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A clinical experience of single agent bevacizumab in relapsing ovarian cancer

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HIGHLIGHTS

- The median time to progression in women with heavily treated recurrent ovarian carcinoma treated with bevacizumab was 4months.
- The most frequent adverse effect was arterial hypertension (62% of patients) and no intestinal perforation was reported.
- The PFS was marginally improved in patients who experienced severe arterial hypertension during the first month of therapy.

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ABSTRACT

Objective. The objective of this study is to report the efficacy and tolerance of single agent bevacizumab (BEVA) in relapsing ovarian cancer patients treated in a single institution outside a clinical trial.

Methods. To receive single agent BEVA, patients must have to relapse after at least one previous line of chemotherapy and to not have clinical conditions associated with high risk of gastrointestinal perforation. Dose-intensity of BEVA was 2.5 mg/kg/week.

Results. 37 previously treated patients (33 with platinum resistant disease) were included in this retrospective analysis. The median number of BEVA infusion by patient was 5 (range: 1–61). The most frequent adverse effect was arterial hypertension, observed in 23 patients (62%), including 11 with G3 (30%) and 1 with G4. No intestinal perforation was reported. Tumor response rate according to CA 125 level (GCIG criteria) was 37% (11 of 30 patients). The median PFS and OS were 4 (range: 1 to +56) and 16 (range: 1 to +65) months (ms), respectively. 12-ms PFS was 25% (95% CI: 11–39%). The PFS tended to be better in patients who experienced grade 3–4 arterial hypertension during the first month of treatment (median: 10 ms) compared to patients who did not (median: 3 ms) (HR: 0.49 (95% CI: 0.18–1.03), p = 0.06 by log rank test).

Conclusion. Single agent BEVA could be a reasonable option with favorable therapeutic index in pretreated ovarian cancer patients who do not want to suffer the side effects of chemotherapy provided to exclude those with high risk of intestinal perforation and carefully monitor blood pressure.

Introduction

Ovarian cancer comes in the eighth rank among the cancers most frequently diagnosed in women and it comes in the seventh rank in cancer related deaths in that population. Each year some 230,000 cases are diagnosed and about 140,000 women die of the disease [1]. Patients with advanced disease who undergo successful cytoreductive surgery have a median survival of just over 4 years after completion of adjuvant platinum-based chemotherapy [2]. The majority of these patients develop recurrent cancer after initial surgery and their disease becomes steadily resistant to platinum salts and finally to other cytotoxic drugs.

Recently, the inhibition of VEGF-dependent tumor angiogenesis appeared as a promising therapeutic strategy in advanced ovarian cancer [3,4]. Folkman et al. described angiogenesis and its role in cancer development, since early 70s [5]. Angiogenesis is a requirement to allow tumor growth beyond 1 to 2 mm because oxygen has limited diffusion capacity in tissue [6]. The angiogenic switch can be represented as a balance, which tips toward neovascularisation when pro-angiogenic factors outweigh anti-angiogenic factors [7]. Epithelial ovarian cancer cell lines frequently express vascular endothelial growth factor (VEGF), which also mediates ascites formation [8]. Bevacizumab (BEVA), a humanized VEGF-neutralizing monoclonal antibody, inhibits tumor angiogenesis [9]. BEVA was evaluated in several tumor types. It was shown to improve chemotherapy efficacy in terms of PFS or OS in breast, lung, colon and ovarian carcinomas but in most cases it did not have significant activity as a single agent [10–12].

By contrast, two phase II trials (GOG-170 and AVF) using single-agent BEVA heavily pretreated relapsing ovarian cancer (ROC) provided the first evidence of activity for a targeted agent in ovarian cancer [13,14].

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However, BEVA was also associated with a significant risk of intestinal perforation and fistula. Thus, the AVF study was prematurely closed because of an 11% rate of gastro-intestinal perforation [14].

Since 2006, BEVA was used in our institution as single agent in ROC patients in a case by case basis. Patients were not receiving other therapeutic agents and could not have symptoms or signs concerning for a high risk of intestinal perforation.

In this retrospective analysis we present the efficacy and tolerance of single agent BEVA within this cohort.

Methods

It is a retrospective analysis of consecutive patients with recurrent epithelial ovarian carcinoma, tubal or primary peritoneal carcinoma treated with single agent BEVA in our hospital from February 1st, 2006 till March 1st, 2011. The criteria for receiving BEVA treatment were the histological diagnosis of ovarian, tubal or primary peritoneal carcinoma and the diagnosis of recurrence after at least one previous line of chemotherapy. Patients were considered to present a high risk of perforation and were considered unable to receive BEVA treatment in case of: recent intestinal occlusion, permanent abdominal pain, personal history of gastrointestinal perforation or fistula and evidence of bowel involvement on physical exam or CT scan.

All patients received BEVA with the same dose-intensity of 2.5 mg/kg/week (5 mg/kg every two weeks or 7.5 mg/kg every three weeks).

CA 125 measurement was performed before each infusion. CT scan was usually done at baseline and then every 3 months.

For every patient, the following baseline criteria were studied: the age at the time of diagnosis, the age at the beginning of treatment by BEVA, the tumor histology and grade, and the number of lines of chemotherapy before the administration of BEVA.

The tumor response was assessed by using the Response Evaluation Criteria In Solid Tumors (RECIST v1.1) [15] in patients with measurable disease at baseline or according to the CA 125 level using the criteria of the Gynecologic Cancer Intergroup [16] in patients without measurable disease. The PFS was defined as the period from the first perfusion of BEVA until the diagnosis of progression, assessed by CT scan or CA 125 measurement. The overall survival (OS) was the period from the first infusion of BEVA to death.

Survival distribution was estimated by the Kaplan–Meier method [17].

Routine follow-up of blood pressure was performed at home every day between the first and the second infusions and then every week. The Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.0) was used to assess adverse events. Proteinuria was assessed before each infusion by dipstick. Positive results were confirmed by 24-h proteinuria. This retrospective analysis of previously treated patients was compliant with guidelines for the protection of human subjects.

Results

37 previously treated patients were included in this retrospective analysis. Patients' characteristics are summarized in Table 1. The median number of previous lines of chemotherapy before BEVA therapy was 4. In most cases, diseases were considered platinum resistant (disease free interval < 6 months). In 4 patients with platinum sensitive disease (disease free interval ≥ 6 months), BEVA was used because they refused or were not able to receive platinum-based CT.

A total of 442 BEVA infusions were performed. The median number of infusion by patient was 5 (range: 1–61). Fifteen patients received BEVA (5 mg/kg) every two weeks, while 22 received BEVA (7.5 mg/kg) every three weeks. We did not observe any case of intestinal perforation, deep venous thrombosis, arterial thrombosis or pulmonary embolism during BEVA treatment. There was one case of superficial venous thrombosis.

Table 1
Patient and disease characteristics (n = 37).

	Median (range)
Age at diagnosis (range)	63 (37–81)
Age at beginning of bevacizumab (range)	68 (40–87)
Number of chemotherapy lines before BEVA (range)	4 (1–13)
FIGO stage at diagnosis	**Number of patients**
Stage I	3
Stage II	1
Stage III	29
Stage IV	4
Histology	
Serous papillary carcinoma	33
Endometrioid carcinoma	2
Mucinous carcinoma	1
Transitional cell carcinoma	1
Grade	
Grade I	1
Grade II	3
Grade III	14
Unknown	19
Platinum sensibility	
Platinum resistant	33
Platinum sensitive	4

Only grade 1 bleeding was observed in two patients with moderate vaginal and rectal hemorrhages, respectively. Arterial hypertension and proteinuria were observed in 23 (62%) and 13 (35%) patients, respectively. They are detailed in Table 2. Twelve patients experienced G3–4 hypertension, most often during the first month of BEVA (8 patients). There were three cases of other clinically significant G2–5 toxicities: one grade 3 left ventricular systolic dysfunction, one grade 2 gastritis, one grade 2 hypersensitivity reaction and one fatal pulmonary artery hypertension which was not related to a pulmonary embolism.

Twenty patients had measurable disease at baseline: 4 of them experienced a partial response according to RECIST and 8 had a stable disease. Among 30 evaluable patients, tumor response according to CA 125 GCIG criteria was reported in 11 (37%, 95% CI: 19–53) (Table 3). In addition, 8 patients experienced disease stabilization. The median PFS was 4 months (range: 1 to +56). 6- and 12-months PFS were 31% (95% CI: 17–45%) and 25% (95% CI: 11–39%), respectively. At the time of the analysis two patients were still under treatment for 41 and 56 months respectively. The median OS was 16 months (range: 1 to +65).

PFS was similar in patients who received 1 to 3 previous lines of CT and in those who received 4 or more CT lines (HR: 0.9 (95% CI: 0.4–2.1), p = 0.77 by logrank test) (Fig. 1).

The PFS tended to be better in patients who experienced grade 3–4 arterial hypertension during the first month of treatment (median: 10 months, 6-months PFS: 56% (95% CI: 28–82%)) compared to patients who did not (median: 3 months, 6-months PFS: 22% (95% CI: 10–34%)) but the difference was of borderline significance (HR: 0.49 (95% CI: 0.18–1.03), p = 0.06 by logrank test) (Fig. 2). PFS was not different in

Table 2
Arterial hypertension and proteinuria (maximal toxicity by patient, n = 37).

	n (%)
Hypertension	
No hypertension	14 (38%)
G1	3 (8%)
G2	8 (22%)
G3	11 (30%)
G4	1 (2%)
Proteinuria	
No proteinuria	24 (65%)
G1	4 (11%)
G2	8 (22%)
G3	1 (2%)