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ORIGINAL ARTICLE

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Phase I study of docetaxel and topotecan in patients with solid tumors

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Abstract *Purpose*: Both docetaxel (DOC), a promoter and stabilizer of microtubule assembly, and topotecan (TOPO), a topoisomerase I inhibitor, have shown antitumor activity in a variety of solid tumor malignancies. This phase I trial was conducted to determine the overall and dose-limiting toxicities (DLT), the maximum tolerated dose (MTD) and the pharmacokinetics of the combination of DOC and TOPO in patients with advanced solid tumor malignancies. *Methods*: DOC was administered first at 60 mg/m^2 without G-CSF and at 60, 70, and 80 mg/m^2 with G-CSF by 1-h infusion on day 1 of the odd-numbered cycles (1, 3, 5, etc.) and on day 4 of the even-numbered cycles (2, 4, 6, etc.). TOPO 0.75 mg/m^2 was administered as a 30-min infusion on days 1, 2, 3 and 4 of each cycle. G-CSF 300 μg was administered subcutaneously (s.c.) on days 5–14. Cycles were repeated every 21 days. All patients were premedicated with dexamethasone 8 mg orally every 12 h for a total of six doses starting on the day before DOC infusion. *Results*: A total of 22 patients were treated. Six patients were treated in cohort I with DOC and TOPO doses of 60 and 0.75 mg/m^2, respectively, without G-CSF, and two patients developed DLT (febrile neutropenia). Four patients were treated in cohort II with DOC and TOPO doses of 60 and 0.75 mg/m^2, respectively, with G-CSF, and no DLT was observed. Four patients were treated in cohort III with DOC and TOPO doses of 80 and 0.75 mg/m^2, respectively, with G-CSF, and three developed DLT (febrile neutropenia). DOC was then de-escalated to 70 mg/m^2 and delivered with TOPO 0.75 mg/m^2 and G-CSF (cohort IV). Eight patients were treated at this dose level, and one DLT (febrile neutropenia) was observed. Two patients developed a severe hypersensitivity reaction shortly after the DOC infusion was started, one in cycle 1 and one in cycle 2. Both patients were removed from the study. Two patients developed severe dyspnea in the presence of progressive pulmonary metastases. Other nonhematological toxicities were mild. One patient with extensively pretreated ovarian carcinoma had a partial response, and eight patients with various solid tumor malignancies had stable disease with a median time to progression of 12 weeks (range 9–18 weeks). Administration of TOPO on days 1–4 and DOC on day 4 resulted in increased neutropenia. *Conclusions*: DOC 80 mg/m^2 given first as a 1-h infusion on day 1 with TOPO 0.75 mg/m^2 given as a 0.5-h infusion on days 1, 2, 3 and 4 with G-CSF was considered the MTD. The recommended phase II dose for DOC given on day 1 is 70 mg/m^2 with TOPO 0.75 mg/m^2 given on days 1, 2, 3 and 4 every 21 days with G-CSF 300 μg s.c. on days 5–14. The alternative schedule with DOC given on day 4 and TOPO on days 1–4 is not recommended.

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Introduction

Docetaxel is a semisynthetic agent of the taxane family. Like other members of its class, docetaxel promotes the assembly and stabilization of microtubules and thus prevents their depolymerization [1]. This leads to the formation of stable microtubule bundles that disrupt the equilibrium between polymerization and depolymerization and subsequently leads to cell death [2–4]. In contrast, the vinca alkaloids and colchicine inhibit tubulin polymerization, leading to disruption of the mitotic spindle [5]. Docetaxel inhibits the depolymerization of the microtubules approximately twice as effectively as paclitaxel. In addition docetaxel is capable of inducing phosphorylation and consequent inactivation of the antiapoptotic gene, bcl-2, with a 100-fold greater efficacy than paclitaxel [6–8]. Mechanisms of resistance to docetaxel are not completely understood.

Topotecan is a semisynthetic derivative of camptothecin, and is a topoisomerase I interactive agent [9, 10]. Topoisomerase I relieves torsional strain in DNA by inducing reversible, single-strand breaks [9, 11]. Topotecan binds to the topoisomerase I/DNA complex and prevents religation of the single-strand breaks [11]. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the complex formed by topotecan, topoisomerase I and DNA [11]. Mammalian cells cannot efficiently repair these double-strand breaks.

Docetaxel is extensively metabolized by cytochrome P450-3A 4, and 98% of the drug is protein bound [12, 13]. The pharmacokinetics of docetaxel are not affected by age or sex, but the clearance of docetaxel is decreased with increasing α_1-acid glycoprotein levels and impaired hepatic function [14, 15]. When docetaxel is administered in combination with cisplatin, its clearance is similar to that of single-agent docetaxel and is unaffected by the timing of cisplatin administration. The clearance of cisplatin is also unaffected, and cisplatin does not displace docetaxel from plasma proteins [16, 17].

Both docetaxel and topotecan are independently active in a wide variety of solid tumors [18–32] and have differing mechanisms of action [9, 14]. Some, though not all in vitro evidence suggests that taxanes and topotecan may have additive, or even synergistic, activity [33, 34]. Therefore, the combination of docetaxel and topotecan has potential for future development in many solid tumors. To date, there have been no studies to determine the sequence and toxicities of the combination of docetaxel and topotecan. We therefore conducted a phase I study of docetaxel and topotecan, alternating the sequence of administration of these agents. Docetaxel was administered on day 1 in odd-numbered cycles (1, 3, 5, etc.), and day 4 in even-numbered cycles (2, 4, 6, etc.), while topotecan was administered on days 1, 2, 3, and 4 of each cycle. The dose of docetaxel was escalated, and that of topotecan remained fixed. The dose of topotecan was not escalated due to our concerns of augmented myelosuppression.

Patients and methods

Patient selection

Patients were required to have metastatic cancer for which no proven standard therapy was available. Radiographic documentation of metastatic disease was required. Patients also had to meet the following eligibility criteria: life expectancy ≥3 months, ECOG performance status ≤2, age ≥18 years, absolute neutrophil count (ANC) ≥1500/μl, platelet count (PLT) ≥100,000/μl, serum creatinine ≤1.5 mg/dl, 24-h urine creatinine clearance (CrCL) ≥50 ml/min, bilirubin ≤1.3 mg/dl, SGOT and/or SGPT not more than 2.5 times the institutional upper limit of normal (ULN) if alkaline phosphatase (AP) was less than ULN, or AP was up to four times ULN if SGOT and SGPT were ULN or less. Patients who had both SGOT and SGPT elevation more than 1.5 times ULN and AP more than 2.5 times ULN were not eligible for this study. At least 4 weeks must have elapsed from prior chemotherapy (6 weeks for nitrosoureas, and mitomycin C). Patients were not allowed to have undergone major surgery or radiation therapy within the 2 weeks preceding the start of treatment. If more than 25% of the pelvis had been irradiated, treatment was postponed for 4 weeks. All premenopausal women were required to have a negative pregnancy test and to use acceptable contraception. Patients with serious medical or psychiatric illnesses, which would prevent informed consent or intensive treatment, were excluded. All patients entering this study were informed of the investigational nature of the treatment and its potential side effects and were required to give written informed consent. This protocol was approved by the University of Maryland Institutional Review Board.

Treatment plan

Docetaxel, at the cohort-specific dose, was administered first by 1-h i.v. infusion on day 1 of odd-numbered cycles (1, 3, 5 etc) and day 4 of even-numbered cycles (2, 4, 6 etc). Topotecan was administered at a fixed dose of 0.75 mg/m^2 by 0.5-h i.v. infusion on days 1, 2, 3 and 4 of each cycle. Cycles were repeated every 21 days. The doses of docetaxel tested are shown in Table 1. In cohorts II, III and IV, G-CSF 300 μg subcutaneously (s.c.) was given on days 5–14 of each cycle of chemotherapy. All patients received oral dexamethasone prophylaxis 8 mg twice daily for six doses, starting on the day before docetaxel treatment. This was done to prevent cumulative docetaxel-related edema. In addition all patients received emesis prophylaxis consisting of dexamethasone 10 mg orally daily and granisetron 2 mg orally immediately before chemotherapy. No other chemotherapy, radiation therapy or immunotherapy was permitted while patients were on study. Patients received full supportive care, including analgesics, transfusions of blood and blood products, antibiotics, and antidiarrheals, as indicated.

A minimum of three patients were treated per cohort, and no intrapatient dose escalation was permitted. Responding patients remained on study until disease progression or the development of unacceptable toxicity. Patients who developed progressive disease at any time were removed from the protocol. Patients with stable disease could continue to receive therapy for up to six cycles beyond their maximum response. Patients were removed from the protocol if they developed an anaphylactic reaction to the chemotherapy agents, or if the termination was deemed in the best interest of the patient. Patients with hematologic dose-limiting toxicity (DLT) but also demonstrating a clinical or radiographic

Table 1 Cohort levels and dose escalation schema (*DOC* docetaxel, *TOPO* topotecan)

Cohort (number of patients)	Treatment schedule
I (6)	DOC 60 mg/m^2 day 1 (cycles 1, 3, 5) or day 4 (cycles 2, 4, 6); TOPO 0.75 mg/m^2 days 1, 2, 3, 4
II (4)	DOC 60 mg/m^2 day 1 (cycles 1, 3, 5) or day 4 (cycles 2, 4, 6); TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14
III (4)	DOC 80 mg/m^2 day 1 (cycles 1, 3, 5) or day 4 (cycles 2, 4, 6); TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14
IV (8)	DOC 70 mg/m^2 day 1 (cycles 1, 3, 5) or day 4 (cycles 2, 4, 6); TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14

benefit from the therapy were allowed to continue at the next lower dose level.

Drug administration

Docetaxel (Rhone-Poulenc Rorer), at the cohort-specific dose, was diluted in 250 ml 0.9% NaCl (USP) and administered as a 60-min i.v. infusion. Topotecan (SmithKline Beecham), at a fixed dose of 0.75 mg/m^2, was prepared in 50 ml of D5W (USP) and administered as a 30-min i.v. infusion.

Dose-limiting toxicity

Toxicities were graded according to the National Cancer Institute's Common Toxicity Criteria, version 1. For this phase I study, DLT was defined as any grade III nonhematologic toxicity (excluding alopecia or nausea/vomiting), or any grade IV hematologic toxicity persisting for more than 7 days, any instance of febrile neutropenia, or any failure to deliver one treatment cycle for more than 2 weeks because of any toxicity-related reason. Febrile neutropenia was defined as temperature ≥100.4° F and WBC ≤1000/μl.

Dose escalation and definition of the maximum tolerated dose

For this Phase I study, the maximum tolerated dose (MTD) was defined as the dose level for which no more than two instances of DLT were observed in a minimum of three and a maximum of six patients any time while on treatment. If one of the first three patients treated at a given dose level experienced a DLT, then up to an additional three patients were treated at that dose level

Dose modification

The following dose modification criteria were used. If febrile neutropenia occurred, G-CSF 300 μg s.c. on days 5–14 of subsequent cycles was started. If the platelet nadir was $<49{,}000/\mu l$, treatment was continued at a 20% dose reduction of both docetaxel and topotecan for subsequent cycles. If toxicity did not resolve by day 1 of the subsequent cycle of therapy, treatment was delayed for 1 week until myelosuppression or other toxicities resolved, and a 20% dose reduction of docetaxel and topotecan was instituted. Up to a 2 week delay was acceptable. Patients were taken off study if a delay of more than 2 weeks occurred despite the use of G-CSF and dose de-escalation. If grade III or IV nonhematologic toxicity occurred (excluding alopecia or nausea/vomiting), therapy was withheld for up to 2 weeks, and the doses of docetaxel and topotecan were reduced by 20%. Only one dose reduction was allowed while on treatment. No dose reductions were made for acute hypersensitivity reactions to docetaxel.

Patient evaluations

Pretherapy evaluation included a complete history and physical examination with performance status assessment, complete blood count with differential, PLT, electrolytes, blood urea nitrogen, serum creatinine, 24-h urine CrCL, total bilirubin, SGOT, SGPT, alkaline phosphatase, calcium, uric acid and urinalysis. Staging studies included chest radiography, bone scan, computed tomography (CT) scan of chest and abdomen, magnetic resonance imaging, or ultrasound as indicated, and were performed within 4 weeks of study entry and utilized for tumor measurements. Physical examinations were repeated at least every 3 weeks during the study and complete blood count with differential, transaminases, alkaline phosphatase, bilirubin were done on a weekly basis. Radiographic staging evaluations were performed after every two cycles of therapy.

Response and toxicity criteria

Complete response (CR) was defined as complete disappearance of all signs and symptoms of tumor for a minimum of 4 weeks. For bone disease this required complete resolution of all lytic lesions. Partial response (PR) was defined as at least a 50% decrease in the sum of the products of all the greatest perpendicular dimensions of measured lesions for a minimum of 4 weeks. No simultaneous increase in size of any lesion or appearance of any new lesion could occur. Progressive disease was defined as a $>25\%$ increase in the size of any measurable lesion or appearance of new lesions. Duration of response was measured from the first evidence of response to the first sign of progression or relapse. Duration of survival was determined from the start of chemotherapy.

Pharmacokinetic sampling

A limited sampling strategy for docetaxel and topotecan was used. Blood samples were obtained on day 1 in cycle 1 and on day 4 in cycle 2. The following sampling times were utilized: preinfusion, 5 min before end of infusion (EOI), EOI + 15 min, EOI + 30 - min, EOI + 1 h, EOI + 2 h, EOI + 4 h, EOI + 6 h, EOI + 23 h [35–38]. Blood samples (5 ml) were taken from an indwelling i.v. cannula placed in the arm contralateral to that used for the docetaxel and topotecan infusions. Samples were collected in heparinized tubes, and plasma obtained by immediate centrifugation (10 min at 2000 *g*) was decanted into a separate tube and stored at −70 °C until analyzed. Plasma docetaxel and topotecan concentrations were measured using high-performance liquid chromatography [39–41]. Clearances of docetaxel and topotecan on day 1 of cycle 1 and day 4 of cycle 2 were determined by compartmental analysis.

Results

Patient characteristics

A total of 22 patients with metastatic solid tumors were enrolled between May 1997 and November 1999, and 65 cycles were administered, 37 odd-numbered (docetaxel on day 1) and 28 even-numbered (docetaxel on day 4). The numbers of cycles per cohort are listed in Table 2. The baseline characteristics and tumor types of the 22 patients are shown in Table 3. One patient in cohort IV developed a severe hypersensitivity reaction shortly after the docetaxel infusion was started in cycle 1 of treatment and refused to continue on therapy. Another patient in cohort IV developed a severe hypersensitivity reaction to docetaxel during the second cycle of therapy, never

Table 2 Number of cycles delivered per cohort

Cohort (patients)	Schedule DOC/ TOPO doses (mg/m^2)	All cycles	Cycles (1, 3, 5 etc.), DOC day 1	Cycles (2, 4, 6 etc.), DOC day 4
Cohort I (6)	60/0.75	11	7	4
Cohort II (4)	60/0.75, G-CSF	26	12	14
Cohort III (4)	80/0.75, G-CSF	9	6	3
Cohort IV (8)	70/0.75, G-CSF	19	12	7

completed the infusion of docetaxel for this cycle and was taken off protocol. This patient did receive topotecan for days 1, 2 and 3 of the second cycle and was evaluable for toxicity. One patient with non-small cell lung cancer died 3 weeks after his first cycle of therapy. His death was due to rapid progression of disease. A second patient with seminoma died on day 8 of the second cycle of therapy. His death was also due to progression of disease. All patients had measurable or evaluable disease and were followed for response as well as toxicity.

Toxicity

Six patients developed DLTs, all febrile neutropenia. Four DLTs occurred in the odd schedule (docetaxel day 1, topotecan days 1, 2, 3, 4), and two DLTs occurred in the even schedule (docetaxel day 4, topotecan days 1, 2, 3, 4) (Table 4). Because of disease progression, five patients did not receive course two of therapy. Two patients developed grade 3 hypersensitivity reaction. One patient was lost to follow-up. The dose was reduced in two patients who experienced febrile neutropenia, one in cohort III and one in cohort IV, and these patients were allowed to remain on study because they were experiencing benefit from chemotherapy. One of these patients developed a severe hypersensitivity reaction to docetaxel during the second infusion (cycle 2) and refused further therapy on protocol. This patient was included in the toxicity evaluation. Two patients developed severe dyspnea in the presence of progressive pulmonary metastases.

In summary, disease progression or hypersensitivity reaction precluded seven patients from receiving a second cycle of therapy. Myelosuppression was the primary toxicity observed. The mean ± SD neutrophil nadirs in cycles 1 and 2 were 4857 ± 6738/μl and 2808 + 4518/μl, respectively ($P = 0.02$). The mean ± SD platelet nadirs in cycles 1 and 2 were 135,000 ± 70,000/μl and 139,000 ± 110,000/μl, respectively ($P > 0.05$). Nonhematologic toxicities were mild.

Table 4 shows the total number of patients per cohort and the DLTs observed any time while on therapy. Table 5 shows WBC, ANC, and platelet nadirs in the first two cycles of therapy only.

Table 3 Patient characteristics

Number of patients	
Total	22
Males	7
Females	15
Number of cycles	65
Race	
Caucasian	15
African American	7
ECOG Performance status (median)	1
0	6
1	13
2	3
Age (years)	
Mean	52
Range	24–72
Number of patients with prior chemotherapy	
No prior chemotherapy	3
One regimen	7
Two regimens	4
Three or more regimens	8
Number of patients with prior radiation	
One regimen	9
Two or more regimens	1
Tumor types	
Head/neck	5
Ovarian	5
Breast	2
NSCLC	3
SCLC	1
Gastric	1
Fallopian tube	1
Testicular	1
Cervical	1
Small bowel	1
Melanoma	1

Pharmacokinetics and pharmacodynamics

The pharmacokinetic data from this study have been reported separately [42]. Briefly the mean ± SD clearances of docetaxel in cycles 1 and 2 were 75.9 ± 79.6 l/h per m^2 and 29.2 ± 17.3 l/h per m^2, respectively ($P = 0.046$). The mean ± SD clearances of topotecan in cycles 1 and 2 were 8.5 ± 4.4 l/h per m^2 and 9.3 l/h per m^2, respectively ($P > 0.05$).

Response evaluation

One partial response was observed in a patient with ovarian cancer. Eight patients in this heavily pretreated patient population (cervical, fallopian tube, ovarian, breast, head and neck, and non-small-cell and small-cell cancer of the lung) had stable disease, with a median time to progression of 12 weeks (range 9–18 weeks).

Table 4 Dose-limiting toxicities (DLT) per cohort (*DOC* docetaxel, *TOPO* topotecan)

Cohort	Treatment schedule	Number of patients	Number of patients with DLT[a] (during cycles of therapy)
I	DOC 60 mg/m^2 day 1 or day 4; TOPO 0.75 mg/m^2 days 1, 2, 3, 4	6	2 (4, 1)
II	DOC 60 mg/m^2 day 1 or day 4; TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14	4	0
III	DOC 80 mg/m^2 day 1 or day 4; TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14	4	3 (2, 1, 3)
IV	DOC 70 mg/m^2 day 1 or day 4; TOPO 0.75 mg/m^2 days 1, 2, 3, 4; G-CSF 300 μg days 5–14	8	1 (1)

[a] Febrile neutropenia

Table 5 Median WBC, ANC, and platelet nadirs in cycles 1 and 2 only. Values are median nadirs (range) $\times 10^3/\mu l$ (*DOC* docetaxel, *TOPO* topotecan)

	Cycles	Cohort I (DOC/TOP 60/0.75 mg/m^2)	Cohort II (DOC/TOPO 60/0.75 mg/m^2 + G-CSF)	Cohort III (DOC/TOPO 80/0.75 mg/m^2 + G-CSF)	Cohort IV (DOC/TOPO 70/0.75 mg/m^2 + G-CSF)
WBC	Cycle 1 (DOC day 1, TOPO days 1, 2, 3, 4)	1.15 (0.5–2.3)	6 (2.7–11.6)	2 (0.6–31.7)	6.7 (4.9–25)
	Cycle 2 (DOC day 4, TOPO days 1, 2, 3, 4)	1.7 (1.2–2)	4.3 (0.9–10.6)	4.2 (1.8–26)	6.9 (3.6–17.4)
ANC	Cycle 1 (DOC day 1, TOPO days 1, 2, 3, 4)	0.428 (0.009–0.847)	4.372 (0.183–8.892)	1.226 (0.216–27.896)	3162 (0.08–23.184)
	Cycle 2 (DOC day 4, TOPO days 1, 2, 3, 4)	0.11 (0.1–0.12)	3.378 (0.162–7.844)	4.813 (0.81–25.74)	3.258 (2.844–15.486)
PLT	Cycle 1 (DOC day 1, TOPO days 1, 2, 3, 4)	88 (38–267)	114 (46–173)	116 (100–209)	78 (51–196)
	Cycle 2 (DOC day 4, TOPO days 1, 2, 3, 4)	85 (64–479)	134 (60–182)	125 (106–157)	80 (73–301)

Discussion

Docetaxel and topotecan are suitable for testing in combination as they possess a unique, non-cross-resistant mechanisms of action and, with the exception of myelosuppression, exhibit non-overlapping toxicities [9]. Docetaxel and topotecan have also each shown marked single-agent activity against a variety of solid tumors, such as ovarian, breast and lung cancer [18–32]. For these reasons, as well as because of preclinical and clinical evidence supporting combinations of taxanes and topotecan, we evaluated docetaxel and topotecan in a phase I study.

Previous studies with the combination of docetaxel and cisplatin have demonstrated that docetaxel clearance is similar to that of single-agent docetaxel and is unaffected by the timing of cisplatin administration [16, 17]. The Cancer and Leukemia Group B conducted a phase I study of topotecan and paclitaxel in patients with advanced solid tumors [43]. The principal toxicity in this study was neutropenia. Topotecan was administered at a fixed dose of 1 mg/m^2 as a 30-min i.v. infusion on days 1–5. Paclitaxel was administered as a 3-h i.v. infusion on day 1. Cycles were repeated every 21 days. When administered with topotecan in the dose specified, the MTD for paclitaxel was 80 mg/m^2 without G-CSF and 230 mg/m^2 with G-CSF.

No previous studies have determined the optimal sequence of administration and associated toxicities of the combination of docetaxel and topotecan. Thus, we elected to evaluate the toxicities and pharmacokinetics of the combination, alternating the sequence of administration of docetaxel on day 1 or 4 in combination with topotecan on days 1–4. Based on the prior data with combinations of docetaxel and cisplatin and topotecan and paclitaxel, we did not expect the pharmacokinetics and toxicities to be different when docetaxel was administered on day 1 as compared to day 4. No provisions were made in the study to assess the MTD separately for the two treatment sequences.

Our phase I study with docetaxel and topotecan has demonstrated the feasibility of administering docetaxel on day 1 or day 4 and topotecan on days 1, 2, 3 and 4 every 21 days. The recommended phase II dose of docetaxel is 70 mg/m^2 given first as a 1-h i.v. infusion on day 1 with topotecan 0.75 mg/m^2 given as a 0.5-h i.v.

infusion on days 1, 2, 3 and 4 every 21 days, with G-CSF 300 μg s.c. injections on days 5–14 after chemotherapy.

Myelosuppression was the primary toxicity, and the DLT was febrile neutropenia. The median WBC nadir was 36% (range 13–66%) and the ANC nadir 53% (range 8–76%) lower respectively in cycle 2 versus cycle 1 of treatment in nine patients. Four patients had lower WBC and ANC nadirs in cycle 1, which may suggest that the metabolism of docetaxel varies in this population, but no conclusions can be drawn due to the small number of patients. The remaining patients were de-escalated or never received cycle 2 of therapy due to progression of disease or hypersensitivity reaction. In summary, treatment with topotecan on days 1, 2 and 3 prior to the administration of docetaxel and topotecan on day 4 of the 3-week treatment cycle is not recommended because of increased neutropenia probably as a consequence of the nearly 50% decrease in docetaxel clearance [42].

G-CSF was required in order to escalate the dose of docetaxel. G-CSF is widely used in clinical practice to ameliorate the myelosuppressive side effects of chemotherapy and to increase the dose intensity of chemotherapy regimens where neutropenia is dose-limiting. Despite the use of G-CSF, our ability to escalate docetaxel was very limited due to significant myelosuppression associated with febrile neutropenia. As in most phase I clinical trials, patients included in our study had been heavily pretreated, and it is possible that patients with less prior exposure to chemotherapy might have experienced less myelosuppression. The question remains as to whether it is reasonable to offer some potentially active phase I chemotherapy combinations to patients with less prior exposure to chemotherapy as it may affect their ability to tolerate better a given regimen, especially when the primary toxicity is expected to be myelosuppression.

In conclusion, the combination of docetaxel and topotecan, at clinically meaningful doses, is feasible when G-CSF is utilized. Growth factor use may not be required in a population with less prior exposure to chemotherapy. An unexpected pharmacokinetic interaction between docetaxel and topotecan established an important difference between this combination and combinations of other chemotherapy agents with docetaxel or topotecan. Docetaxel's metabolism is affected, and the clearance was decreased when patients are pretreated with topotecan on days 1–3 [42]. This study demonstrated that empirically designed chemotherapy schedules may reveal clinically significant drug-drug interactions that can dramatically affect patient management and response to therapy.

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