Phase I clinical trial of alternating belotecan and oral etoposide in patients with platinum-resistant or heavily treated ovarian cancer

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This study was designed to determine the maximum tolerated dose and toxicity profile of belotecan in combination with oral etoposide in patients with platinum-resistant or heavily treated ovarian cancer, fallopian tubal cancer, and primary peritoneal cancer. Belotecan (0.5 mg/m^2/day) was administered daily (days 1–5) followed by etoposide (50, 75 mg/day) for up to 5 days (days 6–10) every 3 weeks. Dose-limiting toxicities (DLT) were defined as follows: grade 4 neutropenia less than 1 week; either neutropenic fever less than 24 h or sepsis; grade 4 thrombocytopenia; and grade of at least 3 nonhematologic toxicity except alopecia. At the first dose level (50 mg) of etoposide, none of the three patients developed DLT, whereas DLT was observed in two of three patients at the next dose level. Thus, the dose level was reduced to 50 mg, and another three patients were enrolled. DLT was found in one of six patients who received etoposide at the dose level of 50 mg/m^2. Thus, the maximum tolerated dose was reached (50 mg of oral etoposide) and the trial was terminated. The response was evaluable in nine patients and an objective response was observed in four patients (44%) including two complete responses. The combined regimen of belotecan followed by oral etoposide showed promising activity in platinum-resistant or heavily pretreated ovarian cancer patients at the dose level of 50 mg of oral etoposide. *Anti-Cancer Drugs* 23:321–325 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Ovarian cancer is the leading cause of death among women with gynecologic cancer [1–3]. Although platinum compounds in combination with paclitaxel have shown a response rate of 70–80%, unfortunately, patients experience disease recurrence in as many as 80% of such cases [4,5]. Although a subset of the patients shows sensitivity to retreatment with platinum-based treatment, eventually these so-called 'platinum-sensitive' patients exhibit platinum resistance [6]. Although there are several cytotoxic drugs that, when administered as single agents, have shown efficacy as second-line treatment in platinum-resistant ovarian cancer, unfortunately, the overall response rates and response durations are suboptimal, because these agents have only moderate activity.

A combination of topoisomerase 1 and 2 inhibitors as a chemotherapeutic regimen is not a novel strategy. Whitacre *et al.* [7] used an in-vivo colon cancer model to demonstrate that inhibition of topoisomerase 1 resulted in a compensatory increase in topoisomerase 2 levels, which rendered the xenografts more sensitive to subsequent etoposide exposure. In ovarian cancer, a few trials suggested the possible benefit of this strategy, especially in platinum-resistant patients [8,9].

Belotecan (CKD 602, 7-[-2(*N*-isopropylamino) ethyl]-(20S)-camptothecin), a novel camptothecin derivative, can inhibit topoisomerase 1 effectively [10], and showed promising antitumor activity in solid tumor [11–14]. Especially in ovarian cancer, the use of belotecan as a single agent resulted in a 21–45% response rate, and using it in combination with cisplatin yielded a 47–69% response rate with acceptable toxicity [14–16].

Therefore, we hypothesized that another topoisomerase 1 inhibitor, belotecan, could be used in a similar paradigm of reciprocal regulation of topoisomerase 1 and 2, in combination with a topoisomerase 2 inhibitor, etoposide. Thus, in this phase I clinical trial, we evaluated the maximum tolerated dose (MTD) of sequential belotecan and oral etoposide. In addition, we assessed the feasibility and toxicity profile of the regimen.

Patients and methods

Patients

This study was approved by the Institutional Review Board of the National Cancer Institute and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients or patients' relatives to receiving protocol. Patients with recurrent

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or progressive ovarian cancer, who were histologically confirmed to have primary ovarian, fallopian tube, or primary peritoneal cancer, were eligible for this study.

Patients were required to meet the following criteria: age of 18–70 years; Eastern Cooperative Oncology Group performance status 0–2; at least one tumor lesion measuring 1 cm or more in the greater dimension [computed tomography (CT)/MRI or chest X-ray] or pretreatment serum CA-125 $> 2\times$ upper normal level (35 U/ml); at least 4 weeks' treatment-free interval from the previous treatment; and free of clinical infection. The exclusion criteria were as follows: patients previously treated with topoisomerase inhibitor, suitable candidates for curative treatment with surgery, those with a history of allergic reactions attributed to compounds of similar chemical structures or biologic composition to agents used in the study, pregnant or nursing women.

Patients were defined as platinum-resistant if they had a platinum-free interval spanning less than 6 months. Patients were defined as heavily treated if they had two or more independent courses of chemotherapeutic treatment regardless of regimens.

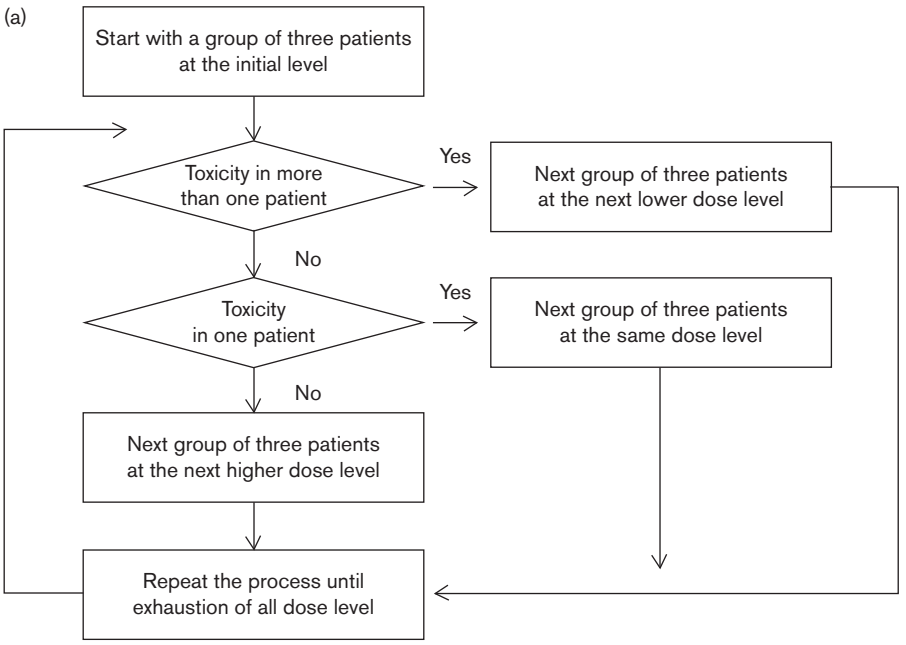
Clinical study design and treatment plan

The current study utilized the conventional design of a dose-escalating phase I trial ('3 + 3 cohort') study. The phase I trial was performed on at least nine and at most 18 patients. If none of the three patients or one of six patients had a dose-limiting toxicity (DLT), then a dose escalation at higher doses can be applied. If DLT was found in one of three patients, three patients would be added to the cohort at the same dose level. If DLT is found in more than one of three or two of six patients, the dose escalation should be terminated. The MTD is defined as one dose level below that at which the dose escalation is terminated. If the size of the MTD cohort (with one dose level below that at which the dose escalation is terminated) is 3, three more patients will be added at the same dose level to provide reliable safety-related information. Pretreatment evaluation was repeated every 3 weeks. The diagnostic imaging for response evaluation was repeated every three cycles. Figure 1 illustrates the doses and schedules for two drugs and the scheme of this study.

Belotecan was administrated as a fixed dose (30 min intravenous infusion on days 1–5, 0.5 mg/m^2/day). Belotecan

Fig. 1

(a)



(b)

Cohort	No. of patients enrolled	Belotecan (D1–D5, Q3W)	Oral etoposide (D6–D10, Q3W)
1	6	0.5 mg/m^2	50 mg
2	3	0.5 mg/m^3	75 mg

(a) Drug dose and schedules by dose level, and (b) number of patients entered.

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is diluted with 100 ml of sterile water. Belotecan was followed by oral etoposide with a starting dose of 50 mg on day 6 until day 10. The dose of etoposide was escalated by 25 mg. Treatment was administered on a 21-day schedule.

Pretreatment assessment

The pretreatment laboratory data required for eligibility are as follows: white blood cell greater than or equal to 3000 mm^3, absolute neutrophil count ANC greater than or equal to 1500, platelet count greater than or equal to 100 000, bilirubin level less than or equal to 1.5 times the institutional upper limit of normal, aspartate aminotransferase/alanine aminotransferase less than or equal to three times the institutional upper limit of normal, and serum creatinine less than or equal to 1.5 mg/dl. Pretreatment evaluation included physical examination, assessment of performance status, and measurement of the target lesion, serum electrolytes, renal and hepatic function, complete blood count, chest radiograph, ECG, and tumor markers such as CA-125 and CA 19-9. A complete tumor assessment, consisting of chest radiography and/or chest CT scan, abdominal CT and/or MRI, and physical examination, was performed within the 3 weeks before the first administration of the study medication.

Toxicity and efficacy assessment

Toxicities were graded in a prospective manner according to the Common Terminology Criteria for Adverse Events, version 3.0 during the treatment at the end of each cycle and follow-up periods. The next treatment course began on schedule provided the following criteria were met by day 21 of the previous treatment course: absolute neutrophil count greater than 1500 cells/mm^3, platelets greater than 75 000/μl. DLT was defined as follows: grade 4 neutropenia that lasted greater than 1 week; either neutropenic fever of 38.5°C that lasted greater than 24 h or sepsis; grade 4 thrombocytopenia or thrombocytopenia with bleeding that required transfusion; and grade 3–4 nonhematologic toxicity except alopecia. Toxicities were assessed after the patients had completed two cycles of treatment.

All measurable lesions were assessed within 1 week before the start of cycle 4, 3 weeks after the end cycle 6 or upon the discontinuation of treatment, and then at least every 3 months until progression was documented. Complete and partial responses were assessed using RECIST (Response Evaluation Criteria in Solid Tumors) guidelines [10]. When there was no measurable disease, the decrease in CA-125 level was used to assess the response [11]. The CA-125 response was confirmed after 4 weeks from the initial assessment. Patients who received fewer than two cycles of treatment were excluded from response evaluation.

Results

From July 2008 to November 2010, a total of nine patients with recurrent or progressive ovarian and primary peritoneal cancer were enrolled in the study. Table 1 shows the demographic data of the participating patients. The median age was 58.5 years (range 46–72). Table 2 presents detailed patient characteristics. All patients had received first-line chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 5). The median platinum-free interval was 5.7 months (range 0.8–17.3). Five of nine patients had platinum-resistant disease, which is indicated by a platinum-free interval of less than 6 months. The remaining four patients were classified as heavily treated patients who had undergone two or more

Table 1 Characteristics of the patients enrolled

	No. of patients (%)
Total enrolled	9
Eligible for response	7 (77.8%)
Age (years)	
Median	58.5
Range	46–72
Origin of disease	
Ovarian cancer	8 (88.9%)
Primary peritoneal cancer	1 (11.1%)
Initial FIGO stage	
I	0
II	1 (11.1%)
III	7 (77.8%)
IV	0
Unknown	1 (11/1%)
Histology	
Serous	7 (77. 8%)
Clear	1 (11.1%)
Poorly differentiated	1 (11.1%)
Platinum-free interval <6 months	5 (55.6%)
Previous two or more platinum-based treatments	4 (44.4%)

Table 2 Patient characteristics and outcomes

No.	Dose level (etoposide)	Indication	Number of cycles	DLT	Response	PFS (months)
1	Etoposide (50 mg)	Platinum resistant	6	No	CR	35.1
2	Etoposide (50 mg)	Heavily pretreated	4	No	PR	5.1
3	Etoposide (50 mg)	Platinum resistant	3	No	PD	3.2
4	Etoposide (75 mg)	Platinum resistant	6	No	CR	20.8
5	Etoposide (75 mg)	Heavily pretreated	3	Yes	PR	8
6	Etoposide (75 mg)	Platinum resistant	1	Yes	PD	4.5
7	Etoposide (50 mg)	Heavily pretreated	1	Yes	PD	10
8	Etoposide (50 mg)	Platinum resistant	2	No	PD	2.5
9	Etoposide (50 mg)	Heavily pretreated	5	No	SD	5.5

CR, complete response; DLT, dose-limiting toxicity; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

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Table 3 Toxicity profile by patients and by cycle

	By patients ($N=9$)			
Adverse event	Grade 0–1	Grade 2	Grade 3	Grade 4
Hematologic toxicity				
Anemia	2	3	2	2
Leukopenia	3	2	2	2
Neutropenia	2	1	2	4
Thrombocytopenia	8	0	1	0
Cardiac toxicity				
Palpitation	8	0	1	0
Gastrointestinal toxicity				
Anorexia	2	5	2	0
Diarrhea	7	1	1	0
Nausea/vomiting	4	3	2	0
Infection				
Febrile neutropenia	8	0	1	0
Fever without neutropenia	8	0	1	0
Fatigue	5	3	1	0
Metabolic toxicity				
Hyponatremia	8	0	1	0

prior episodes of platinum-based chemotherapy. A total of 31 courses of chemotherapy were administered, with a median of three courses per patient (range 1–6).

Among the first three patients, oral etoposide at 50 mg/day was well tolerated in combination with a standard dose of belotecan at 0.5 mg/m^2/day, and there was no DLT. Thus, the dose of etoposide was escalated. In the second three patients, oral etoposide at 75 mg/day resulted in DLTs in two out of three. One patient in this cohort developed grade 3 palpitation during the first cycle. Another patient developed grade 3 infection without neutropenia. Thus, the dose of oral etoposide was decreased to 50 mg/day, and the first cohort was expanded to six patients, resulting in DLT in one out of six patients. This patient developed episodes of grade 3 nausea, vomiting, and diarrhea combined with grade 3 hyponatremia. Therefore, 50 mg/day of oral etoposide was considered to be the MTD that could be combined with intravenous belotecan. Table 3 describes the toxicities of patients by treatment and by severity.

Among nine evaluable patients, an objective response was observed in four patients (44%, 95% CI = 14–79%) including two complete responses. One of these two patients received oral etoposide at a dose level of 75 mg. The detailed outcome is summarized in Table 2. After a median follow-up of 8.0 months (range 4.5–35.1 months), seven patients demonstrated disease recurrence or progression. The time to progression or recurrence ranged from 2.5 to 20.8 months. At the time of analysis, one patient had died at 15 months.

Discussion

Several clinical trials have reported on the sequential inhibition of topoisomerase 1 and 2 to treat recurrent ovarian cancer. The first phase I trial using this strategy was reported by Rose *et al.* [8]. The authors tested the feasibility of a sequential regimen consisting of prolonged oral topotecan and oral etoposide. The sequential strategy yielded objective responses in two of 13 patients (15.3%) with platinum-resistant disease, whereas the toxicity profile was tolerable in general. By combining intraperitoneal topotecan and oral etoposide, Sood *et al.* [9] observed an overall response rate of 38% including complete responses among patients with platinum-resistant disease in their phase II trial. The authors observed that the toxicity profile of the sequential regimen was tolerable without treatment-related death. Another phase I study also tested the feasibility of this sequential strategy in recurrent ovarian cancer. In the study, Gronlund *et al.* [17] could not determine the MTD of sequential intravenous topotecan and oral etoposide regimen because of hematologic toxicity. Nevertheless, they observed a high objective response rate (32%), suggesting that this strategy may be promising. Another phase I study by Levitt *et al.* [18] also tested the feasibility of this sequential regimen. They also observed a high response rate (28%) and suggested that this regimen was not cross-resistant with paclitaxel. The conclusion from the three phase I studies and one phase II study was that the sequential inhibition of topoisomerase 1 and 2 was a promising strategy with a higher toxicity profile.

Although the hypothesis of reciprocal downregulation of the topoisomerase 1 and 2 inhibitor to inhibit the development of chemoresistance has a theoretical rationale, the benefit of the combined regime has not been proven in randomized phase III trials. The recent phase III randomized trial by AGO reported that topotecan with etoposide was not more effective than topotecan monotherapy [19]. Among 208 platinum-resistant and 294 platinum-sensitive patients, the authors observed overall response rates of 27.8% (95% CI = 20.4–36.3) in the topotecan monotherapy arm and 36.1% (27.6–45.3) in the topotecan–etoposide combination arm, respectively. Thus, the authors proposed that monotherapy should be the treatment of choice, if topotecan is considered for treating recurrent ovarian cancer.

In the current phase I dose-finding study, we propose that a novel combined regimen of intravenous belotecan and oral etoposide is feasible. Our study has several merits. First, the combination has never been tried previously. Although the topotecan–etoposide failed to demonstrate superiority to topotecan monotherapy, the hypothetical rationale of combining topoisomerase 1 and 2 inhibitors may be effective in other combinations. Second, we observed encouraging antitumor activity against recurrent or progressive ovarian cancer, with a response of four patients in evaluable patients and a median progression to survival of 8.5 months. Although the small number of patients in this phase I study should be carefully considered to avoid overinterpretation of efficacy, this response rate in a study population

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consisting of platinum-resistant or heavily pretreated patients is promising. Third, the toxicity profile was easily manageable, especially when used with the 50 mg dose of etoposide. Although hematologic toxicities greater than or equal to grade 3 were seen in five patients (55.6%), we observed a favorable nonhematologic toxicity profile.

In conclusion, we found that the combined regimen of belotecan (0.5 mg/m^2 on days 1–5) and oral etoposide (50 mg on days 6–10) was feasible in patients with recurrent or progressive ovarian cancer. In addition, the use of this combination might be effective for platinum-resistant or heavily treated patients. Considering the favorable antitumor activity and manageable toxicity profile, the results from this study underscore the need for a subsequent phase II trial of this regimen in patients with recurrent or progressive ovarian cancer.

Acknowledgements

Conflicts of interest

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