Phase I Trial of Concurrent Administration of Topotecan and Docetaxel for Cancer Treatment

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ABSTRACT

Docetaxel and topotecan have been used as individual chemotherapy agents in cancer treatment. However, the combined effect of these two drugs has not been thoroughly investigated. In a phase I clinical trial, patients previously treated with chemotherapy were treated with concurrent administration of the two drugs; topotecan was administered as a 30-minute infusion, followed by a 30-minute docetaxel infusion. The treatment cycle was a bi-weekly regimen with three infusions of topotecan and docetaxel (6 weeks in all) followed by a one-week rest. The original protocol started with 3 mg/m^2 of topotecan and 60 mg/m^2 of docetaxel; 3 of the 6 patients treated at this level experienced grade 4 neutropenia dose-limiting-toxicity (DLT). The dose level was subsequently revised to start with 3 mg/m^2 of topotecan and 40 mg/m^2 of docetaxel and then escalated to 4 mg/m^2 of topotecan and 50 mg/m^2 of docetaxel. Twenty-one patients were treated with the revised dose levels; only two patients experienced grade 4 neutropenia during the treatment and maximum tolerated dose was not reached. Other hematologic toxicities, such as thrombocytopenia and anemia, were noticeably absent in the patients treated with the revised protocol. Non-hematologic toxicity was rare and only at low levels for all the patients. Among the 8 breast cancer patients, 1 complete response (CR), 2 partial responses (PR), 1 minor response (MR) and 2 stable disease (SD) were observed; among the 6 small cell lung cancer patients (SCLC), 1 CR, 1 PR and 1 SD were observed. Among the 8 assessable 6 non-small cell lung cancer (NSCLC) patients, one gave a complete response and one gave a minor response. The results of this phase I study showed that the revised dose levels were well tolerated by the patients and the patient responses indicated the effectiveness of the topotecan-docetaxel combination.

Table 1. The Designed Topotecan-Docetaxel Dose Levels for One Treatment Cycle and Number of Patients Treated at Each Level

Original Dose Design for One Treatment Cycle*			
Dose Level	**Topotecan**	**Docetaxel**	**No. Patients**
1	3 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	6
2	3.5 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
3	4 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
4	4.5 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
5	5 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
6	5.5 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
7	6 mg/m^2 day 1, 15, and 29 (7 wk.)	60 mg/m^2 day 1, 15, and 29 (7 wk.)	
Revised Dose Design for One Treatment Cycle†			
Dose Level	**Topotecan**	**Docetaxel**	**No. Patients**
1R	3 mg/m^2 day 1, 15, and 29 (7 wk.)	40 mg/m^2 day 1, 15, and 29 (7 wk.)	6
2R	3.5 mg/m^2 day 1, 15, and 29 (7 wk.)	40 mg/m^2 day 1, 15, and 29 (7 wk.)	6
3R	4 mg/m^2 day 1, 15, and 29 (7 wk.)	40 mg/m^2 day 1, 15, and 29 (7 wk.)	4
4R	4 mg/m^2 day 1, 15, and 29 (7 wk.)	50 mg/m^2 day 1, 15, and 29 (7 wk.)	5

*A one-week rest was taken between 2 consecutive treatment cycles.
†After the maximum tolerable dose (MTD) was reached at level 1 of the original protocol, the patients were treated with the revised dose levels of 1R to 4R.

INTRODUCTION

The effectiveness of docetaxel in the treatment of human cancer, either as a single agent or in combination with other chemotherapeutic agents, has been shown by a number of studies. Recently, dose responses have been studied using different chemotherapy agents in a human breast cancer cell line in tissue culture.[1] The most effective drug in this tissue culture system was docetaxel. Because of its superior activity in tissue cultures and its known activity in a variety of cancers, it was tested with other drugs to determine its additive, subtractive, or synergistic effects. Different schedules were applied to these combinations. When simultaneously administered with other drugs, docetaxel's activity was reduced significantly with most chemotherapy agents. However, synergism was noted when topotecan was given simultaneously with docetaxel. When these two drugs were used sequentially (with a 24-hour time difference), only an additive effect in tumor cell killing was observed. In fact, the concurrent use of docetaxel and topotecan showed an increased effect of docetaxel in tumor cell killing, with at least 2 logs more than that using the two drugs sequentially.[2]

Docetaxel is a very active chemotherapeutic agent. Its mode of action is through binding to microtubules promoting their assembly and stabilization in order to inhibit their depolymerization. It has shown activity in breast, lung, head and neck, and other cancers.[3-14] Docetaxel shows the schedule dependence by blocking cells in the G2M phase.[15]

Topotecan is a specific inhibitor of topoisomerase I.[16] In cancer treatment, topotecan exerts its action by covalently bonding with DNA (a cleavable complex) resulting in the breakage of one of the DNA strands through a nucleophilic

Table 2. Patient Characteristics

Characteristics	Number of Patients	
Assessable for Toxicity Evaluation / Treated	24/ 27*	
Assessable for Response Evaluation / Treated	22/ 27†	
Age, Years		
Median	64	
Range	42-90	
Primary Tumor‡	Number	%
Breast	8	30%
Lung (NSCLC)	13	48%
Lung (SCLC)	6	22%

*Three NSCLC patients were not assessable for toxicity evaluation due to early death.
†Five NSCLC patients were not assessable for response evaluation, either due to early death (not related to the treatment) or due to incomplete treatment.
‡All patients had metastases to liver, lung, bone, or other sites.

attack of the phosphodiester bond. This results in lethal DNA damage during the course of DNA replication.[17]

Topotecan may delay the metabolism of docetaxel by the liver. Since topotecan and docetaxel have different modes of action and seem to have synergism as shown by in vitro and in vivo studies, a phase I clinical trial was conducted using concurrent administration of topotecan and docetaxel.

PATIENTS AND METHODS

Chemotherapy Agents

The topotecan was obtained from Glaxo SmithKline Pharmaceuticals (Collegeville, Pa) and the docetaxel was obtained from Aventis Oncology (Parsippanti, NJ). The docetaxel was premedicated with dexamethazone according to accepted protocols.

Treatment Plan

A protocol was devised to concurrently administer docetaxel and topotecan in the treatment of cancer patients. The dosage of docetaxel in the original protocol was fixed at 60 mg/m^2, based on previous clinical studies using docetaxel.[4] The initial topotecan dose of 3 mg/m^2 was derived from a weekly dose of 1.75 mg/m^2 used in another clinical trial.[18] The dose escalation of topotecan was allowed with an increment of 0.5 mg/m^2 to a maximum dose of 6 mg/m^2. Both drugs were administered as 30-minute infusions, with topotecan given one hour before docetaxel. This protocol was revised with reduced docetaxel doses (40-50 mg/m^2) when the maximum tolerable dose was reached among the first 6 patients. Both the original and the revised dose levels are given in Table 1. The administration of the agents was on a bi-weekly basis with one cycle of 3 infusions followed by a one-week rest.

Patient Inclusion Criteria

Patients were eligible for enrollment if they had metastatic or locally advanced malignancy by histologic or cytologic diagnoses. All the patients had malignancies that were either refractory to standard therapy or for which no standard therapies existed. Patients were males or females of at least 18 years of age. Prior radiation therapy was allowed if it was completed at least 4 weeks before the study entry. Prior chemotherapy was also allowed if it was completed at least 4 weeks prior to study entry, and if the patient had recovered from the

Table 3. Results of Patient Hematologic Toxicity at Different Dose Levels

Dose Level*	Toxicity†	Grade 1 / 2		Grade 3		Grade 4		Total No. of Assessable Patient
		No.	%	No.	%	No.	%	
1								5
	Neutropenia (N)	0	0%	2	40%	3	60%	
	Thrombocytopenia (T)	0	0%	2	40%	0	0%	
	Anemia (A)	0	0%	1	20%	0	0%	
1R								6
	Neutropenia (N)	1	16.7%	0	0%	1	16.7%	
	Thrombocytopenia (T)	0	0%	0	0%	0	0%	
	Anemia (A)	0	0%	0	0%	0	0%	
2R								
	Neutropenia (N)	1	25	1	25%	0	0%	4
	Thrombocytopenia (T)	0	0%	0	0%	0	0%	
	Anemia (A)	0	0%	0	0%	0	0%	
3R								
	Neutropenia (N)	2	50%	0	0%	0	0%	4
	Thrombocytopenia (T)	0	0%	0	0%	0	0%	
	Anemia (A)	0	0%	0	0%	0	0%	
4R								
	Neutropenia (N)	1	20%	1	20%	1	20%	5
	Thrombocytopenia (T)	0	0%	0	0%	0	0%	
	Anemia (A)	0	0%	0	0%	0	0%	

*See Table 1 for dose levels.
†According to the National Cancer Institution Common Toxicity Criteria.

acute toxicities of that therapy. For patients with prior nitrosoureas or mitomycin C therapy, the therapy must have been completed at least 6 weeks prior to enrollment. They all had performances of 0 to 2 on the SWOG/ECOG scale,[19] and had life expectancies of at least 12 weeks. The organ functions of all patients were adequate by the following laboratory values, obtained 15 days prior to registration: serum creatinine less than 2.0 mg/dL or a calculated creatinine clearance greater than 60 mL/min, or serum bilirubin less than or equal to 1.5 mg/dL, regardless of whether patients had liver involvement with cancer. Patients must have had a SGOT/SGPT less than 3 times the institutional upper limit of normal (ULN) values unless the liver was involved with the tumor, in which case the SGOT/SGPT must have been less than 5 times the institutional upper limit of normal. Patients must have had an absolute neutrophil count (ANC) greater than 1.5 □ 10^9/L and platelets greater than 100 □ 10^9/L. Female patients with childbearing potential must have had a negative serum pregnancy test within 7 days of study enrollment. Men and women of reproductive potential must have used an effective contraceptive method while enrolled in the study. A written informed consent was required of each participating patient.

Patient Exclusion Criteria

In addition to the above inclusion criteria, patients were carefully screened and extensive exclusion criteria were enforced in the selection of participants for this study using the criteria given below.

Table 4. Patient Responses

Group	No. of Patients Evaluable/Treated	Status before Enrollment	Responses After Treatment Number of Patients (%)					
			CR	PR	MR	SD	PD	Total
Breast Cancer	8/8	PD (8)	1 (12.5%)	2 (25%)	1 (12.5%)	2 (25%)	2 (25%)	8 (100%)
Lung Cancer (SCLC)	6/6	PD (6)	1 (16.7%)	1 (16.7%)	0 (0%)	1 (16.7%)	3 (50%)	6 (100%)
Lung Cancer (NSCLC)	8/13	PD (13)	1 (12.5%)	0 (0%)	1 (12.5%)	4 (50%)	2 (25%)	8 (100%)

Patients with known hypersensitivity to the study drugs or analogs were excluded. They could not have used any prior investigational agent within 21 days. Excluded also were the patients with any active or uncontrolled infection and patients with psychiatric disorders that would interfere with consent or follow-up. Patients must not have had concurrent active second malignancies with the exception of non-metastatic, non-melanoma skin cancer, which did not require chemotherapy or radiation therapy. The presence of symptomatic, uncontrolled central nervous system metastases or carcinomatous meningitis disqualified patients from entering the study. Patients with any other concurrent diseases, which, in the judgment of the investigator, would have made the patient inappropriate for entry into this study, were also excluded. They could not have had a history of significant myocardial disease (functional class III-IV, unstable angina, recent MI) or elevated bilirubin (see inclusion criteria).

Dose Modification

In this study, every attempt was made to maximize the full single agent doses of each drug that could be given in combination. Further dose escalation beyond the assigned levels was not allowed. Dose de-escalation by one dose level would be allowed for patients who had experienced dose-limiting-toxicity (DLT).

Hematologic and non-hematologic DLT were observed during the treatment. Following the Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria,[20] hematologic DLT in this study was defined as any of the following occurring during cycle 1 (day 1 to 29):

1. Grade 4 neutropenia (ANC < 0.5 $\times 10^9$/L) lasting at least 4 days or associated with fever of at least grade 2 or infection of at least grade 3.
2. Grade 4 thrombocytopenia (nadir platelets < 25$\times 10^9$/L).
3. Grade 4 anemia (hemoglobin < 6.5 g/dL).

In the study design, if hematologic DLT was noted in more than 2 of 6 patients at a particular dose level, dose escalation was stopped. The topotecan was to be escalated until consistently unacceptable toxicity resulted. This was done to achieve maximally tolerated doses (MTD) of both drugs, for dose recommendation in Phase II studies. The MTD is defined as the highest dose at which more than 2 of 6 patients experience hematologic DLT during cycle 1 of the treatment.

RESULTS

Twenty-seven patients were enrolled in this study for treatment using different dose levels (see Table 1). The patient information is summarized in Table 2. Weekly CBC's were obtained and the

patients were observed during the treatment for hematologic and non-hematologic toxicities.

Six patients were treated on the original dose level 1 (3 mg/m^2 of topotecan and 60 mg/m^2 of docetaxel). Three patients underwent 3 infusions of the two-drug combination, completing only one cycle of treatment. One patient underwent 6 infusions and another 4 infusions. One patient died after first infusion due to advancing, late-stage cancer, hence not assessable for evaluation. Three patients experienced dose-limiting hematologic toxicity with grade 4 neutropenia; 2 of them also experienced neutropenic fever. The other 2 patients experienced grade 3 neutropenia. Grade 3 thrombocytopenia was observed in 2 patients and grade 3 anemia was observed in one patient. The detailed toxicity data for this group is summarized in Table 3.

Twenty-one patients were treated using the revised dose levels from 1R (3 mg/m^2 of topotecan and 40 mg/m^2 of docetaxel) to 4R (4 mg/m^2 of topotecan and 50 mg/m^2 of docetaxel) (see Table 1). The toxicity data for these 4 groups are summarized in Table 3. Among the 19 patients assessable for toxicity evaluation, only 2 (one in 1R group and one in 4R group) experienced dose-limiting hematologic toxicity with grade 4 neutropenia. In addition, 4 patients experienced grade 3 neutropenia and 5 experienced neutropenia at lower levels. The revised doses did not cause any noticeable thrombocytopenia and anemia, as shown in Table 3.

Only minor non-hematologic toxicity was noted in some of the patients treated with the revised doses, except for hair loss.

The patient responses to the treatment are given in Table 4. Among the 8 breast cancer patients, one gave a complete response (CR), 2 gave a partial response (PR), and one gave a minor response (MR). Two small-cell lung cancer patients gave one CR and one PR. Even one non-small-cell lung cancer patient showed a complete response and one showed a minor response, as shown by the data in Table 4.

DISCUSSION

Hematologic dose-limiting toxicity was observed in 3 patients treated (see results in Table 3) at the first dose level of the original protocol (see Table 1), with 3 mg/m^2 topotecan and 60 mg/m^2 docetaxel, respectively. The major toxicity was neutropenia, experienced by all 5 assessable patients at different levels. Such toxicity exceeded the maximally tolerated dose (MTD) level in this protocol.

The subsequent patients were treated under a revised protocol with lowered doses of docetaxel (see Table 1). The patients tolerated the new doses (3-4 mg/m^2 of topotecan and 40-50 mg/m^2 of docetaxel). Only 2 patients (11%) experienced dose-limiting toxicity (grade 4 Neutropenia) while most patients experienced lower level hematologic toxicity and minor non-hematologic toxicity. Our clinical trial, therefore, established the maximum tolerable dose for the topotecan-docetaxel combination.

It should be noted that with the revised docetaxel doses, most of other hematologic toxicities, such as thrombocytopenia and anemia, were absent. Our results suggest a lower dosage (50 mg/mg^2) for the treatment in combination with other chemotherapy agents.

The concurrent administration of the 2 chemotherapy agents also showed effectiveness in treating cancer patients who have been previously treated by different chemotherapy agents. The breast cancer patients showed a combined 38% CR/PR rate, while the SCLC patients showed a combined 33% CR/PR rate, as shown in Table 4. Even

among the 8 assessable NSCLC patients, one gave a complete response, one gave a minor response (see Table 4).

CONCLUSION

The toxicity and response results of our Phase I study indicate that the concurrent use of the topotecan-docetaxel combination in a bi-weekly schedule could be used as a means in chemotherapy. Further studies are needed to determine the optimal doses of the 2 drugs.

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