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Phase II study of irinotecan in combination with bevacizumab in recurrent ovarian cancer

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HIGHLIGHTS

- Combination bevacizumab and irinotecan have anti-tumor activity in recurrent ovarian cancer
- Combination of bevacizumab and irinotecan has acceptable toxicity.
- Patients were heavily pre-treated and had received prior topotecan and bevacizumab.

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ABSTRACT

Objectives. To evaluate the efficacy and safety of irinotecan and bevacizumab in recurrent ovarian cancer. The primary objective was to estimate the progression free survival (PFS) rate at 6 months. Secondary objectives included estimation of overall survival (OS), objective response rate (ORR), duration of response, and an evaluation of toxicity.

Methods. Recurrent ovarian cancer patients with no limit on prior treatments were eligible. Irinotecan 250 mg/m2 (amended to 175 mg/m2 after toxicity assessment in first 6 patients) and bevacizumab 15 mg/kg were administered every 3 weeks until progression or toxicity. Response was assessed by RECIST or CA-125 criteria every 2 cycles.

Results. Twenty nine patients enrolled (10 were platinum-sensitive and 19 were platinum-resistant). The median number of prior regimens was 5 (range 1–12); 13 patients had prior bevacizumab and 11 prior topotecan. The PFS rate at 6 months was 55.2% (95% CI: 40%–77%). The median number of study cycles given was 7 (range 1–34). Median PFS was 6.8 months (95% CI: 5.1–12.1 months); median OS was 15.4 months (95% CI: 11.9–20.4 months). In this study, no complete response (CR) was observed. The objective response rate (ORR; PR or CR) for all patients entered was 27.6% (95% CI: 12.7%–47.2%) and the clinical benefit rate (CR + PR + SD) was 72.4% (95% CI: 52.8%–87.3%); twelve patients experienced duration of response longer than 6 months. In the 24 patients with measurable disease, a partial response (PR) was documented in 8 (30%) patients; 13 patients maintained stable disease (SD) at first assessment. The most common grade 3/4 toxicity was diarrhea. No treatment-related deaths were observed.

Conclusions. Irinotecan and bevacizumab has activity in heavily pre-treated patients with recurrent ovarian cancer, including those with prior bevacizumab and topoisomerase inhibitor use.

1. Introduction

Ovarian, fallopian tube and primary peritoneal cancers are the leading cause of mortality in gynecologic malignancies. Despite excellent response rates with platinum-based chemotherapy, most patients with advanced stage disease at presentation will relapse. Some patients with recurrent disease have a long disease course punctuated by multiple regimens of chemotherapy to control tumor growth and related

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symptoms. However, treatment options for women with multiple recurrences are limited, particularly if they have platinum resistant disease [1]. An additional challenge in this setting is to identify chemotherapy regimens that are tolerable in women who have been heavily pre-treated and thus have diminished reserve. The purpose of this trial was to investigate the combination of irinotecan and bevacizumab in patients with recurrent ovarian, fallopian tube and primary peritoneal cancers in a prospective open-label phase II clinical trial.

Camptothecin analogues bind to both the topoisomerase I enzyme and DNA resulting in a stabilizing ternary complex that prevents DNA re-ligation leading to double stranded breaks during synthesis [2]. Irinotecan, a camptothecin analog with more convenient scheduling than topotecan has demonstrated activity in ovarian cancer [3–6]. Different dosing schedules have been widely investigated in Japan. In the United States, Bodurka et al. investigated irinotecan in recurrent ovarian cancer at two doses: 300 mg/m^2 every 21 days (25 patients) and 250 mg/m^2 every 21 days (5 patients) [6]. The overall response was 17.2% and major toxicities were neutropenia, diarrhea, nausea and asthenia. A less understood mechanism of action includes inhibition of hypoxia-inducible factor 1 alpha (HIF1A), a transcriptional regulator of the cellular response to low oxygen conditions [7,8]. Overexpression of HIF1A is an important mediator of angiogenesis and tumor neovascularization, an essential pathway in metastatic disease [9]. Preclinical data suggests that SN38, the active metabolite in irinotecan, a camptothecin analog, significantly decreased the HIF1A and VEGFA (vascular endothelial growth factor A) expression of glioma cells in a dose and time-dependent manner under normoxic and hypoxic conditions. SN38 has dual anti-angiogenic actions, including both the inhibition of endothelial proliferation and tube formation, and the inhibition of the angiogenic cascade in glioma cells [10]. Similar experiments have not been performed in ovarian cancer cell lines, however, the anti-angiogenic strategy has been successful in clinical studies. Bevacizumab, a targeted inhibitor of VEGFA, has been extensively studied in ovarian cancer [11]. Strategies combining bevacizumab with chemotherapy in both the upfront and the recurrent setting have been shown to improve progression free survival [11–14]. We hypothesized that the combination of a camptothecin analog and bevacizumab would provide a tolerable regimen with activity in a unique population of heavily pre-treated patients with recurrent disease. In a phase II study of the combination of weekly topotecan with biweekly bevacizumab in platinum resistant ovarian cancer, McGonigle et al. noted greatest benefit of the regimen in patients who had received >2 prior regimens [15]. For our study, we included both platinum sensitive and platinum recurrent patients in order to capitalize on targeting a population who had been exposed to multiple lines of chemotherapy, including prior bevacizumab and prior topotecan. Because convenience of scheduling is a priority in palliative regimens for patients with recurrent disease, we selected irinotecan as our camptothecin analog to pair with bevacizumab [16] for this trial and planned a starting dose of irinotecan of 250 mg/m^2 IV as per Bodurka et al. [6]. The combination of these two agents (at a higher dose) has been previously used with safety in recurrent glioblastoma [17].

Table 1
Demographic characteristics.

Characteristic	Number of patients ($N = 29$)	%
Age, years		
Median	62	
Range	47–79	
Range	1–12	
Prior Regimens		
Median	5	
Race		
Unknown	2	7
American Indian/Alaska	0	0
Asian	3	10
Black/African-American	1	3
Native Hawaiian/Pacific	0	0
White	23	79
Ethnicity		
Hispanic/Latino	3	10
Other	24	83
Unknown	2	7
Stage of disease		
Unknown	8	28
II	1	3
III	16	55
IV	4	14
ECOG performance status		
0	8	28
1	21	72
Primary site		
Ovarian	27	93
Primary peritoneal	2	7
Number of prior regimens		
≤2	4	14
3–5	14	48
≥6	11	38
Previous regimens		
Prior bevacizumab	13	45
Prior topotecan	11	38
Response to prior platinum		
Sensitive (≥6 months)	10	34
Resistant (<6 months)	19	66

2. Subject and methods

2.1. Patients

Eligible patients had histologically confirmed ovarian epithelial, fallopian tube or primary peritoneal carcinoma that was recurrent, refractory or persistent and had either measurable or non-measurable but evaluable disease (Table 1). In the case of non-measurable disease, patients had to have at least two CA125 levels ≥ 50 at least one week apart. Patients were eligible regardless of the number or type of prior chemotherapy regimens, prior exposure to bevacizumab, or prior treatment with topotecan. Patients had Karnofsky Performance Scores ≥ 60%, adequate hematologic (ANC ≥ 1000, platelets ≥ 75,000), renal (creatinine clearance ≥ 30 mL/min, urine protein:creatinine ratio < 1) and hepatic function (bilirubin ≤ 1.5 times upper limit of normal (ULN), AST or ALT ≤ 2.5 times ULN, alkaline phosphatase ≤ 2.5 times ULN). Important exclusion criteria included contraindication to either agent, an active secondary malignancy, poorly controlled hypertension (SBP ≥ 150 and/or DBP ≥ 100), prior history of hypertensive crisis or cardiovascular disease (NYHA grade II or greater congestive heart failure, history of myocardial ischemia, unstable angina, stroke or transient ischemic attack) within six months of trial initiation. Patients were also excluded for history of abdominal fistula or if perceived to be high risk for GI perforation (history of prior perforation, partial or complete small bowel obstruction or need for total parenteral nutrition). The trial was approved by the New York University Institutional Review Board and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice policy. Each patient provided written informed consent. The trial was registered on ClinicalTrials.gov under NCT01091259.

2.2. Study design and treatment

The study was designed as a phase II open-label study. Patients were initially treated with irinotecan 250 mg/m^2 and bevacizumab 15 mg/kg IV on day 1 every 21 days until disease progression, development of toxicity or withdrawal of consent. The protocol was amended to adjust the initial dose of irinotecan to 175 mg/m^2 after dose-related toxicity was observed in the first 6 enrolled patients.

Clinical and laboratory evaluation including urine dipstick and/or urine protein to creatinine ratio were performed within 4 days of the

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