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Phase I Trial of Weekly Topotecan and Gemcitabine in Patients With Solid Tumors

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Abstract

Objective—This phase I trial was designed to determine the maximal tolerated dose (MTD) of the combination of topotecan and gemcitabine given in a weekly schedule.

Materials and Methods—In this single-arm, open label, dose-escalation study, we administered topotecan (0.75–1.5 mg/m²) and gemcitabine (1000 mg/m²) on days 1, 8, and 15 every 4 weeks to 25 patients with advanced solid tumors.

Results—The topotecan MTD, when combined with gemcitabine, was 1.25 mg/m²/wk. Dose-limiting toxicities consisted of febrile granulocytopenia in 2 patients at the highest dose level. At the MTD, no episodes of granulocytopenia were observed, whereas 2/9 patients exhibited grade 3 thrombocytopenia. Other common grades 3–4 adverse events across all cohorts included non-neutropenic infections, fatigue, skin reactions, vomiting, and fever. One partial response and 2 stable diseases were observed in patients with nasopharyngeal carcinoma. Disease stabilization was also observed in patients with squamous cell carcinoma of the head and neck (3), nonsmall cell lung cancer (1), and thymoma (1).

Conclusions—Topotecan and gemcitabine combined in a weekly schedule exhibit a favorable toxicity profile. Efficacy results support the further evaluation of this regimen in patients with head and neck cancer (particularly nasopharyngeal carcinoma).

Keywords

gemcitabine; topotecan; weekly

Topotecan is a camptothecin derivative which forms a stable, cleavable complex with DNA-topoisomerase I, leading to breaks in the DNA strand resulting in apoptosis and cell death.¹

This cytotoxic agent is currently approved for the treatment of relapsed ovarian² and small cell lung cancers³ (single agent) and as first-line treatment for incurable cervical cancer⁴ (in combination with cisplatin).

The most commonly employed topotecan dosing schedule consists of an intravenous infusion for 3–5 consecutive days (0.75–1.5 mg/m²/d) repeated every 3 weeks.^{2–4} This standard mode of administration is associated with significant hematologic toxicities, with approximately 70% of patients experiencing grade 4 neutropenia and 29% of patients experiencing grade 4 thrombocytopenia.³ As a result, alternate intermittent topotecan regimens have been developed in an attempt to improve the side effect profile and increase efficacy.⁵ The design of these schedules is supported by preclinical rationale: nonsmall cell lung cancer cell lines exhibit a decrease in sensitivity to topotecan after 8–24 hours of exposure to the drug, accompanied by a reduction in the levels of topoisomerase I. However, 7 days after removal of topotecan from the culture medium, topoisomerase I levels return to normal, suggesting reversal of the resistance to the drug.⁶ Likewise, in a Lewis lung carcinoma mouse model, intermittent topotecan administration (maximal tolerated dose) causes sustained complete responses of tumors in the majority of the animals.⁷

Weekly topotecan regimens have been investigated in patients with a variety of solid tumors. In these early, single-agent, phase I trials, dose intensities as high as 10 mg/m² have been achieved and responses have been observed in patients with sarcoma, prostate cancer, and ovarian cancer.^{8,9} Hence, the favorable toxicity profile and the weekly schedule have opened up a window of opportunity for studying the use of topotecan in combination with other cytotoxic drugs.

Topotecan and gemcitabine have a different mechanism of action, partially nonoverlapping toxicities, and activity on tumor cells in the S-phase of the cell cycle. Preclinically, additive and synergistic cytotoxic effects of these drugs have been observed in nonsmall cell lung cancer cell lines.^{10,11} Furthermore, topotecan also has been shown to increase the expression of deoxycytidine kinase in vitro (an enzyme responsible for the activation of gemcitabine and a rate-limiting factor for the antineoplastic activity of the latter drug)¹¹, and to decrease the phosphorylation of Akt (an event demonstrated to be correlated with enhancement of gemcitabine-induced apoptosis).^{11,12}

Hence, the aim of the present study was to determine the maximal tolerated dose of the combination of weekly topotecan and gemcitabine in patients with solid tumors.

MATERIALS AND METHODS

This was a single-arm, open label, phase I, dose-escalation study using a standard “3 + 3” design. Eligible patients had a histologically confirmed diagnosis of a solid tumor not eligible for a curative treatment, and measurable disease. Additionally, patients had to be 18-year-old, have a Zubrod performance status 2, life expectancy 12 weeks, and provide written informed consent. Main exclusion criteria were defined as follows: absolute granulocyte count <1500/mm³, platelet count <100,000/mm³, hemoglobin <8 g/dL, aspartate aminotransferase and alanine aminotransferase >2× upper normal limit, bilirubin

>1.5× upper normal limit, creatinine >1.5 mg/dL, concurrent severe medical problems, pregnancy, chemotherapy received within prior 4 weeks, and prior treatment with topotecan, irinotecan, or gemcitabine.

Topotecan and gemcitabine were given as weekly intravenous infusions over 30 minutes on 3 consecutive weeks (days 1, 8, and 15 of each cycle). Each cycle was repeated every 28 days. The dose of gemcitabine was fixed at 1000 mg/m² and the dose of topotecan was initiated at 0.75 mg/m²/wk in the first cohort and escalated to 1.0, 1.25, and 1.5 mg/m²/wk in the subsequent cohorts. No inpatient dose escalations were permitted. Chemotherapy premedication consisted of granisetron 2 mg orally at the discretion of the primary physician.

Toxicity was evaluated for each dosage level and each course of therapy by weekly interviews and hematology tests. The National Cancer Institute Common Toxicity Criteria (version 2.0) was used for grading of adverse events. Chemotherapy doses within courses were adjusted as follows: absolute granulocyte count 500–999/mm³ or platelet count 50,000–99,000/mm³ or grade 2 nonhematologic toxicity (excluding alopecia, nausea, and vomiting)—75% dose administered; absolute granulocyte count <500/mm³ or platelet count <50,000/mm³ or grade 3 nonhematologic toxicity—dose was held. For subsequent courses, patients were treated on day 28, provided complete recovery of blood counts, and all nonhematologic toxicities (excluding alopecia) had occurred. Otherwise, the onset of the course was delayed for 1 week. Treatment was permanently discontinued if a subsequent course had to be delayed for 2 or more weeks. The doses for subsequent courses were reduced by 1 level if the patients had experienced grade 3 or 4 neutropenia 7 days in duration, neutropenia complicated by documented infections, or grade 4 thrombocytopenia 7 days in duration during the precedent cycle. Treatment continued until disease progression, documentation of stable disease for 4 courses, occurrence of unacceptable toxicity (and, in the investigator's opinion, the patient should not continue at a lower dose level), or development of other severe medical problems occurred.

Cohorts of 3 patients were treated in a dose-escalating fashion until the MTD was determined. Escalation to the next cohort was only allowed after the last patient enrolled in the current cohort had been followed for a minimum of 30 days after the first treatment course. The cohorts were expanded to a total of 6 patients if any patient experienced a dose-limiting toxicity, defined by grade 3 or 4 neutropenia 7 days in duration, neutropenia complicated by documented infections, or grade 4 thrombocytopenia 7 days in duration. If 2 or more patients experienced the aforementioned toxicities at a given dose level, the immediately preceding dose level was considered the MTD. A minimum of 6 patients was enrolled at the MTD level.

Assessment of response was performed every 2 courses and was determined by the World Health Organization criteria.¹³ Only patients who completed at least 2 courses of chemotherapy were evaluable for response.

The primary objective of the trial was to determine the maximal tolerated dose of the combination of weekly intravenous topotecan and gemcitabine in the study population. Data

on response rates, survival, and time to progression were also collected. Time-to-endpoint events were calculated by the Kaplan-Meier method.

The study was approved by the Institutional Review Board and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

RESULTS

Patient Characteristics

From March 1998 to May 2001, 25 patients were enrolled in the trial. All patients were evaluable for toxicity and 17 were evaluable for response. Their baseline characteristics are described in Table 1.

Treatment Characteristics

Cohorts 1, 2, 3, and 4 were assigned 7, 3, 9, and 6 patients, respectively. Number of cycles received, number of cycles delayed, and the reason for treatment discontinuation for each cohort are described in Table 2. One patient in cohort 1 and 1 patient in cohort 3 had 1 dose reduction after the first and fifth cycles, respectively.

Tolerability and Safety

In the first cohort, one of the 3 initial patients presented grade 4 granulocytopenia of more than one week duration, which prompted the expansion of the cohort. Four other patients were treated at the first dose level, with no other dose-limiting toxicities identified. Three patients were treated at the second dose level and only one grade 3 granulocytopenia of limited duration (<7 days) was observed. The third cohort initially accrued 3 patients, also with no hematologic toxicities. At the fourth dose level, one patient presented an episode of grade 3 febrile granulocytopenia after the second cycle. This cohort was expanded to a total of 6 patients, with one other episode of grade 3 febrile granulocytopenia observed. Therefore, the MTD was declared at the third dose level and additional patients were accrued to that cohort to achieve a total number of 9 treated patients at the MTD.

At the MTD, grades 3–4 hematologic toxicities were as follows: granulocytopenia (0 patients), anemia (1 patient, grade 3), and thrombocytopenia (2 patients, grade 3). The grade 3 nonhematologic toxicities were infection, pain, fever, vomiting, fatigue, candidiasis, and hemorrhage (1 patient each). One patient presented a grade 4 adverse event consisting of ototoxicity.

The complete list of grades 3–4 adverse events among all dose levels is described in Table 3.

Efficacy

Among the 17 evaluable patients, 1 partial response was observed (nasopharynx carcinoma with recurrent disease 8 months after completion of primary treatment with concurrent cisplatin, 5-fluorouracil and radiotherapy. This patient had not received treatment for recurrent disease before enrolling in this study). Two other patients with nasopharynx carcinoma (both previously exposed to platinum and 5-fluorouracil) exhibited stable disease

as best response, yielding a disease control rate of 50% among the 6 patients with this histologic diagnosis enrolled in the study. The median time to progression in this patient population was 2.8 months (range 1.9–8.3 months) and median survival was 13.2 months (range 4.3–21.7 months). Three patients (all platinum-refractory/resistant) with head and neck squamous cell carcinoma (of 7 evaluable), 1 patient with nonsmall cell lung cancer, and 1 patient with thymoma also had stable disease as best response. All other 9 patients presented disease progression upon first reimaging evaluation.

DISCUSSION

The combination of topotecan and gemcitabine has been previously studied in phase I and phase II clinical trials. Most of the phase I studies have used the 5 consecutive-day topotecan dosing schedule and demonstrated significant hematologic toxicities.^{14–16} This high incidence of bone marrow suppression associated with this combination is further illustrated by a more recent gynecologic oncology group study, which failed to find a safe regimen of gemcitabine combined with consecutive-day dosing schedule of topotecan in women with previously treated ovarian and peritoneal cancers.¹⁷

Phase II studies were subsequently launched in nonsmall cell lung cancer and ovarian cancer, based on the results of the early phase I trials.^{18–20} These studies had in common a relatively low planned dose-intensity of gemcitabine (267–500 mg/m²/wk) and grade 3 thrombocytopenia and granulocytopenia rates of 10–57% and 34–53%, respectively. No promising efficacy signal was observed so as to justify the investigation of this relatively toxic combination in phase III trials.

Two phase I trials evaluated the use of alternate, weekly topotecan regimens combined with gemcitabine in patients with advanced solid tumors and nonsmall cell lung cancer. The maximal tolerated doses were topotecan 2.0–2.5 mg/m² and gemcitabine 1000–1250 mg/m² on days 1, 8, and 15 of a 28-day cycle. At the maximal tolerated dose levels, grades 3–4 thrombocytopenia was seen in 1/13 and 0/4 patients, and grades 3–4 granulocytopenia in 2/13 and 1/4 patients, suggesting considerably less myelotoxicity than the consecutive-day dosing schedules.^{21,22} These results are in accordance with our study. The MTD defined herein was topotecan 1.25 mg/m² and gemcitabine 1000 mg/m² on days 1, 8, and 15 every 28 days, with no episodes of granulocytopenia observed at this dose level and only 2/9 patients with grade 3 thrombocytopenia. The nonhematologic toxicity profile was also favorable, with fatigue and infection representing the most common grades 3–4 treatment-related adverse events across all cohorts (4 patients each, of 25 patients). Taken together, these phase I trials demonstrate that weekly administration of gemcitabine and topotecan allows for safe delivery of both drugs, while maintaining adequate dose intensity.

Although efficacy was not the primary end point of the study, the analysis of objective responses observed in this phase I trial might lead to the identification of patients who may benefit from this cytotoxic combination. To this end, a unique patient population was enrolled in this trial, consisting mostly of squamous cell carcinomas of the head and neck and nasopharynx. Interestingly, 3 of 6 patients with nasopharyngeal carcinoma experienced a partial response or disease stabilization. Also, 3 of 7 patients with squamous cell

carcinoma of the head and neck had disease stabilization (all 3 had been exposed to platinum-based therapy in the past). Although no responses were observed in a previous phase II trial of gemcitabine conducted by the Southwest Oncology Group,²³ the European Organization for Research and Treatment of Cancer demonstrated response rates of 13% in advanced/recurrent squamous cell carcinoma of the head and neck.²⁴ Gemcitabine monotherapy has also been shown to be active in previously treated or untreated patients with nasopharyngeal carcinoma of the undifferentiated type.²⁵ On the other hand, topotecan has not demonstrated significant activity in head and neck squamous cell carcinoma²⁶ and, to our knowledge, has not been formally evaluated in phase II trials of nasopharyngeal carcinomas. Of note, one complete and one partial response have been observed in patients with nasopharyngeal carcinomas in another phase I trial of topotecan and docetaxel at our institution.²⁷

It is unclear, from the present study, whether the combination of gemcitabine and topotecan has higher antitumor activity than either drug alone. However, the tolerability of this regimen and the efficacy results seen in patients with head and neck cancers (particularly of the nasopharynx) support the further evaluation of the drugs in this disease.

Treatment of squamous cell carcinomas of the head and neck has recently incorporated the use of epidermal growth factor receptor (EGFR)-targeted agents (ie, cetuximab), either alone²⁸ or in combination with radiotherapy²⁹ or chemotherapy,³⁰ eliciting increase in survival rates in randomized phase III trials.^{29,30} Cetuximab (with carboplatin) has also been demonstrated to be active in nasopharyngeal carcinomas as well.³¹ The efficacy signal observed in this trial, combined with the fact that gemcitabine and topotecan interact with Akt (a signaling molecule downstream EGFR)^{11,12} provide a rationale for possibly adding EGFR-targeted drugs to the platform of gemcitabine- and topotecan-based treatment in future phase II studies of head and neck cancers.

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TABLE 1

Baseline Characteristics of Eligible Patients

Characteristic	No. Patients (%), N = 25
Median age, yrs (range)	54 (21–74)
Performance status	
0	1 (4%)
1	21 (84%)
2	3 (12%)
Sex	
Women	6 (24%)
Men	19 (76%)
Histological diagnosis	
Head and neck squamous cell carcinoma	12 (48%)
Nasopharynx carcinoma	7 (28%)
Small cell lung cancer	2 (8%)
Nonsmall cell lung cancer	2 (8%)
Thymoma	1 (4%)
Mesothelioma	1 (4%)
No. prior systemic treatments	
0	6 (24%)
1	13 (52%)
2	5 (20%)
3	1 (4%)
Prior systemic treatments	
Platinum	19 (76%)
Paclitaxel	12 (48%)
Iphosphamide	9 (36%)
5-fluorouracil	5 (20%)
Etoposide	3 (12%)
Doxorubicin	3 (12%)
Cyclophosphamide	2 (8%)
Other	4 (16%)
Prior radiation	
Yes	23 (92%)
No	2 (8%)

TABLE 2

Treatment Characteristics

	Cohort			
	1	2	3	4
No. patients	7	3	9	6
Total no. cycles	19	8	31	12
Median no. cycles/patient (range)	4 (1-4)	2 (1-5)	2 (1-8)	2 (1-4)
No. cycles with delays within cycle (>7 d)	2	0	1	2
No. cycles with delays in between cycles (>7 d)	2	0	2	1
No. patients (%) discontinuing treatment due to				
Disease progression	6 (86%)	3 (100%)	9 (100%)	6 (100%)
Death (not treatment-related)	1 (14%)*	0	0	0

* Death due to pulmonary edema followed by cardiac arrest.

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TABLE 3

Worst Toxicities by Grade (3–4) per Patient at Each Dose Level

Dose Level	1		2		3		4		All	
	N = 7	N = 3	N = 3	N = 9	N = 6	N = 6	N = 6	N = 25		
Grade	3	4	3	4	3	4	3	4	3	4
Hematologic toxicities										
Anemia	1		1						2	
Granulocytopenia	1	2	1				1	1	1	3
Thrombocytopenia	1	1	1	2	2				6	
Nonhematologic toxicities										
Febrile granulocytopenia					2				2	
Infection	2		1	1	1				4	
Fever	1		1						2	
Edema	1								1	
Pain	2	1	1	1	1				5	
Dyspnea	1								1	
Skin Reaction	1		1		1				2	
Vomiting			1	1					2	
Fatigue			1	1	2				4	
Candidiasis			1	1					2	
Hemorrhage			1						1	
Headache					1				1	
Epistaxis				1					1	
Ototoxicity					1				1	
Hypotension				1					1	