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Activity of bevacizumab-containing regimens in recurrent low-grade serous ovarian or peritoneal cancer: A single institution experience☆

Heather J. Dalton [a,1], Nicole D. Fleming [a], Charlotte C. Sun [a], Priya Bhosale [b], Kathleen M. Schmeler [a], David M. Gershenson [a,*]

[a] Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, United States
[b] Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

HIGHLIGHTS

- Bevacizumab has significant activity in recurrent low-grade serous carcinoma.
- A significant proportion of women discontinued bevacizumab due to adverse events.
- Based on this large, retrospective experience, a prospective clinical trial is warranted.

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ABSTRACT

Objective. The aim of this study was to evaluate the activity of bevacizumab in a cohort of women with recurrent low-grade serous carcinoma of the ovary or peritoneum.

Methods. This single-institution retrospective study assessed all patients at MD Anderson Cancer Center with recurrent low-grade serous ovarian or peritoneal cancer who received bevacizumab from 2007 to 2016. Study endpoints included best response, median progression-free survival, median overall survival, and toxicity.

Results. Forty patients received 45 separate "patient-regimens." Most received bevacizumab in combination with chemotherapy. Complete response (CR) was seen in 7.5%, while 40% had partial responses (PR) and 30% achieved stable disease (SD). Disease progression occurred in nine patients (22.5%). Overall response rate (CR + PR) to bevacizumab-containing regimens was 47.5%. Clinical benefit (CR + PR + SD) was seen in 77.5% of patients. Median progression free survival was 10.2 months (95% CI 7.9, 12.4). Median overall survival was 34.6 months (95% CI 29.5, 39.7). Fifteen patients discontinued bevacizumab related to toxicity.

Conclusions. Bevacizumab, most often in combination with chemotherapy, has activity in recurrent low-grade ovarian cancer and should be considered a treatment option for these patients. Further investigation into the most effective chemotherapeutic agent in combination with bevacizumab is warranted.

1. Introduction

Low-grade serous ovarian cancer (LGSOC) or peritoneal cancer (LGSPC) presents unique clinical challenges. While this histology accounts for only 10% of serous ovarian cancers, these tumors are more chemoresistant than their high-grade serous counterparts [1–5]. Standard platinum-based chemotherapy is less effective in this subtype, prompting the exploration of alternative treatment approaches, including greater emphasis on surgical resection, the use of hormonal therapies, alternative chemotherapy combinations, and targeted agent therapies [6–11].

Given the importance of angiogenesis in tumor growth, therapies targeting VEGF and other angiogenic pathways have been the subject

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* Corresponding author at: Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Unit 1362, 1155 Pressler Drive, Houston, TX 77030, United States.
E-mail addresses: Heatherjdalton@gmail.com (H.J. Dalton), Nfleming@mdanderson.org (N.D. Fleming), CCSun@mdanderson.org (C.C. Sun), Priya.Bhosale@mdanderson.org (P. Bhosale), KSchmele@mdanderson.org (K.M. Schmeler), dgershen@mdanderson.org (D.M. Gershenson).
[1] Present Address: Arizona Oncology, 2222 E. Highland Ave, Phoenix, AZ.

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of intense investigation. Bevacizumab (Avastin©, Roche) is a monoclonal VEGF-A antibody with demonstrated activity in ovarian cancer, both alone and in combination with chemotherapeutic agents. Although several trials have demonstrated activity of bevacizumab in multiple clinical settings including primary; recurrent, platinum-sensitive; and recurrent, platinum-resistant epithelial ovarian cancer [12–18], the majority of patients included had high-grade serous ovarian cancer.

In 2010, Schmeler et al. reported our preliminary experience in treating 17 women with recurrent low-grade serous carcinoma of the ovary or peritoneum with bevacizumab [19]. In that report, an objective response rate of 39% and an overall clinical benefit rate of 62% were observed. Subsequent retrospective cohort studies of bevacizumab in low-grade serous carcinoma reported similar findings [20,21]. The purpose of this study is to examine our single-institution, updated experience with the use of bevacizumab in the treatment of recurrent low-grade serous carcinoma of the ovary or peritoneum.

2. Methods

An institutional review board–approved longitudinal database—the Low-Grade Serous Tumor Database—was established in 2007. Data collection is both retrospective and prospective in nature. A waiver of informed consent was granted for patients who had not been seen at our institution for ≥1 year. All others provided written informed consent. Eligibility criteria for inclusion in this study were: 1) pathologically confirmed, recurrent low-grade serous carcinoma of the ovary or peritoneum, 2) treatment with bevacizumab, and 3) adequate clinical information.

Pathology slides of all patients in the database were reviewed by MD Anderson gynecologic pathologists and documented as LGSOC or LGSPC. Criteria for the diagnosis of low-grade serous carcinoma have been previously reported [22,23].

Database elements included demographic information, number of prior treatment regimens, details of the bevacizumab-containing regimen, duration and dates of bevacizumab therapy, platinum status at the time of treatment with bevacizumab, reasons for discontinuation of bevacizumab, associated adverse events of bevacizumab therapy, date of disease progression on bevacizumab, disease status at date of last contact, and date of last contact or death.

Imaging studies were reviewed by a single radiologist (PB), and clinical response was determined using RECIST 1.1 criteria [24]. Stable disease (SD) was reported for those patients who met RECIST 1.1 criteria for a minimum of 12 weeks.

Statistical analyses were performed using IBM SPSS Statistics (version 21, Armonk, NY). Progression-free survival (PFS) was calculated from the date of the start of bevacizumab therapy to date of disease progression or the date of death, whichever occurred first. Overall survival (OS) was calculated from the date of the start of bevacizumab therapy to date of last contact or death resulting from any cause. Cumulative distributions of OS and PFS were estimated using the Kaplan-Meier method [25].

3. Results

Between 2007 and 2016, 40 patients evaluated at our institution with recurrent low-grade serous carcinoma of the ovary or peritoneum received bevacizumab therapy. Five of these 40 patients received bevacizumab on two separate occasions, for a total of 45 "patient-regimens." Characteristics of these 40 patients are summarized in Table 1.

The median age of patients was 43.8 years (range 20.8–80.2 years). The median number of prior regimens was 4 (range, 1–15). The average duration of bevacizumab treatment was four months, with a range of 0.7 to 43.9 months. Of the 45 patient-regimens administered, ten (22.2%) were platinum-sensitive at the initiation of bevacizumab treatment, while 35 (77.8%) were considered platinum-resistant.

Table 1
Patient characteristics ($N = 40$).

Characteristic	Median (range)
Age at start of bevacizumab (years)	43.8 (20.8, 80.2)
Number of prior regimens	4.0 (1,15)
[a]Duration on bevacizumab (months)	4.0 (0.7, 43.9)
Characteristic	**n (%)**
Primary site	
Ovary	28 (70)
Peritoneum	12 (30)
[a]Platinum status at time of treatment with bevacizumab	
Sensitive	10 (22.2)
Resistant	35 (77.8)

[a] Based on 45 "patient-regimens" for 40 patients.

Of the 45 patient-regimens, 40 were evaluable for response while five patients had no measurable disease. The specific regimens and response data are presented in Table 2. Complete responses (CR) were seen in three patients (7.5%). Sixteen patients (40.0%) had partial responses (PR), while 12 patients (30.0%) achieved stable disease (SD) (Table 2). Disease progression occurred in nine patients (22.5%). Overall response rate (CR + PR) to bevacizumab-containing regimens was 47.5%. Clinical benefit (CR + PR + SD) was achieved in 77.5% of patients. For the nine patients with measurable platinum-sensitive disease, two (22.2%) had a CR, two (22.2%) had a PR, two (22.2%) had SD, and three (33.3%) had PD, for an overall response rate of 44.4% and a clinical benefit rate of 66.7%. For the 31 patients with platinum-resistant disease, one (3.2%) had a CR, 14 (45.2%) had a PR, 10 (32.3%) had SD, and six (19.4%) had PD, for an overall response rate of 48.4% and a clinical benefit rate of 80.6%.

Median progression-free survival (PFS) was 10.2 months (95% CI 7.9, 12.4). Median overall survival was 34.6 months (95% CI 29.5, 39.7). Two patients remained on bevacizumab treatment at last contact at 14.3 and 43.9 months.

Reasons for discontinuation of bevacizumab and associated adverse events are shown in Table 3. The most common reason for discontinuation of bevacizumab was progressive disease (20/45, 44.4%). Attending physicians discontinued bevacizumab therapy in four patients who were responding to therapy (1 CR and 3 PR) and in one patient who began therapy without measurable disease and was clinically disease-free after 4 months of treatment. Fifteen patients discontinued

Table 2
Best response by regimen.

Regimen	Total no. pts.	CR	PR	SD	PD	NE
Bev + paclitaxel/carboplatin	4	2	0	2	0	0
Bev + gemcitabine/carboplatin	2	0	1	0	1	0
Bev + docetaxel/carboplatin	1	0	0	0	0	1
Bev + pegylated liposomal doxorubicin/carboplatin	1	0	1	0	0	0
Bev + carboplatin	1	0	0	0	1	0
Bev + cyclophosphamide	8	0	3	3	1	1
Bev + weekly paclitaxel	4	0	1	2	0	1
Bev + docetaxel	3	0	3	0	0	0
Bev + gemcitabine	2	0	0	0	2	0
Bev + topotecan	2	0	1	1	0	0
Bev alone	3	0	0	2	0	1
Bev + gemcitabine + fulvestrant	1	0	0	1	0	0
Bev + tamoxifen + carboplatin	1	0	0	0	1	0
Bev + aromatase inhibitor	3	1	0	1	1	0
Bev + leuprolide acetate	1	0	0	0	1	0
Bev + pegylated liposomal doxorubin + temsirolimus	1	0	1	0	0	0
Bev + sorafenib	3	0	2	0	0	1
Bev + temsirolimus	1	0	1	0	0	0
Bev + everolimus	1	0	1	0	0	0
Bev + sorafenib + temsirolimus	1	0	1	0	0	0
Bev + autologous vaccine	1	0	0	0	1	0

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable for response; Bev = bevacizumab.