting side effect was myelotoxicity in studies on 21-day continuous infusion. The latter studies did not report severe diarrhea. Diarrhea is a well-known side effect of camptothecin and its derivatives.

CPT-11 administered i.v. can cause acute onset diarrhea or delayed onset diarrhea starting around day 5. CPT-11 delayed-onset diarrhea is controllable by vigorous administration of loperamide (29). Oral administration of camptothecin for 21 days every 28 days and 9-nitro-camptothecin for 5 days/week resulted in severe diarrhea in 40 and 33% of patients, respectively (30, 31). Local intestinal effects of camptothecin and its derivatives seem to be responsible for diarrhea (32). Diarrhea that was induced by oral topotecan was always self-limiting but did not respond to loperamide administration.

The data from our studies suggest that local intestinal exposure is an inducing factor for the observed diarrhea, although the exact mechanism of topotecan-induced diarrhea is unknown. DLT consisted of a combination of both myelotoxicity and diarrhea in the studies with 10-day administration of oral topotecan. Thus, with the oral administration of topotecan, the toxicity profile seemed to change gradually from granulocytopenia to diarrhea when administration was prolonged.

Neutropenia is the major side effect of daily × 5 i.v. topotecan, with the nadir of granulocytes being reported between days 8 and 15 (2–5). The continuous i.v. administration of topotecan for 21 days every 28 days showed a granulocyte nadir on day 18 (range, 12–28) (19). Granulocyte nadirs of the daily × 5 administration of oral or i.v. topotecan were similar, as were those of myelotoxicity of the o.d. × 10 (days 12 and 16) and b.i.d. × 10 (days 8–14) oral schedules. In none of the schedules of oral administration of topotecan was myelotoxicity cumulative. These findings are consistent with previous reports on daily × 5 administration of topotecan. Neutropenia had a median duration of 6.5 days (range, 2–12 days) and was uncomplicated in the daily × 5 administration of oral topotecan. In contrast, cumulative myelotoxicity requiring dose reductions was seen in schedules with 21 days of continuous infusion (19, 22).

With the 21 days of oral administration, plasma concentrations of topotecan lactone >1 ng/ml never lasted for more than 3 h per administration. In contrast, 20 (91%) of the 22 patients analyzed in the daily × 5 study had a plasma concentration of topotecan lactone >1 ng/ml lasting for more than 3 h, as did 5 patients (50%) on o.d. × 10 days and 1 patient (10%) with b.i.d. administration. The duration of topotecan lactone plasma-concentration >1 ng/ml per course however was highest with the 21-day schedule and lowest for o.d. × 5 days. Because granulocytopenia was significantly more frequent in the o.d. × 5-day administration, myelotoxicity seems to be related to the plasma concentration per dose administered rather than the duration of exposure to >1 ng/ml topotecan per course.

Compared with oral administration o.d. × 5 days, AUC(t) of topotecan lactone is substantially higher with i.v. administration, and neutropenia is more pronounced (33–37). Furthermore, mild myelotoxicity was the major side effect of 21 days’ continuous infusion of topotecan with achieved mean steady-state topotecan lactone plasma-concentrations varying from 0.62 ± 0.17 (22) to 4.4 ± 0.99 ng/ml (19). Together with the finding of mild myelotoxicity in the b.i.d. × 21-day oral administration, with a low mean C_max of 1.40 ± 0.74, myelotoxicity may be related to the topotecan plasma level rather than to the time of duration of exposure to the drug. Systemic exposure from low-dose prolonged administration of camptothecin and its derivatives 9-amino-camptothecin and 9-nitro-camptothecin showed more efficacy in tumor reduction in studies with human xenografts (14, 15), and these schedules were tolerated better than the i.v. schedules with higher doses. Apparently myelotoxicity can be circumvented by prolonged administration of low-dose topoisomerase I inhibitors.

Interpatient and—especially—intrapatient variation seemed to be most limited with o.d. × 5-day oral administration. As in previous studies with i.v. topotecan, a significant correlation of the AUC(t) day-1 topotecan and percentage decrease of leukocytes was found with all schedules. When AUC(t) per course is plotted against the percentage of decrease of leukocytes, similar sigmoidal curves are found. At MTD, AUC per course and AUC per week were similar for all oral schedules. Thus, AUC per week, as a measure of dose intensity, was not significantly different in the four schedules studied.

For oral administration of topotecan, as yet only preclinical studies on prolonged administration show remarkable antitumor effects with less toxicity as compared with shorter schedules. The four Phase I studies presented here are the first studies with oral administration of topotecan in patients with solid tumors and were not designed to confirm the above information obtained in animal models. Oral administration of topotecan, especially in the o.d. × 5-day schedule, is safe, with uncomplicated granulocytopenia as the main side effect, limited intrapatient variation, and similar dose intensity as compared with the other schedules of oral administration. Phase II studies with the daily × 5-day schedule will show whether this schedule is an active regimen. The 10-day and especially the 21-day administrations can result in unpredictable and sometimes clinically severe uncontrollable diarrhea. For these reasons and because a 5-day schedule is more convenient to patients, the o.d. × 5-day oral administration of topotecan is preferred for future studies.

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