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ORIGINAL ARTICLE

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# Phase-I dose escalation and sequencing study of docetaxel and continuous infusion topotecan in patients with advanced malignancies

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**Abstract** *Purpose*: Anti-tumor activity can often be enhanced with combination therapy in managing patients with metastatic cancer. However, dose sequence and schedule of delivery can alter the pharmacokinetics, toxicity, and anti-tumor response. Therefore, attention to drug–drug interactions which may be sequence or schedule-dependent are necessary. Docetaxel and topotecan are non-cross-resistance cytotoxic agents with activity in a variety of malignancies. The goal of this study was to determine the maximum tolerated dose of docetaxel and continuous infusion topotecan using two sequences of administration. *Experimental design*: Patients were randomized to schedule A or B and enrolled in four escalating-dose cohorts. On schedule A, docetaxel was administered over 1 h and followed by topotecan administered over 72 h. On schedule B, topotecan was given as a 72 h continuous infusion followed by a 1 h infusion of docetaxel. While the doses for the docetaxel and topotecan were the same for schedule A and schedule B, the toxicities, and thus the determination of maximum tolerated dose (MTD), were assessed independently. The plasma pharmacokinetic disposition of topotecan and docetaxel were evaluated during the first cycle of each sequence to assess drug interactions. *Results*: Thirty patients, 20 males and 10 females were evaluable for toxicity and response. Four patients were chemonaive. Mean number cycles given were 3. Grade 3/4 thrombocytopenia and neutropenia were comparable on both schedules, as was the dose-limiting toxicity (DLT) for both schedules. There were no apparent differences in absolute neutrophil count or platelet nadirs between schedules A and B for three of the four cohorts. The principal non-hematologic toxicity was nausea and vomiting. The time of overlap of topotecan lactone or total concentrations and docetaxel concentrations were greater on schedule A as compared with schedule B and was associated with reduced clearance of docetaxel on schedule A as compared to schedule B. However, the mean clearance for docetaxel (18∀16 L $h^{-1}$ $m^{-2}$ and 29∀28 L $h^{-1}$ $m^{-2}$ on schedules A and B, respectively, and topotecan 16∀10 L $h^{-1}$ $m^{-2}$ and 7∀6 L $h^{-1}$ $m^{-2}$ on schedules A and B, respectively) were not statistically different ($P > 0.05$). *Conclusions*: The observed toxicity was not sequence-dependent, despite the observed change in kinetics. Docetaxel and topotecan can be administered with acceptable toxicity at the recommended phase-II dose of docetaxel 60 mg $m^{-2}$ and topotecan 0.85 mg $m^{-2}$ $day^{-1}$×3 days.

**Keywords** Docetaxel · Topotecan · Dose-sequence · Phase-I

**Abbreviation** ECOG: Eastern Cooperative Oncology Group · ULN: Upper limit of normal · MTD: Maximum tolerated dose · DLT: Dose-limiting toxicity · PBS: Phosphate-buffer solution · AEs: Adverse events · NLIN: Non-linear · ROI: Region of interest · ANC: Absolute neutrophil count

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## Introduction

In an effort to improve survival and time to progression many solid tumors are managed with combination chemotherapy in the locally advanced or metastatic setting in patients that have adequate performance status [9, 11, 13, 14, 18]. The sequence of administration can often affect the anti-tumor activity and toxicity [1, 4]. Therefore, it is important to establish or confirm from preclinical models the optimal schedule and dose of agents when given in combination.

Camptothecins are an expanding class of anti-tumor agents, and topotecan, like other camptothecin derivatives, targets DNA topoisomerase I [19]. This nuclear enzyme reduces the torsional stress of supercoiled DNA during various phases of cellular maturation. Because topoisomerase I is cell-specific for S-phase, it was expected that protracted infusion would result in improved efficacy [6]; therefore, we pursued a Phase-I study to determine the maximum tolerated dose (MTD) and the safety of continuous infusion topotecan. Clinical activity with the agent has been observed in a variety of solid tumors [15]. The dose-limiting toxicity (DLT) as a single agent has been non-cumulative myelosuppression. Topotecan is primarily eliminated via the kidney with a small component of its metabolism via cytochrome P450 (CYP450) hepatic enzymes.

Docetaxel is a taxoid with a broad spectrum of anti-tumor activity and has produced impressive clinical results as a single drug and in combination regimens [8]. Relative to other agents in this class, intracellular retention of docetaxel may account for its lack of schedule-related myelosuppression and greater potency [5]. Docetaxel binds polymerized beta tubulin promoting assembly of the tubulin dimers to form stabilized microtubules against disassembly causing G 2/M arrest. Docetaxel principally undergoes hepatic metabolism via CYP3A4 [2]. It was expected that combining topotecan with an agent that causes arrest in the G2/M phase might result in greater cytotoxicity.

This phase-one trial was undertaken to determine the MTD of the combination and to assess the effect of sequence of administration upon MTD, toxicity, and pharmacokinetics. Although the preclinical data for studying this combination were not compelling [10], broad clinical activity for each agent and non-cross resistance make the combination worthy of evaluation in the clinic.

## Materials and methods

### Patients

Signed informed consent was obtained from each patient prior to treatment on protocol. The protocol and informed consent procedures were reviewed and approved by our Institutional Review Board of The University of Alabama at Birmingham. Patients were required to meet the following eligibility criteria:

1. histologically confirmed, non-hematologic tumors resistant to standard chemotherapy or for which no effective therapy existed;
2. measurable or evaluable disease;
3. age greater than 18 years;
4. a median survival of at least 3 months;
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leq 2$; and
6. adequate hematopoietic function (hemoglobin $>9.0$ g $dL^{-1}$; total leucocyte count $>3{,}000$ $\mu L^{-1}$; platelet count $>100{,}000$ $\mu L^{-1}$), hepatic function [bilirubin $<2.0$ g $dL^{-1}$; transaminases or alkaline phosphatase levels $<4$ times upper limit of normal (ULN)] and renal function (serum creatinine $<2.0$ g $dL^{-1}$).

The major exclusion criteria were:

1. central nervous system metastasis;
2. any woman pregnant or breast feeding;
3. major surgery, cytotoxic chemotherapy, or radiotherapy within the previous 4 weeks;
4. clinically significant cardiac disease;
5. inability to comply with or understand informed consent; and
6. serologic evidence of hepatitis or HIV infections.

### Treatment plan, and dosage and administration

The patients were randomized to receive schedule A or schedule B. On schedule A, docetaxel was administered as a 1-h infusion and followed by topotecan administered as a 72-h infusion. On schedule B, topotecan was administered as a 72-h infusion and docetaxel was administered as a 1-h infusion at the completion of the topotecan infusion. Cycles were administered every 21 days. Docetaxel was administered at doses of 50 mg $m^{-2}$ and 60 mg $m^{-2}$. Topotecan was administered at doses of 0.68, 0.85, or 1.05 mg $m^{-2}$ $day^{-1}$ for 3 days. The sequence of administration was not changed during the course of study. The DLT was determined independently for each sequence.

Patients were treated in cohorts of three to six patients at escalating doses of docetaxel and topotecan ranging from 50 to 60 mg $m^{-2}$ and 0.68 to 1.05 mg $m^{-2}$ $day^{-1}$, respectively. If one of the initial three patients demonstrated a DLT, three more patients were entered on to the cohort. If additional patients were added to a schedule because of a DLT, this arm would accrue patients at a 2:1 ratio.

The MTD was defined as one dose below the dose that induced a DLT in two or more patients in a cohort. The dose of docetaxel used in the first two cohorts was 50 mg $m^{-2}$ and was increased to 60 mg $m^{-2}$ for the third and fourth cohorts. The doses of topotecan were

0.68, 0.85, 0.85 and 1.05 mg $m^{-2}$ $day^{-1}$, respectively, for cohorts 1–4.

Patient toxicities were evaluated and graded DLT according to the modified National Cancer Institute (NCI) Common Toxicity Criteria version 2. The expected DLT included grade-4 neutropenia requiring intravenous antibiotics, grade-4 thrombocytopenia, or bleeding episodes requiring platelet transfusion. Other DLT include grade-3 fatigue, hypotension, weight gain/peripheral edema, cardiac toxicity, pulmonary toxicity, kidney/bladder toxicity, grade-2 neurocortical or neurocerebellar, urine protein $>3$ g $dL^{-1}$ 24 h, and serum albumin $<2.0$ g $dL^{-1}$.

## Pharmacokinetics

### *Sample collection and preparation*

Pharmacokinetic studies of docetaxel and topotecan were performed on cycle 1 schedules A and B. For docetaxel pharmacokinetic studies, blood samples (3 mL) were collected before administration, at 0.25, 0.5, and 1 h after the start of the infusion, and at 0.25, 2, 6, and 24 h after the end of the infusion. Blood was placed into heparinized tubes, centrifuged at 2,000*g* for 2 min, and the resulting plasma was decanted into a separate tube and stored at −70°C until analyzed.

For topotecan pharmacokinetic studies, blood samples were obtained before administration, at 0.25, 1, 6, 24, 48, and 72 h after the start of the infusion, and at 0.25, 1, 6, and 24 h after the end of the infusion. Blood was placed into heparinized tubes, centrifuged at 2,000*g* for 2 min, and the resulting plasma was decanted into a separate tube. For determination of topotecan lactone, 200 μL plasma was added to 600 μL cold methanol (−20°C), vortex mixed for 10 s, and centrifuged at 2,000*g* for 2 min. The resulting methanolic solution was removed and stored at −20°C until analyzed. For determination of topotecan total (sum of lactone and hydroxy acid), 20 μL 20% phosphoric acid was added to 400 μL methanolic solution.

## High-pressure liquid chromatography analysis

High-pressure liquid chromatography (HPLC) assay for docetaxel was modified from the assays of Loos et al. [12]. The HPLC system consisted of an HP 1050 HPLC fitted with a diode-array detector and a $C_{18}$ silica bonded separation column. (5 μm, 3×250 mm; Hypersil, Jones Chromatography, Littleton, CO, USA). The mobile phase was methanol–water, 70:30 (*v*/*v*) with a pH adjusted to 2.6 using orthophosphoric acid, and the flow rate was 0.6 mL $min^{-1}$. Docetaxel and the internal standards were detected at 230 nm. The lower limit of quantitation was 30 ng $mL^{-1}$.

Plasma concentrations of topotecan lactone and total were measured with a modification of an isocratic HPLC assay using fluorescence detection [16]. Excitation and emission wavelengths were 320 nm and 540 nm, respectively. The retention time for topotecan lactone and total was 7 min. The lower limit of quantitation was 0.5 ng $mL^{-1}$.

## Pharmacokinetic analysis

Pharmacokinetic analysis of docetaxel was performed using MAP Bayeisan estimation in ADAPT II [3]. Parameters that were estimated included the volume of the central compartment ($V_c$), intercompartment rate constants ($k_{12}$, $k_{21}$, $k_{13}$, $k_{31}$), and the elimination rate constant from the central compartment ($k_{10}$). Using standard equations, systemic clearance ($CL_{DOC}$) of docetaxel was calculated from parameter estimates.

Pharmacokinetic analysis of topotecan lactone and total were also performed using MAP Bayesian estimation in ADAPT II [3]. A two compartment, linear model was fitted to both topotecan lactone and total plasma concentration versus time profiles. Individual parameters estimated included $V_c$, and intercompartment rate constants ($k_{12}$, $k_{21}$) and $k_{10}$. Standard equations were used to calculate topotecan lactone ($CL_{LAC}$) and total ($CL_{TOT}$) systemic clearance from the parameter estimates.

To evaluate the effect of topotecan exposure on docetaxel clearance, we evaluated the duration of time that docetaxel and topotecan were simultaneously above defined concentrations. The time of overlap of docetaxel and topotecan lactone, docetaxel and topotecan total concentrations both above and measured 0.5 ng $mL^{-1}$ were calculated.

## Statistical analysis

The $CL_{DOC}$, $CL_{LAC}$, and $CL_{TOT}$ and overlap of docetaxel and topotecan lactone above 0.5 ng $mL^{-1}$ were compared between schedules A and B. Comparisons between schedules A and B were made using the exact, two-sided, Wilcoxon signed-rank test [3].

# Results

## Patient characteristics

Thirty patients were accrued to this phase-I trial. All but four patients had received at least one prior therapy. Table 1 details the patient characteristics. Patients were treated over four cohorts. There were six patients in the first two cohorts, ten in the third, and eight in the last cohort. Eighty-five courses of treatment were given during the study and twice as many males as females were treated with the combination. The median age was 53 ranging from 24 to 76 years of age. While the typical varieties of solid tumors were treated on this phase-I, the five sarcomas treated were uncommon for a solid tumor trial.

**Table 1** Patient characteristics

| | |
|---|---|
| Courses | 85 |
| Male/female | 20:10 |
| White/black | 22:8 |
| ECOG | |
| 0 | 10 |
| 1 | 17 |
| 2 | 3 |
| Age (yrs) | 53 (24–76) |
| Chemotherapy | 26 |
| 1 | 17 |
| 2 | 9 |
| Radiation | 11 |
| 1 | 8 |
| 2 | 3 |
| Tumor types | |
| Sarcoma | 5 |
| NSCLC | 4 |
| SCLC[a] | 3 |
| HCC | 3 |
| Adeno unk primary | 3 |
| Colorectal | 2 |
| Head/neck | 2 |
| RCC | 1 |
| Esophageal | 1 |
| Thyroid | 1 |
| Adrenal | 1 |
| Gallbladder | 1 |
| Testicular | 1 |
| Carcinoid | 1 |
| Breast | 1 |

[a]One mixed NSCLC/ SCLC; one small cell prostate

## Toxicity

The first patient treated on study received docetaxel 60 mg $m^{-2}$ and topotecan 0.85 mg $m^{-2}$ $day^{-1}$ doses subsequently reached in the third cohort. He developed by day 7 febrile neutropenia and was found to have urosepsis. The patient developed multi-organ failure and died. The study was closed temporarily and reopened with doses of taxotere at 50 mg $m^{-2}$ over 1 h and topotecan at 0.68 mg $m^{-2}$ $day^{-1}$ for 72 h as a continuous infusion on either schedule A or B. Grade-1 and 2 toxicities principally asthenia and nausea were observed, but there were no toxicities which required expansion of cohorts 1 and 2 (Table 2). The toxicities were notably different for schedules A and B. Hematologic toxicity was limited to manageable grade-1 or 2 changes in white blood cell counts and hemoglobin.

In the third cohort, the non-hematologic toxicity did not worsen in grade and there was no clear difference in toxicity among the two schedules. Nausea, vomiting, diarrhea, and anorexia were the most common side-effects. A grade-4 absolute neutrophil count (ANC) observed in one patient resulted in expanding the third cohort to six patients on schedule B. This degree of hematologic toxicity was not observed in patients treated on schedule A. However, the first patient treated in this trial, received the same dose and sequence used in cohort 3 of schedule A.

**Table 2** Grade 1 and 2 toxicities during cycle 1

| | Cohort 1 ($n=6$) | | Cohort 2 ($n=6$) | | Cohort 3 ($n=10$) | | Cohort 4 ($n=8$) | |
|---|---|---|---|---|---|---|---|---|
| | A | B | A | B | A | B | A | B |
| Nausea | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 |
| Vomiting | – | – | 1 | – | – | – | – | – |
| Constipation | | | | | | | 2 | – |
| Anorexia | 1 | – | – | – | – | 1 | 2 | 1 |
| Edema | – | – | – | – | – | – | 1 | – |
| Diarrhea | – | – | – | – | 2 | 2 | – | – |
| Fever | – | – | – | 1 | – | 1 | 1 | – |
| Rash | – | – | – | – | – | 1 | 1 | – |
| Hyperglycemia | – | – | – | 1 | – | – | 1 | – |
| Pain | – | – | 2 | 2 | – | 1 | 1 | – |

In the fourth cohort, six patients were treated on schedule A and two on schedule B. Two of the six patients had grade-4 ANCs and one patient required hospitalization for febrile neutropenia. Both patients treated on schedule B, cohort 4 experienced prolonged neutropenia neither required hospitalization for associated fever.

While the number of patients varied per cohort and schedule, no trend was observed for ANC and PLT nadirs between schedules A and B in the four cohorts. The ANC nadirs were lower for schedule B in cohorts 1 and 3, but higher for cohorts 2 and 4 similarly; the PLT nadirs were lower for schedule B in cohorts 1 and 4, but higher for in cohorts 2 and 3. The PLT nadir was lowest in the two patients treated on schedule B cohort 4 and the lowest ANC average was noted in the six patients treated on schedule B of cohort 3.

## Clinical response

Twenty-seven patients were evaluable for response. One patient with breast cancer who had failed or progressed on four prior chemotherapy regimens including paclitaxel had a minor response with regression of symptomatic mediastinal metastases. This response lasted for approximately 6 weeks. One patient with NSCLC had a minor response which lasted for approximately 12 weeks. Seven patients had stable disease after completing six cycles of the combination. Eighteen patients had progressive disease after two cycles.

## Pharmacokinetics

Pharmacokinetic data were not obtained for six patients due to logistical issues and sampling difficulties. This included five patients that received taxotere at 50 mg $m^{-2}$ and topotecan 0.85 mg $m^{-2}$ $day^{-1}$ on both schedules and one patient who received 60 mg $m^{-2}$ of taxotere and 0.85 mg $m^{-2}$ $day^{-1}$ of topotecan on schedule A. Pharmacokinetic studies were performed on 13 and 8 patients, respectively, from schedules A and B (Table 3).

**Table 3** Grade-3 and 4 toxicities during cycle 1

| | Cohort 1 ($n=6$) | | Cohort 2 ($n=6$) | | Cohort 3 ($n=10$) | | Cohort 4 ($n=8$) | |
|---|---|---|---|---|---|---|---|---|
| | A | B | A | B | A | B | A | B |
| ANC | – | – | – | – | 1[a] | 1 | 2 | 2 |
| Hemoglobin | – | – | 1 | – | – | – | – | – |
| Platelets | | | | | 1[a] | | 1 | 1 |

[a]First patient treated on this study

Representative plasma concentration versus time profiles of docetaxel and topotecan on schedules A and B within the same patients are presented in Figs. 1 and 2, respectively. Docetaxel pharmacokinetic data from schedules A and B are listed in Table 4. Mean ± SD clearance of docetaxel on schedules A and B were $18.3 \pm 15.6$ L $h^{-1}$ $m^{-2}$ and $29.6 \pm 27.8$ L $h^{-1}$ $m^{-2}$, respectively ($P = 0.14$). Topotecan lactone and total pharmacokinetic data from schedules A and B are listed in Tables 5 and 6, respectively. Mean ± SD $CL_{LAC}$ on schedules A and B were $42.5 \pm 13.1$ L $h^{-1}$ $m^{-2}$ and $25.0 \pm 16.6$ L $h^{-1}$ $m^{-2}$, respectively ($P = 0.12$). Mean ± SD $CL_{TOT}$ on schedules A and B were $16.6 \pm 9.8$ L $h^{-1}$ $m^{-2}$ and $8.8 \pm 6.3$ L $h^{-1}$ $m^{-2}$, respectively ($P = 0.13$).

The time of overlap of docetaxel and topotecan lactone concentrations above 0.5 ng $mL^{-1}$ on schedules A and B were $35.7 \pm 30.6$ h and $11.2 \pm 5.9$ h, respectively ($P = 0.15$). The time of overlap of docetaxel and topotecan total concentrations above 0.5 ng $mL^{-1}$ on schedules A and B were $39.8 \pm 28.4$ h and $10.6 \pm 5.3$ h, respectively ($P = 0.15$).

## Discussion

The use of combination chemotherapy in advanced disease has become more common as agents with non-overlapping toxicity profiles demonstrate improved response rates and median survivals [17]. The development of such combinations often results from observed single-agent activity in a tumor type and demonstration of added or synergistic effect in preclinical models. In addition to improved clinical activity, a combination should be tolerable. Therefore, it becomes relevant if the clinical application is limited by time or sequence-dependent dosing of agents given in combination. The agents studied in this trial have demonstrated single-agent activity in the same tumor types (ovarian, small cell lung, and breast), but cytotoxicity occurs via different molecular pathways.

The pharmacokinetic interaction between docetaxel and topotecan has previously been reported in a pharmacokinetic and pharmacodynamic study of this combination in patients with solid tumors [20]. In that trial, the pharmacokinetics and pharmacodynamics of docetaxel and topotecan were evaluated when co-administered on two different sequences of administration in each patient. On cycle 1, docetaxel was administered as a 1-h infusion on day 1 and topotecan was administered as a 0.5-h infusion on days 1–4. On cycle 2, topotecan was administered as a 0.5-h infusion on days 1–4 and docetaxel was administered on day 4. Cycles were repeated every 21 days. The mean ± SD clearance of docetaxel in cycles 1 and 2 were $75.9 \pm 79.6$ L $h^{-1}$ $m^{-2}$ and $29.2 \pm 17.3$ L $h^{-1}$ $m^{-2}$, respectively ($P < 0.046$). In addition, the mean ± SD ratio of docetaxel clearance in cycle 2 to cycle 1 calculated for individual patients was $0.53 \pm 0.46$. The authors concluded that administration of topotecan on days 1–4 and docetaxel on day 4 resulted in a decrease in docetaxel clearance and increased neutropenia.

The results of our current study would seem to be the opposite of those from the prior study. However, there are important differences in study design and pharmacokinetics between the two studies. Patients enrolled on the current trial were assigned to a sequence without cross-over which may hinder the ability to detect pharmacokinetic differences between sequences when there is high inter-patient PK variability. In the previous study topotecan was administered as a 0.5-h infusion and in

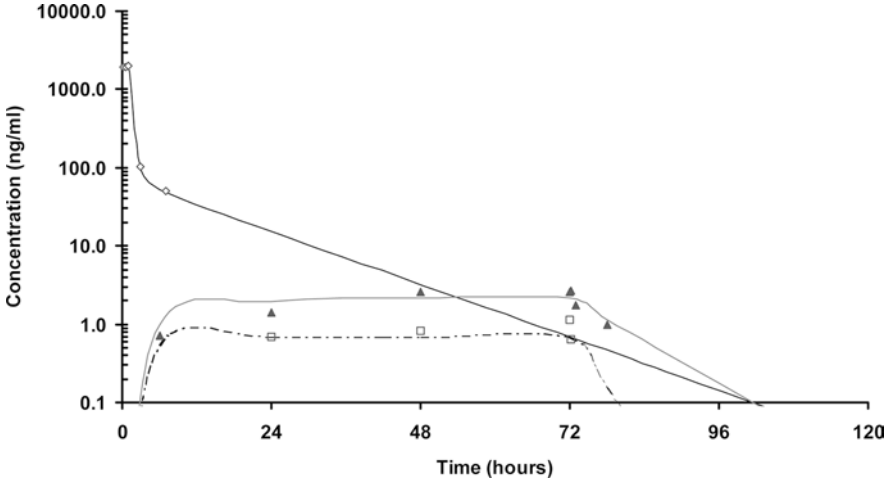


**Fig. 1** Concentration versus time profiles for docetaxel and topotecan plasma concentrations for schedule A from the same patient. Individual data and best-fit lines for docetaxel (*black line*), topotecan (total *gray line* and lactone *dashed line*, respectively) are presented

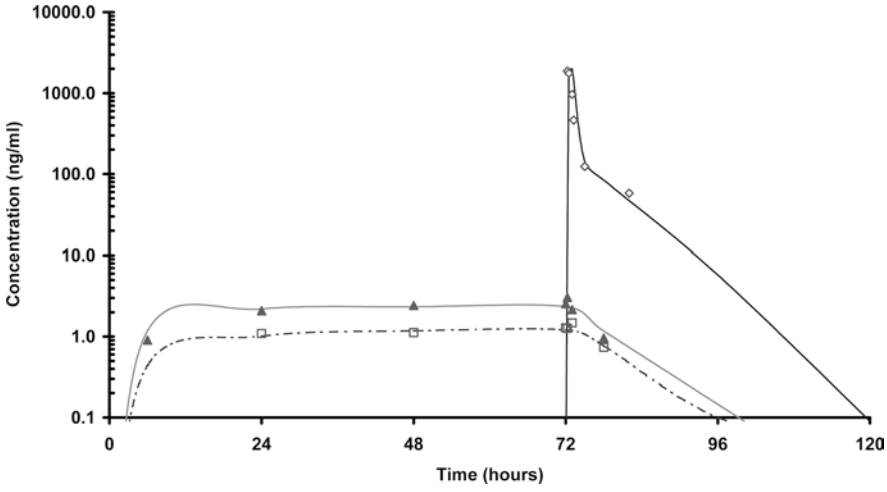


**Fig. 2** Representative docetaxel and topotecan plasma concentrations over time profiles on schedule B

**Table 4** Docetaxel pharmacokinetic parameters

| Parameter | Unit | Schedule A | | Schedule B | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| CL | $L\ h^{-1}\ m^{-2}$ | 18.3 | 15.6 | 29.6 | 27.8 |
| $k_{10}$ | $h^{-1}$ | 3.3 | 3.4 | 4.4 | 3.6 |
| $V_c$ | $L\ m^{-2}$ | 10.4 | 8.1 | 12.8 | 15.2 |
| $k_{12}$ | $h^{-1}$ | 1.8 | 0.8 | 2.4 | 0.4 |
| $k_{21}$ | $h^{-1}$ | 0.8 | 0.4 | 0.7 | 0.4 |
| $k_{31}$ | $h^{-1}$ | 39.7 | 143.0 | 0.06 | 0.01 |
| $k_{13}$ | $h^{-1}$ | 0.6 | 0.9 | 0.7 | 0.8 |

**Table 5** Topotecan lactone pharmacokinetic parameters

| Parameter | Unit | Schedule A | | Schedule B | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| CL | $L\ h^{-1}\ m^{-2}$ | 42.5 | 13.1 | 25.0 | 16.6 |
| $k_{10}$ | $h^{-1}$ | 0.5 | 0.6 | 0.8 | 1.0 |
| $V_c$ | $L\ m^{-2}$ | 229.2 | 197.4 | 317.0 | 423.0 |
| $k_{12}$ | $h^{-1}$ | 0.5 | 1.0 | 1.5 | 2.1 |
| $k_{21}$ | $h^{-1}$ | 0.4 | 0.2 | 0.3 | 0.2 |

**Table 6** Topotecan total pharmacokinetic parameters

| Parameter | Unit | Schedule A | | Schedule B | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| CL | $L\ h^{-1}\ m^{-2}$ | 16.2 | 9.8 | 8.8 | 6.3 |
| $t^{1/2}$ | h | $2.7\times10^5$ | $9.81\times10^5$ | 24.8 | 45.2 |
| $k_{10}$ | $h^{-1}$ | 0.4 | 0.5 | 0.7 | 1.1 |
| $V_c$ | $L\ m^{-2}$ | 99.6 | 79.8 | 152.7 | 185.3 |
| $k_{12}$ | $h^{-1}$ | 1.0 | 1.4 | 1.7 | 2.3 |
| $k_{21}$ | $h^{-1}$ | 0.3 | 0.2 | 0.3 | 2.0 |

the current study topotecan was administered as a 72-h infusion, and the associated topotecan concentrations were significantly lower in the current study.

There is also a significant difference in the duration of time that docetaxel and topotecan are simultaneously above the lower limit of quantitation on schedules A and B. On schedule A, topotecan is administered at the end of the docetaxel infusion as a 72-h infusion that results in a detectable concentration of topotecan for greater than 72 h whereas on schedule B docetaxel is administered after the end of the topotecan infusion and the concentration of topotecan rapidly drops below the lower limit of detection and thus was not likely to be sufficient to alter the pharmacokinetics of docetaxel. Thus, the higher and longer duration of exposure of topotecan on schedule A as compared to schedule B may result in greater alteration in docetaxel pharmacokinetics.

As a result, we evaluated the duration of time that docetaxel and topotecan were simultaneously above a concentration of 0.5 ng $mL^{-1}$. The time of overlap of topotecan lactone or total concentrations and docetaxel concentrations were greater on schedule A than on schedule B and was associated with the reduced clearance of docetaxel on schedule A compared with schedule B. The duration of time that topotecan and docetaxel are simultaneously present may determine the significance of drug–drug interactions and influence the metabolism of docetaxel. This relationship between duration of drug exposure and alteration of metabolism is consistent with drugs that inhibit metabolism via competitive mechanisms [7].

In this trial, docetaxel and topotecan were given safely with predictable toxicities and without compromising the dose of each as single agents. The recommended Phase-II dose of this combination is docetaxel 60 mg $m^{-2}$ and topotecan 0.85 mg $m^{-2}$ $day^{-1}$ every 21 days. While both schedules can be administered safely at the recommended dose, topotecan as a protracted infusion preceding taxotere is least likely to alter the kinetics of docetaxel. Although little anti-tumor response was observed in this trial, Phase-II studies designed to assess the response of this combination in the appropriate tumor types would be a rational consideration for this combination.

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