

Safety of bevacizumab in clinical practice for recurrent ovarian cancer: A retrospective cohort study

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Abstract. The poor outcome of patients with recurrent ovarian cancer constitutes a continuous challenge for decision-making in clinical practice. In this setting, molecular targets have recently been identified, and novel compounds are now available. Bevacizumab has been introduced for the treatment of patients with ovarian cancer and is, to date, the most extensively investigated targeted therapy in this setting. However, potential toxicities are associated with the use of this monoclonal antibody. These toxicities have been reported in clinical trials, and can also be observed outside of trials. As limited data is currently available regarding the safety of bevacizumab treatment in daily clinical practice, the current retrospective study was designed to evaluate this. Data from 156 patients with recurrent ovarian cancer who had received bevacizumab treatment between January 2006 and June 2009 were retrospectively identified from the institutional records of five French centers. In contrast to clinical trials, the patients in the present study were not selected and had a heterogeneous profile according to their prior medical history, lines of treatment prior to bevacizumab introduction and number of relapses. The results first confirm the effect of heavy pretreatment on the occurrence of serious and fatal adverse events in clinical practice, as previously reported

for clinical trials and for other retrospective cohort studies. Importantly, the data also demonstrates, for the first time, that medical history of hypertension is an independent predictive risk factor for the development of high-grade hypertension during bevacizumab treatment. These results thus suggest that treating physicians must consider all risk factors for managing bevacizumab toxicity prior to its introduction. Such risk factors include the time of bevacizumab introduction, a patient's history of hypertension and a low incidence of pre-existing obstructive disease.

Introduction

The response rate of advanced epithelial ovarian carcinoma treated with standard first-line platinum/taxane-based chemotherapy is ~80% (1-5). However, the majority of patients will relapse within 18-24 months (2-5). Decision-making regarding the treatment of recurrent ovarian cancer has been a continuous challenge. Since 1990, treatment selection has been based on whether patients have platinum-sensitive or platinum-resistant disease (6,7). For patients relapsing >6 months after the completion of the initial platinum-based chemotherapy, platinum-containing regimens are given, as long as the patients have platinum-sensitive disease (8). By contrast, for patients with platinum-resistant or platinum-refractory disease, single-drug regimens, including pegylated liposomal doxorubicin, gemcitabine or topotecan are indicated (9).

In addition to cytotoxic drugs, the development of molecular-targeted agents has emerged based on the increasing knowledge of key biological pathways driving tumor progression (10). Among the several targeted therapies investigated, the most promising approach for treating ovarian cancer is the inhibition of angiogenesis by bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF). Accordingly, the level of VEGF expression in ovarian

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cancer has been associated with ascites formation and poor prognosis (11-15).

Promising data regarding efficacy have emerged from trials that have evaluated bevacizumab, alone or in combination, for the management of patients with recurrent ovarian cancer (16-20). Two phase III trials were recently conducted and led to the approval of bevacizumab by the European authorities for treating the first recurrence of platinum-sensitive or platinum-resistant ovarian cancer (21,22).

It is well known that the administration of bevacizumab is frequently associated with adverse events (AEs), including hypertension and proteinuria. In patients who are extensively pretreated or who exhibit pelvic disease or bowel obstructive symptoms, bevacizumab may also result in bowel perforation or fistula formation (17).

Importantly, the toxicities associated with the use of bevacizumab may also be observed outside of clinical trials and may be prominent, particularly when the drug is used in non-approved regimens. To date, limited data are available regarding the safety of this treatment in daily clinical practice (23-30). Thus, the present study was designed to assess the tolerance of bevacizumab in the management of recurrent ovarian cancer in routine clinical practice. A retrospective analysis was conducted using data from patients who were treated for ovarian cancer in five French referral centers. The safety of the treatment and its outcomes were evaluated from a cohort of heavily pretreated patients, the majority of whom were ineligible for inclusion in clinical trials.

Materials and methods

Patient population. A total of 156 women with recurrent ovarian cancer who had received bevacizumab between January 2006 and June 2009 were retrospectively identified from the institutional records of five centers: Hôpital Tenon (Paris, France); Centre Léon Bérard (Lyon, France); Institut Gustave Roussy (Villejuif, France); Hôpital Cochin (Paris, France); and Hôtel-Dieu (Paris, France). This study was approved by the French authority Commission Nationale d'Informatique et des Libertés.

Data were collected using case report forms designed for the current study. Detailed information regarding the history of the disease and its management began at the time of clinical presentation and diagnosis. Following first-line platinum-based chemotherapy, patients were categorized as having platinum-resistant or platinum-sensitive disease, depending on whether recurrence was detected within 6 months or not, respectively.

Bevacizumab was administered to patients who relapsed following alternative chemotherapy. Bevacizumab was given as a second-line therapy (in patients following a first relapse) or as a subsequent line of treatment. It was given up to the eighth line for patients who went through seven previous lines of chemotherapy and underwent a seventh relapse at the time of bevacizumab introduction.

Bevacizumab was either administered in combination with other chemotherapy, or as a single agent. For certain patients, bevacizumab was initially combined with alternative chemotherapy, and subsequently used as a maintenance monotherapy following the completion of the initial therapy.

Endpoints assessment. The safety profile of bevacizumab was the primary endpoint of the study. Secondary endpoints included the usage conditions of bevacizumab (e.g., dose schedule, concurrent chemotherapy) and survival rates. During bevacizumab therapy, AEs potentially attributable to the monoclonal antibody were described according to the Common Terminology Criteria for Adverse Events, Version 3.0 (31). The AEs of particular interest in the present study were defined prior to data collection, and focused on the following: Hypertension, proteinuria, epistaxis, bleeding or hemorrhage, venous thromboembolic event, arterial thromboembolic event, wound healing complication, intestinal perforation, gastrointestinal (GI) fistula, reversible posterior leak-encephalopathy syndrome and pulmonary hypertension.

Overall survival (OS) was determined from the time of bevacizumab introduction to the time of the mortality of the patients (due to any cause). Progression-free survival (PFS) was determined from the time of bevacizumab introduction to disease progression or patient mortality. The data for patients who were alive without undergoing disease progression were censored at the date of their last assessment.

During bevacizumab treatment, disease progression was evaluated by each treating physician through clinical examination and/or carbohydrate antigen 125 (CA125) levels and/or radiological examination. Biological progression was defined, according to the Gynecological Cancer Intergroup criteria (32), as an increase of CA125 levels. Determination of radiological and clinical progression relied on physician judgement.

Statistical analysis. OS and PFS Kaplan-Meier estimates were determined for the entire cohort and for various subgroups. The long-rank test was used to compare data between subgroups.

The population who received bevacizumab for only one relapse (n=136) served to identify predictive factors using the Cox proportional hazards regression analysis. Predictive factors for AEs were explored for all grades (grades 1-5) or for only severe grades (grades 3-5). The same population served to establish predictive factors for PFS and OS. The factors taken into account for the univariate analysis of PFS and OS were platinum sensitivity, first (or unique) line of bevacizumab, combination of bevacizumab with other chemotherapy and bevacizumab dose scheduling at the time of the first (or unique) bevacizumab administration. $P < 0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using Statistical Analysis System version 9.1 (SAS France, Brie-Comte-Robert, France).

Results

Patients and study treatment. The majority of the patients who were included in this study presented advanced disease (stage III or IV) at diagnosis. Chemotherapy was the most common first-line treatment; >70% of the patients received the standard chemotherapy based on platinum and taxane, while only 2 patients were treated with bevacizumab in this setting. The majority of the patients presented platinum-sensitive disease at the time of their first relapse. Platinum-sensitive disease was defined as recurrent disease occurring >6 months following the end of the first-line of platinum based chemotherapy.

Table I. Clinical and demographic characteristics of the study population (n=156).

A, At baseline	
Characteristic	Value
Median age, years (range) [n=156]	55 (22-81)
FIGO stage, n (%) [n=152]	
I	6 (3.9)
II	5 (3.3)
III	111 (73.0)
IV	30 (19.7)
Histological type at diagnosis, n (%) [n=148]	
Serous	115 (77.7)
Mucinous	3 (2.0)
Endometrioid	14 (9.5)
Clear cell	5 (3.4)
Other	11 (7.4)
Histological grade at diagnosis, n (%) [n=100]	
I	12 (12.0)
II	36 (36.0)
III	52 (52.0)
Initial surgery, n (%) [n=154]	
Initial debulking	97 (63.0)
Optimal [n=91]	52 (57.1)
Suboptimal [n=91]	39 (42.8)
Intestinal resection	36 (30.5)
First-line chemotherapy, n (%) [n=154]	
Paclitaxel/platinum	113 (73.4)
Platinum sensitivity, n (%) [n=148]	
Resistant	54 (36.5)
Sensitive	94 (63.5)
Prior medical history, n (%)	
GI [n=156]	31 (19.9)
Cardiovascular [n=156]	44 (28.2)
Hypertension [n=154]	30 (19.5)
Proteinuria [n=52]	1 (1.9)
B, At bevacizumab introduction	
Median previous chemotherapies, n (range) [n=156]	2 (0-12)
Median relapses per patient, n (range) [n=156]	4 (1-15)
Site of relapse, n (%) [n=181]	
Peritoneum	101 (55.8)
Lymph node	64 (35.5)
Liver	25 (13.8)
Lung	17 (9.4)
Pelvis	12 (6.6)
Other	11 (6.1)
Ascites, n (%) [n=181]	48 (26.5)
Pleural effusion, n (%) [n=181]	21 (11.6)
GI obstructive syndrome, n (%) [n=181]	9 (5.0)

Table I. Continued.

Characteristic	Value
Chemotherapy combined with bevacizumab, n (%) [n=181]	151 (83.4)
Taxane	67 (37.2)
Platinum	60 (33.3)
Gemcitabine	28 (15.5)
Pegylated liposomal doxorubicin	27 (15.0)
Other	22 (12.2)
Bevacizumab alone, n (%)	30 (16.6)
FIGO, International Federation of Gynecology and Obstetrics; GI, gastrointestinal.	

Bevacizumab was administered to the 156 patients who relapsed following chemotherapy. At the time of bevacizumab introduction, the median number of previous lines of chemotherapy received by patients was two. At that time, the majority of the patients (for example, 95% of the treated patients in the second line and 58.3% of the treated patients in the eighth line) had a favorable performance status, corresponding to an Eastern Cooperative Oncology Group/World Health Organization grade <2 (33) or a Karnofsky performance status $\geq 70\%$ (34). Only 9 patients presented GI sub-obstructive disease when bevacizumab was introduced.

The majority of patients (n=136) who received bevacizumab were treated for a single relapse. Given that some patients received bevacizumab for more than one relapse, a total of 181 cycles of bevacizumab were administered to the 156 patients. The median number of relapses per patient was 4, with 33.3% of patients having ≥ 6 relapses.

Bevacizumab was administered in combination with alternative chemotherapy to 118 patients and continued as a maintenance monotherapy for 42 patients. The median duration of the maintenance therapy was 4 months (range, 0.2-27 months).

The median duration of bevacizumab treatment (alone or in combination) was 6.3 months for patients treated in the second line, and 3.4 months for patients treated in the fifth line.

The doses of bevacizumab used were 2.5 and 5 mg/kg/week in 36.5% and 45.3% of the cases studied, respectively. Various other bevacizumab regimens were used for the remaining cases (18.2%). The median duration of follow-up after bevacizumab introduction was 15.3 months (range, 0.3-47.9 months).

The clinical and demographic characteristics of the studied patients are summarized in Table I.

Safety. At least one AE (all grades included) that was possibly due to bevacizumab was observed for 110 patients (70.5%) among the 156 patients participating to the study and during the 181 cycles administered. AEs of grades 3-5 were observed in 43 cases (29.5%; Table II).

None of the patients experienced congestive heart failure. There were 4 treatment-related mortalities. Causes of mortality included pulmonary hypertension (1 patient), bowel perforation (1 patient), GI hemorrhage (1 patient) and

Table II. Adverse events of particular interest potentially associated with bevacizumab treatment (n=156).

Event type	Patients, n (%)	
	Any grade	Grade 3-5
Hypertension	65 (41.7)	18 (11.3) ^a
Proteinuria	42 (27.9)	7 (4.5)
Epistaxis	43 (27.6)	1 (0.6) ^a
Bleeding or hemorrhage	15 (9.6)	4 (2.6)
Venous thromboembolic event	5 (3.2)	3 (1.9)
Arterial thromboembolic event	2 (1.3)	2 (1.3)
Wound healing complication	1 (0.6)	0 (0.0)
Gastrointestinal fistula	5 (3.2)	5 (3.2)
Reversible posterior leukoencephalopathy syndrome	2 (1.3)	2 (1.3)
Pulmonary hypertension	1 (0.6)	1 (0.6)

^aAll grade 3.

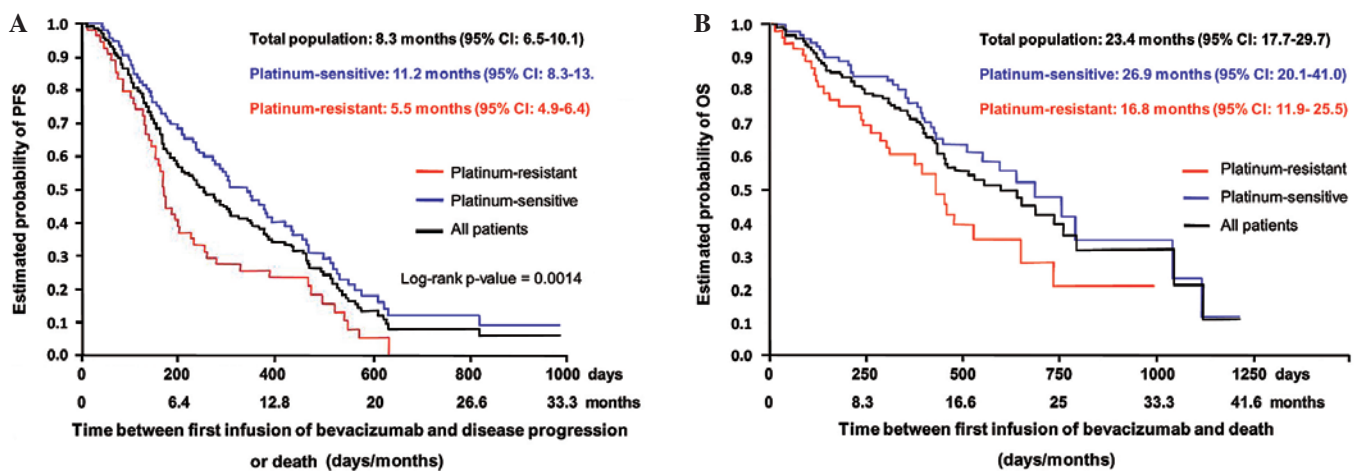


Figure 1. Kaplan-Meier plots for (A) PFS and (B) OS for the entire cohort (black line), platinum-resistant patients (red line) and platinum-sensitive patients (blue line). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

pulmonary embolism (1 patient). The latter two patients had a history of deep-vein thrombosis and received anticoagulation therapy. All mortalities occurred in patients who underwent a fifth or sixth relapse. There were 2 mortalities (from a GI hemorrhage and from a venous thromboembolic event) that occurred during concomitant bevacizumab/taxane therapy, and 2 mortalities (from pulmonary hypertension and from bowel perforation) during bevacizumab monotherapy.

On univariate analysis (performed using a cut-off point of $P < 0.15$) identified three predictive parameters for bevacizumab-associated AEs: Bevacizumab dose [odds ratio (OR), 1.143; 95% confidence interval (CI), 1.034-1.264; $P = 0.0091$], peritoneal relapse (OR, 1.829; 95% CI, 0.835-4.005; $P = 0.1310$) and history of hypertension (OR, 3.377; 95% CI, 0.944-12.082; $P = 0.0613$). However, using a cut-off point of $P < 0.05$, only bevacizumab dose remained a significant predictive factor on multivariate analysis (OR, 1.190; 95% CI, 1.065-1.330; $P = 0.0021$), while peritoneal relapse (OR, 1.424; 95% CI, 0.616-3.294; $P = 0.4087$) and history of hypertension (OR, 3.517; 95% CI, 0.923-13.396; $P = 0.0654$) did not.

Considering severe AEs (grade 3-5), history of hypertension (OR, 4.875; 95% CI, 1.906-12.472; $P = 0.0009$) and peritoneal relapse (OR, 3.224; 95% CI, 1.218-8.538; $P = 0.0185$) were significant predictive factors in univariate analysis. Both history of hypertension (OR, 3.959; 95% CI, 1.482-10.575; $P = 0.0060$) and peritoneal relapse (OR, 2.782; 95% CI, 1.024-7.560; $P = 0.0448$) remained significant on multivariate analysis.

Efficacy. At the end of the bevacizumab therapy, patients underwent clinical and/or biological and/or radiological evaluation of the disease. For the global cohort of patients ($n = 156$), the median PFS was 8.3 months (95% CI, 6.5-10.1 months) and the median OS was 23.4 months (95% CI, 17.7-29.7 months) (Fig. 1). The 6-month PFS rate was 60.0% for the entire cohort. The 6-month PFS rate was 79.1% for patients treated for a first relapse, and 63.0, 44.4, 47.1, 42.9 and 58.0% for patients treated for a second, third, fourth, fifth, and sixth or more relapses, respectively. Median PFS and OS were 11.2 months (95% CI, 8.3-13.8 months) and 26.9 months (95% CI, 20.1-41.0 months),

respectively, in patients with platinum-sensitive disease, while these values were 5.5 months (95% CI, 4.9-6.4 months) and 16.8 months (95% CI, 11.9-25.5 months), respectively, in patients with platinum-resistant disease.

The significant factors predictive of longer PFS time on univariate Cox regression analysis that were also confirmed on multivariate analysis were platinum sensitivity [hazard ratio (HR), 0.53; 95% CI, 0.36-0.77; $P=0.001$], early introduction of bevacizumab as second- or third-line therapy (HR, 0.67; 95% CI, 0.46-0.99; $P=0.042$) and combination with chemotherapy (HR, 0.52; 95% CI, 0.31-0.86; $P=0.011$). The two significant factors for longer OS time on multivariate analysis were platinum sensitivity (HR, 0.44; 95% CI, 0.27-0.73; $P=0.002$) and early introduction of bevacizumab as second- or third-line therapy (HR, 0.37; 95% CI, 0.21-0.65; $P<0.001$).

Discussion

The present multi-center observational retrospective study, designed to analyze the safety profile of bevacizumab in relapsed ovarian cancer, identified predictive factors for the development of severe AEs during bevacizumab treatment. The results presented here are of particular interest, as this study included patients treated with bevacizumab in clinical practice. Indeed, data regarding treatment and outcomes of patients outside of clinical trials remains scarce, even though it may more accurately reflect the events that occur in the management and outcomes of patient with ovarian cancer in normal clinical practice.

Patients included in the current study, in contrast to those selected for clinical trials, did not conform to strict mandatory inclusion criteria, diagnostic procedures, management and follow-up protocols. The patients had a heterogeneous profile according to their previous medical history, lines of treatment prior to bevacizumab introduction and number of relapses. However, the clinical profiles of the patients at relapse were relatively homogeneous with regard to the sites of relapse and the general conditions of the patients. A majority of them had platinum-sensitive disease, and a low fraction exhibited GI obstructive disease.

The primary aim of the present study was to describe the safety profile of bevacizumab in routine practice. The most common AEs observed were hypertension, proteinuria and epistaxis, which are known side effects of bevacizumab treatment. The risk of the occurrence of such events may be dose-associated, as indicated by the multivariate Cox regression analysis and by previously published data (35-37).

Hypertension is a frequent side effect of anti-VEGF therapy (38). However, the impact of baseline hypertension on the development of high-grade hypertension during bevacizumab therapy is less well documented. For instance, in a phase III trial of bevacizumab treatment in ovarian cancer (39), and the studies included in the meta-analyses conducted by Zhu *et al* (35) and by Ranpura *et al* (40), an increased risk of high-grade hypertension associated with bevacizumab treatment was reported; however, the histories of the hypertensive patients were not analyzed. The OCEANS 20 trial reported similar findings (21). Indeed, while the baseline incidence of hypertension in enrolled patients was similar in the different groups of the study (37.6 vs. 39.7% for placebo

and bevacizumab arms, respectively), and while grade ≥ 3 was only reported for 1 patient in the placebo arm (compared to 43 patients in the bevacizumab arm) the increased incidence of hypertension observed during bevacizumab treatment was not analyzed with regard to the hypertensive history of the patients.

In the current study, the incidence of history of hypertension for the entire cohort was 19.5%. On multivariate analysis, this feature was identified as an independent predictive risk factor for the development of high-grade hypertension during treatment. Therefore, previous history of hypertension must be taken into account for the management of patients receiving bevacizumab treatment for recurrent ovarian cancer.

All treatment-related mortalities in the current cohort occurred in patients who were previously treated with ≥ 4 lines of chemotherapy. This observation confirms that heavy pretreatment is an important factor involved in the occurrence of serious and fatal AEs, in clinical practice or in clinical trials (17,41).

GI perforation has been associated with the use of bevacizumab in various types of cancer (36,37,42). In trials where only ovarian cancer patients experiencing a first relapse (21) or patients treated with ≤ 2 regimens (43) were included, GI perforation were reported. In the present study, the rates of GI perforation ($<1\%$) and GI fistula (3.2%) were low compared with that of other studies conducted in relapsed patients heavily pretreated with bevacizumab (17,44). This is likely due to the good performance status and relatively low incidence of pre-existing obstructive disease at the time of bevacizumab introduction in the current patients. Indeed, obstructive disease and peritoneal relapse have been reported to be the primary risk factors for GI perforation (45,46). Thus, the present results reveal that treating physicians are considering these known risk factors for bevacizumab toxicity before introducing the drug. Accordingly, multivariate analysis indicated peritoneal relapse as an independent predictive factor for grade 3-5 AEs.

The secondary endpoints for the present study included PFS and OS rates. Median PFS and OS were better for patients with platinum-sensitive disease compared with those having platinum-resistant disease. Accordingly, multivariate analysis revealed that patients who benefitted the most from bevacizumab were those treated in the second or third lines with the antibody, and who presented a platinum-sensitive disease.

In summary, as previously reported by clinical trials and other retrospective studies, the current findings confirm the impact of heavy pre-treatment on the occurrence of serious and fatal adverse events in patients treated with bevacizumab in daily practice. Notably, the present study demonstrated that a medical history of hypertension is an independent predictive risk factor for the development of high-grade hypertension during bevacizumab treatment. The current findings confirm the feasibility and toxic acceptability of the use of bevacizumab for treating relapsed ovarian cancer patients. Although these results are of importance and contribute to improved understanding of the management of adverse events attributable to the use of bevacizumab in ovarian cancer, more studies in this field are required. In particular, studies aimed at characterizing and applying biomarkers that could contribute to safer administration of bevacizumab, through the identification of patients with ovarian cancer most likely to benefit

from the treatment, should be performed. Thus, retrospective analysis of patient cohorts may be of interest to validate such biomarkers and to determine whether they can be applied in clinical trials.

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