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ORIGINAL ARTICLE

A Phase I trial of weekly docetaxel and topotecan for solid tumors

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Abstract

Background/Aims. Topotecan and docetaxel are active agents in the treatment of various malignant diseases. Both drugs cause dose-limiting hematologic toxicity. This study defines the maximum tolerated dose (MTD) and dose-limiting toxicity of weekly topotecan when administered in combination with docetaxel 25 mg/m^2 given day 1, 8,15 every 28 days. *Methods.* Thirteen patients were enrolled. Median age was 62 years. Majority of the patients had lung cancer. *Results.* The maximum tolerated dose was docetaxel 25 mg/m^2 and topotecan 3 mg/m^2 administered weekly. Dose-limiting toxicity was febrile neutropenia. Eight patients developed at least grade 3 neutropenia in all cycles. Non-hematologic toxicities were mild. No objective responses were noted. Two patients with non-small cell lung cancer had stable disease as a best response. *Conclusion.* Combination docetaxel and topotecan given weekly is tolerable. The recommended phase II dose is docetaxel 25 mg/m^2 and topotecan 3 mg/m^2 day 1, 8, 15 every 28 days.

Combination cytotoxic chemotherapy remains the mainstay of treatment for solid tumors, either alone or with newer targeted agents. Novel combinations of cytotoxic chemotherapy regimens are being studied using different doses and scheduling.

Topotecan is a topoisomerase I inhibitor derived from the campthotecin family of drugs. It interferes with re-ligation of cleaved DNA and leads to double stranded DNA breaks and apoptosis [1,2]. Achieving a threshold dose and sufficient exposure is important for drug efficacy [3–5]. The standard dose is 1.5 mg/m^2 daily for 5 days every 3 weeks. This results in 13–33% response rates in second-line treatment of ovarian cancer [6–8], and 11–15% in small cell lung cancer [9,10]. Dose-limiting toxicity is hematological [6–10]. Grade 3 fatigue is common. It is poorly tolerated in patients who have been heavily pre-treated.

Weekly dosing of topotecan is being studied to minimize toxicity and improve patient convenience. Weekly dosing of topotecan is effective in human melanoma xenografts and lung cancer xenografts [11]. Hoskins et al. [12] compared weekly topotecan <2 mg/m^2/week to a standard every 3 week topotecan regimen and concluded that the latter was more effective. On closer scrutiny, the clinical benefit rate (partial response + stable disease, PR + SD) was similar and achieved with less toxicity. In a separate study in ovarian cancer, Homesley et al. [13] demonstrated that anti-tumor activity was higher at doses of topotecan >2 mg/m^2 weekly compared to doses <2 mg/m^2 weekly. There was no dose-limiting myelotoxicity.

Docetaxel is a semisynthetic taxane that stabilizes microtubules and also causes drug-induced apoptosis by way of G2-M block. It is effective in lung, prostate, breast, and ovarian cancers. The incidence of grade 4 neutropenia is high when docetaxel is administered at a dose of 100 mg/m^2 every 3 weeks [14]. Other toxicities include asthenia, dermatologic effects, and fluid retention [15]. Weekly administration of docetaxel decreases hematological and other toxicities and maintains dose intensity over the conventional three week schedules. In a phase I trial, docetaxel was administered weekly for 6 weeks followed by 2 weeks rest. In this study [16], no patient experienced grade 4 neutropenia and the incidence of grade 3 neutropenia was only 14%.

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Asthenia was the dose limiting toxicity when docetaxel was administered at a dose of 52 mg/m^2 on a weekly basis.

Similar toxicity profiles occurred in phase 2 studies of weekly docetaxel. Weekly docetaxel at 36 mg/m^2 in patients with metastatic non-small cell lung cancer showed a one-year survival rate of 27% with only 8% incidence of neutropenia and 10% incidence of grade 3 fatigue [17]. This compares favorably to docetaxel given every 21 days, which obtained a 1-year survival rate of 25%, but with 28% of patients developing grade 4 neutropenia [18]. Weekly docetaxel in patients with metastatic breast cancer was similarly well tolerated. Only 14% of patients developed grade 3 neutropenia and 14% developed grade 3 fatigue [19]. The response rate was comparable to docetaxel administered every 3 weeks. Several other phase 2 studies of weekly docetaxel report similar results [20,21].

Taxanes and campthotecins combined have preclinical activity in cell lines [22]. Both docetaxel and topotecan can have pronounced hematological toxicity when given on a three-week schedule; however, each agent has proven efficacy and decreased toxicity when given on a weekly schedule. Therefore, it is reasonable to perform a phase I study of weekly docetaxel and topotecan to study this combination in patients. The principal goals of the present study were: a) to define the maximum tolerated dose (MTD) of topotecan that could be administered weekly in combination with weekly administration of docetaxel at a dose of 25 mg/m^2, b) to determine the dose-limiting toxicity (DLT) of weekly docetaxel and topotecan, c) to determine the incidence and severity of other toxicities of this combination therapy.

Patients and methods

Patient selection

Patients with histologically or cytologically proven malignancy with no curative therapy available were enrolled. Other eligibility criteria were: $\geq$18 years old; ECOG performance status 0–2 with a life expectancy $\geq$3 months; no more than 2 prior chemotherapy regimens (exclusive of any chemotherapy received in the adjuvant setting); absolute neutrophil count $\geq$1 500/mm^3, Hb $>$8 g/dl, and platelet count $\geq$100 000/mm^3; adequate liver function defined as bilirubin $\leq$upper limit of institutional normal and SGOT $\leq$2 x institutional normal, and serum creatinine $\leq$2.0 mg/dl. Patients with brain metastases were eligible if they had completed and recovered from radiation therapy. Patients who had peripheral neuropathy grade 2 or more and those who were on anticonvulsant therapy were excluded. Previous history of severe hypersensitivity reaction to docetaxel or other drug formulated with Polysorbate 80 was exclusion criteria. All patients signed informed consent. The study was approved by the Human Studies Committee of Washington University School of Medicine.

Dosage and administration

Docetaxel 25 mg/m^2 was administered intravenously over 30 minutes on Day 1 followed by administration of topotecan intravenously over 30 minutes. Five escalating dose levels of topotecan were planned (4 mg/m^2, 4.5 mg/m^2, 5 mg/m^2, 5.5 mg/m^2, 6 mg/m^2). A de-escalation dose level was planned at 3 mg/m^2 in case DLT was encountered at dose level 1. The chemotherapy was dosed weekly for 3 weeks followed by a week rest. A maximum of 6 cycles were planned. Patients received dexamethasone 8 mg orally every 12 hours for 3 doses, starting 12 hours before the planned docetaxel infusion. Patients were premedicated for nausea and vomiting using an antiemetic regimen at the discretion of treating physician.

Dose escalations proceeded as follows: If DLT occurred in 0 of 3 patients enrolled in a cohort, then the dose was escalated and enrollment started for the next cohort. If DLT occurred in 1 of 3 patients at a given dose level, up to 3 additional patients were evaluated at that dose level. If 0 of these 3 additional patients experienced DLT, then the dose was escalated and enrollment begun for the next cohort. If DLT occurred in 1 or more of the additional 3 patients, the MTD has been exceeded then up to 3 more patients were treated at the previous lower dose level for a total of 6 patients total treated at that level. If DLT occurred in 2 patients in a cohort of 2 to 6 patients at a given dose level, the MTD was exceeded and up to 3 more patients were treated at the next lower dose level for a total of 6 patients at that lower level. There was no intra-dose escalation for individual patients.

Dose-limiting toxicity

All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC version 2). The MTD was defined as the dose level immediately below the dose level at which 2 patients of a cohort (of 2 to 6 patients) experience dose-limiting toxicity during the first cycle. To be considered the MTD, a total of 6 patients had to be treated at this dose with fewer than 2 occurrences of DLT. Hematological DLT was defined as follows: grade 4 neutropenia of $>$7 days duration, neutropenic fever, grade 4 anemia or

grade 3-4 thrombocytopenia. Non-hematologic DLT was defined as any grade 3 or grade 4 non-hematologic toxicity, with the specific exclusion of grade 3 or grade 4 nausea and vomiting or diarrhea which does not respond to symptomatic treatment prior to the time for the next treatment course. Any toxicity causing a total of 14 days delay was considered dose limiting.

Pretreatment and follow-up studies

Complete physical examination and complete blood counts and baseline laboratory investigations were done before enrollment. Complete blood counts were carried out weekly. Radiographic imaging was done within 28 days of starting therapy and after every two cycles of treatment. Patients who had dose-limiting toxicities were taken off trial and were not evaluated for anti-tumor activity but remained evaluable for toxicity. Response was defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria for measurable disease [23].

Results

Thirteen patients (Table I) received 28 cycles of treatment. Patients were treated on two dose levels (Table II). The median number of cycles administered to each patient was 2 (range 1–6).

Table I. Patient characteristics.

Total	13
Sex	
Male	6
Female	7
Age	
Median	62
ECOG status	
0	5
1	8
2	0
Disease site	
Lung	9
Adrenal	1
Bladder	1
Breast	1
Oropharyngeal	1
Previous treatments	
Chemotherapy	11
Radiotherapy	6
No. of previous chemotherapy	
Median	2 (Range: 1–6)

Abbreviations: ECOG (Eastern Cooperative Oncology Group).

Table II. Dose escalation schedule.

Dose Level	Docetaxel* (mg/m^2)	Topotecan* (mg/m^2)	Total No. Patients	Total No. Cycles
−1	25	3	6**	16
1	25	4	7**	12

*Docetaxel and topotecan were given on Day 1, 8, 15 every 28 days. Docetaxel was dosed prior to topotecan.
**Two patients in each cohort did not complete full cycle due to progressive disease or toxicity.

Toxicities

Febrile neutropenia was the main dose-limiting toxicity of this regimen (Table III). Two patients on the first dose level required hospitalization for neutropenic fever as dose-limiting toxicity was reached at dose level 1. The dose was de-escalated to dose level −1. One patient had DLT at this dose defined as grade 4 thrombocytopenia. However no platelet transfusions were required. Overall grade 3/4 neutropenia occurred in 8 of 13 patients. The MTD was determined at dose level −1 (docetaxel 25 and topotecan 3 mg/m^2).

The grade 3/4 non-hematologic effects of this combination are noted in Table IV. Minimal fatigue was experienced with this regimen. Grade 3/4 dyspnea was attributed to disease progression and pneumonia in two patients. A third patient had severe unexplained back pain. He was subsequently treated for dyspnea and pneumonia from progressive disease.

Antitumor activity

Three patients were not evaluable for response as protocol therapy was discontinued after one cycle because of dose-limiting toxicities Ten patients were evaluable for anti-tumor activity. Two of the ten evaluable patients had stable disease, lasting 12

Table III. Neutrophil Nadirs.

Docetaxel/ Topotecan (mg/m^2)	No. of patients	ANC Nadir ($\times 10^9$ cells/l) Median	ANC Nadir ($\times 10^9$ cells/l) Range	Toxicity Grade (no. of pts) 1	2	3	4
Cycle 1							
25/3	6	1.19	0.54–3.08	1		3	
25/4	7	1.40	0.08–3.92		1	1	2
All Cycles							
25/3	6	2.51	0.54–4.99	3		3	
25/4	7	2.47	0.08–5.54		1	3	2

Table IV. Non-hematologic toxicity.

Cycle	Cycle 1				Overall			
Docetaxel/Topotecan (mg/m2)	25/3		25/4		25/3		25/4	
Toxicity/Grade	3	4	3	4	3	4	3	4
Dizziness					1			
Depression					1			
Insomnia						1		
Pain						1		
Shortness of breath			1		1			1

weeks and 24 weeks respectively. There were no responses. The patients who progressed did so after a median of 2 cycles of therapy.

Discussion

The combination of docetaxel 25 mg/m^2 weekly and topotecan 3 mg/m^2 weekly administered on days 1, 8, 15 on a 28 day schedule is feasible. Despite the concern for hematological toxicities in the use of each of these two agents, this combination does not require prophylactic use of filgrastim. Neutropenia observed in this study was not prolonged or cumulative.

The MTD was determined to be topotecan 3 mg/m^2 with docetaxel 25 mg/m^2. However, dose escalation was not possible and a de-escalation dose level was pre-planned in these pre-treated patients. Two patients who experienced DLT had at least 2 previous chemotherapeutic regimens, and 11 of 13 patients had at least 1 previous line of chemotherapy.

Two patients with non-small cell lung cancer achieved stable disease in this study. Both had previous radiotherapy (brain metastasis, locoregional disease). Nevertheless, achieving stable disease in this subset of patients represents a beneficial endpoint. Other studies using this combination [24] had 1 partial response in a patient with ovarian cancer and 8 patients had disease stabilization (lung, ovarian, fallopian tube, and head and neck) on an every 3 week standard dosing schedule. The same schedule and combination in a group of patients with head and neck cancers produced no responses [25]. A third study [26] using a slighter higher dose of docetaxel produced one complete response in a patient with nasopharygeal cancer and two partial responses in patients with nasopharyngeal cancer and small cell lung cancer. Each of these three trials required the use of growth factor support and had a dose-limiting toxicity of grade 4 neutropenia with fever. Unfortunately, one patient died of neutropenic sepsis in the third trial.

Since the size of these trials was so small, it would be difficult to draw any conclusions on the activity of this combination but it is promising. The results of this phase 1 study suggest that this is a feasible and safe combination when given on a weekly schedule. The recommended dose for phase II trials is docetaxel 25 mg/m^2 weekly and topotecan 3 mg/m^2 weekly for days 1,8,15 on a 28 day schedule. This regimen is worthy of further studies in small cell lung cancer, non-small cell lung cancer and ovarian cancer.

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