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Bevacizumab shows activity in patients with low-grade serous ovarian and primary peritoneal cancer

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Abstract

Objective—Low-grade serous (LGS) ovarian and primary peritoneal cancer is a rare disease with limited therapeutic options. Low response rates are observed with cytotoxic chemotherapy. However, significant responses have been reported in patients treated with bevacizumab. The objective of this study was to determine the response rate to bevacizumab with or without concurrent chemotherapy in patients with recurrent serous borderline or LGS ovarian or primary peritoneal cancer.

Methods—This single-institution, retrospective study examined the response rate to treatment with bevacizumab in patients with serous borderline or LGS cancer. Patients were treated at Memorial Sloan Kettering Cancer Center between 2005 and 2012. Best overall response was determined by RECIST criteria.

Results—A total of 17 patients were identified, 15 of whom were evaluable for the primary endpoint of best overall response. Two patients were treated with bevacizumab as a single agent and the remainder received bevacizumab in conjunction with chemotherapy (paclitaxel, topotecan, oral cyclophosphamide, gemcitabine, or gemcitabine and carboplatin). The median duration of bevacizumab administration in evaluable patients was 23 weeks (mean, 32.2; range, 6–79.4). There were no complete responses. Partial responses were observed in 6 patients (5 received concurrent paclitaxel, and 1 received concurrent gemcitabine). The overall response rate was 40%, with a response rate of 55% amongst the subgroup of patients with LGS cancer.

Conclusions—These results indicate that bevacizumab in combination with chemotherapy is an active treatment for recurrent LGS ovarian cancer. A prospective trial of bevacizumab in combination with paclitaxel for treatment of LGS ovarian cancer should be considered.

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Keywords

low-grade serous; ovarian cancer; serous borderline; low malignant potential; bevacizumab

Introduction

Low-grade serous ovarian cancer accounts for 10% of serous ovarian cancers and is characterized by an early age of onset (median age, 46 years), indolent growth rate, and resistance to cytotoxic chemotherapy [1-4]. Low-grade serous ovarian or primary peritoneal cancers can arise de novo, or from serous borderline disease (also called serous tumors of low malignant potential) [5-13]. It is histologically, molecularly, and clinically distinct from high-grade serous ovarian cancer [1,3,4,9,14-19]. Response rates to cytotoxic chemotherapy in both the neoadjuvant and recurrent settings are typically 4% [20-22]. Despite these low response rates, systemic chemotherapy is still the standard of care for unresectable low-grade serous ovarian cancer, primarily due to the lack of alternative effective therapeutic agents for this disease.

Patients with recurrent disease are generally treated with operative resection when feasible, while systemic chemotherapy or hormonal therapies are utilized in the unresectable setting. Hormonal therapies including tamoxifen, anastrozole, and letrozole have modest anti-tumor activity with an observed response rate of 9% in patients with recurrent low-grade serous carcinoma of the ovary or peritoneum [7].

Angiogenesis is a hallmark of neoplastic transformation and is critical for tumor growth and invasion [23]. Tumor angiogenesis is regulated by a number of cytokines and growth factors, including fibroblast growth factors, platelet-derived growth factor (PDGF), tumor necrosis factor α , interleukins 6 and 8, and vascular endothelial growth factor (VEGF). VEGF-A and its receptors, VEGF receptors 1 and 2, comprise a central signaling pathway in developmental and tumor angiogenesis [24].

Bevacizumab is a humanized anti-VEGF-A monoclonal antibody that is Food and Drug Administration (FDA) approved for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, and renal cell carcinoma. Bevacizumab has shown promising results for the treatment of recurrent ovarian cancer, either alone [25,26] or in combination with chemotherapy [27-29]; however, the vast majority of patients treated on those studies carried a diagnosis of high-grade serous ovarian cancer.

Due to the rarity of the disease, prospective trials investigating the treatment of low-grade serous ovarian cancer are lacking. Indeed, only one prospective therapeutic trial in patients with low-grade serous ovarian cancer has been completed to date, a trial in which the mitogen-activated protein kinase (MEK1/2) inhibitor selumetinib was administered to patients with recurrent low-grade serous ovarian cancer. This study reported a 15% response rate in patients treated with single-agent selumetinib [30]. Several case reports have shown responses to treatment with bevacizumab in heavily pretreated patients with low-grade serous ovarian or primary peritoneal cancer [31,32]. In the largest series reported, 17 patients with recurrent low-grade serous ovarian cancer were treated at MD Anderson

Cancer Center with bevacizumab in combination with various chemotherapies. Five partial responses were observed by Response Evaluation Criteria In Solid Tumors (RECIST) criteria out of 13 evaluable patients, yielding a surprisingly high response rate of 39% [33].

Encouraged by these results, and in an attempt to help remedy the dearth of effective therapies for this disease, we chose to conduct the current study. We examined patients with serous borderline or low-grade serous ovarian or primary peritoneal cancer who were treated with bevacizumab for recurrent disease at Memorial Sloan Kettering Cancer Center (MSK) in order to determine the response rate to anti-angiogenic therapy.

Materials and Methods

After Institutional Review Board Approval, clinical data were collected on all patients with a diagnosis of serous borderline or low-grade serous ovarian or primary peritoneal cancer who were treated with bevacizumab for recurrent disease at MSK. The dates of treatment were between July of 2005 (the date that bevacizumab was first administered off-label at MSK for this indication) and June of 2012.

Tumor histology was reviewed and confirmed by a gynecologic pathologist. Original pathology reports were reviewed to determine stage at time of diagnosis based on the 2010 American Joint Committee on Cancer (AJCC) staging system (7th edition) for ovarian and primary peritoneal cancer. All included patients were required to have had computed tomography (CT) imaging performed at MSK. CT scans were reviewed by a reference radiologist for determination of best overall response by RECIST 1.1 criteria. Stable disease (SD) was reported for those patients who achieved SD lasting ≥ 3 months. Descriptive statistics were used to summarize the data. Overall survival (OS) was calculated from the diagnosis date to date of last follow-up or death. The median OS was obtained using the Kaplan-Meier method.

Results

Seventeen patients were included in this analysis, 15 of whom were evaluable for the primary endpoint of best overall response: 10 patients with low-grade serous ovarian cancer, 3 patients with low-grade serous peritoneal cancer, and 4 patients with serous borderline disease. The mean number of prior cytotoxic therapies was 3.4 (range, 1-9; median, 2). Five patients received hormonal therapy (letrozole=2, leuprolide=1, exemestane=1, anastrozole=1) prior to treatment with bevacizumab. Patient characteristics are summarized in Table 1. Two patients, one with low-grade serous ovarian cancer and one with low-grade serous primary peritoneal cancer, experienced toxicity during treatment with bevacizumab, necessitating discontinuation of treatment prior to their first radiographic evaluation (one due to poorly healing leg ulcer, the other due to small bowel fistula formation). These 2 patients were not evaluable for the primary endpoint of best overall response.

Two patients were treated with single agent bevacizumab. The remainder (n=15) received bevacizumab in combination with weekly paclitaxel (n=7), topotecan (n=1), oral cyclophosphamide (n=3), gemcitabine (n=2), or gemcitabine and carboplatin (n=2) (Figure 1). The dose of bevacizumab administered was 10 mg/kg (n=7), 15mg/kg (n=7), or 7.5

mg/kg (n=3). The median duration of treatment for evaluable subjects, measured as date of first bevacizumab administration to date of last bevacizumab administration, was 23 weeks (mean, 32.2; range, 6-79.4).

Fifteen patients were evaluable for best overall response by RECIST 1.1 criteria. There were no complete responses (CR). A partial response was observed in 6 patients (5 received concurrent paclitaxel, and 1 received concurrent gemcitabine). Stable disease lasting 3 months was observed in 5 patients, yielding a response rate (CR+PR) of 40% and a clinical benefit rate (CR+PR+ SD) of 73.3% (Table 2). Best overall response for each patient is described in Table 3. The 5-year overall survival rate was found to be 61.8% (95% CI: 33.6-80.8%). Median overall survival was found to be 102.5 months (95% CI: 39.3-not evaluable). This is comparable to historical survival rates for low-grade serous carcinomas, where 5- and 10- year survival rates have been reported as 70% and 50% respectively[34].

Discussion

In this single-institution, retrospective study, we show that bevacizumab in combination with chemotherapy may offer a promising treatment strategy for patients with low-grade serous ovarian cancer. Our data validate those results previously reported by Schmeler et al [33], with comparable response rates to bevacizumab-based treatment.

Patients with serous borderline disease are generally unresponsive to treatment with cytotoxic chemotherapy [34-36]. It is therefore not surprising that no complete or partial responses were observed in the four patients with serous borderline disease treated here. Six of the eleven patients with low-grade serous ovarian or primary peritoneal cancer who were evaluable for objective response were found to have a partial response, yielding a response rate of 55% within this group. The finding of stable disease in 33% of patients is of limited clinical significance, given the relatively slow growth pattern of low-grade serous ovarian cancer.

This study is limited by small numbers and heterogeneous treatment schedules with regards to bevacizumab dosing and concomitant therapies. Bevacizumab was administered at doses of 15mg/kg, 10mg/kg, or 7.5mg/kg; notably, responses were seen in patients treated with each of these doses. Weekly paclitaxel was the most common chemotherapy administered in conjunction with bevacizumab and accounted for 5 of the 6 responses seen. The most commonly administered dose of weekly paclitaxel was 60mg/m² (n=3), followed by 80mg/m² (n=2), and 70mg/m² (n=2). No responses were seen in the 2 patients treated with bevacizumab as a single agent.

Prior prospective studies of bevacizumab in combination with chemotherapy for treatment of recurrent epithelial ovarian cancer have shown response rates of 24%-78.5% [27-29]; however, the majority of patients enrolled on those trials were treated for high-grade serous ovarian cancer and prospective data regarding treatment of patients with low-grade serous ovarian cancer are lacking.

The observed 40% response rate overall, and 55% response rate among patients with low-grade serous histology, is substantially higher than the anticipated 4% response rate to

chemotherapy alone and is remarkably similar to data reported in abstract form by Schmeler et al. [33]. The results presented here indicate that bevacizumab in combination with chemotherapy is an active treatment for recurrent low-grade serous ovarian cancer. A prospective trial of bevacizumab in combination with weekly paclitaxel for treatment of recurrent low-grade serous ovarian cancer is recommended.

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Figure 1. Treatments Administered and Best Response

Bev: bevacizumab, PD: progressive disease, NE: not evaluable, PR: partial response, SD: stable disease.

Table 1
Characteristics of 17 patients with serous borderline or low-grade serous cancer treated with bevacizumab for recurrent disease

Stage at Diagnosis	# of Patients	%
IC	1	5.9%
IIC	1	5.9%
IIIA	2	11.8%
IIIB	1	5.9%
IIIC	10	58.8%
IV	2	11.8%
Total	17	
Age at Diagnosis		
Median (Mean)	47 years (47.4)	
Range	15-71 years	
Patients treated with prior hormonal therapy	# of patients	%
	5	29.4%
Number of Prior Cytotoxic Therapies		
Median (Mean)	2 (3.4)	
Range	1-9	

Table 2
Best overall response by RECIST 1.1

Response	# Patients (out of 15 evaluable)	%	Mean # of prior cytotoxic treatments (range)
Complete Response	0		
Partial Response	6	40%	3.2 (1-7)
Stable Disease	5	33.3%	4 (2-9)
Progressive Disease	4	26.7%	3.5 (2-5)

Table 3
Summary of histology, treatment, and best overall response for all included patients

Patient #	Histology	Treatment	Bev dose	Best overall response by RECIST 1.1
1	LGSOC	Bev + Paclitaxel	10 mg/kg	PR
2	LGSOC	Bev + Paclitaxel	10 mg/kg	PR
3	LGSOC	Bev + Paclitaxel	15 mg/kg	PR
4	LGSOC	Bev + Paclitaxel	15 mg/kg	PR
5	LGSP	Bev + Paclitaxel	10 mg/kg	PR
6	LGSOC	Bev + Paclitaxel	10 mg/kg	SD
7	SB(MP)	Bev + Paclitaxel	7.5 mg/kg	PD
8	LGSP	Bev + Topotecan	10 mg/kg	NE
9	LGSOC	Bev + oral cyclophosphamide	7.5 mg/kg	SD
10	LGSOC	Bev + oral cyclophosphamide	10 mg/kg	PD
11	LGSOC	Bev + oral cyclophosphamide	10 mg/kg	PD
12	LGSOC	Bev + Gemcitabine	7.5 mg/kg	PR
13	SB(II)	Bev + Gemcitabine	15 mg/kg	SD
14	SB(NII)	Bev + Gemcitabine + Carboplatin	15 mg/kg	SD
15	SB(NII)	Bev+ Gemcitabine + Carboplatin	15 mg/kg	PD
16	LGSP	Bev	15 mg/kg	SD
17	LGOC	Bev	15 mg/kg	NE

LGSOC: low-grade serous ovarian cancer, LGSP: low-grade serous primary peritoneal cancer, S (II): serous borderline with invasive implants, SB (NII): serous borderline with non-invasive implants, SB (MP): serous borderline with micropapillary features, Bev: bevacizumab, PR: partial response, SD: stable disease lasting 3 months, PD: progressive disease, NE: not evaluable.