ANTICANCER RESEARCH *40*: 5285-5290 (2020)
doi:10.21873/anticanres.14533

Continuous Administration of Bevacizumab After Disease Progression in Recurrent Ovarian Cancer: A Retrospective Observational Study

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Abstract. *Background/Aim: Chemotherapy with additional bevacizumab is the standard treatment for primary and recurrent ovarian cancer. We aimed to investigate the clinical utility and safety of bevacizumab when used in combination with chemotherapy after disease progression. Patients and Methods: This retrospective, observational study recruited patients treated for recurrent ovarian cancer from 2014 to 2016. We evaluated the effects of bevacizumab with chemotherapy in patients whose disease had progressed following treatment with bevacizumab. We assessed progression-free survival and adverse events. Results: Thirty-three patients received post-progression treatment with bevacizumab. The median progression-free survival was 8.7 months (95% confidence interval=5.5-11). The progression-free survival was compared pre- and post-progression treatment, and was longer in platinum-resistant than platinum-sensitive cases after treatment (p=0.06). The most common non-hematological toxicity was proteinuria. The incidence of serious adverse events was low. Conclusion: Continuous administration of bevacizumab may be beneficial for ovarian cancer patients after disease progression.*

The incidence of ovarian cancer is rising in Japan. In 2001, the prevalence per 100,000 people was 9.1 but increased to 11.2 in 2014 (1). In Japan, the 5-year survival rates for stage III and IV ovarian cancer, for which treatment was started in 2010, are 46.3% and 36.2%, respectively (2). Furthermore, treatment of recurrent ovarian cancer is often unsuccessful, and the development of improved treatments is needed.

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Key Words: Bevacizumab, disease progression, continuous administration, recurrent ovarian cancer, progression-free survival.

Bevacizumab is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF). In 2013, bevacizumab was approved for the treatment of primary and recurrent ovarian cancer in Japan. However, the efficacy of continued administration of bevacizumab after ovarian cancer progression is unknown. Previous studies have reported that progression-free and overall survival in colorectal, lung, and breast cancer are improved by continued administration of bevacizumab beyond disease progression (BBP) (3-6). Clinical studies are currently underway to examine the utility of BBP in ovarian cancer (7, 8).

The purpose of this study was to examine the efficacy and safety of BBP in patients receiving treatment for recurrent ovarian cancer.

Patients and Methods

Study design and population. We performed a retrospective, observational study by collecting data from the medical records of patients who were receiving treatment for recurrent ovarian cancer at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research between 2014 and 2016. We recruited patients with histologically confirmed epithelial ovarian cancer and measurable metastatic tumor who had undergone more than three previous treatment courses of bevacizumab plus chemotherapy and those with recurrence who had survived more than 30 days from the start of treatment. The exclusion criteria were double cancer, more than four regimens of previous treatment, fewer than three previous courses of chemotherapy, previous surgery for recurrence with combined bevacizumab as adjuvant chemotherapy, previous radiotherapy, and participation in clinical trials with the latest treatment. This study and its protocols were approved by the institutional review board at our hospital (2018-1088).

We evaluated the effects of the addition of bevacizumab to chemotherapy in patients with primary and recurrent ovarian cancer whose disease had progressed after treatment with bevacizumab plus chemotherapy or bevacizumab maintenance therapy. Post-progression disease treatment was defined as any systemic anticancer therapy. We evaluated progression-free survival (PFS), response rates, and adverse events. We defined the treatment period as the period from the start to

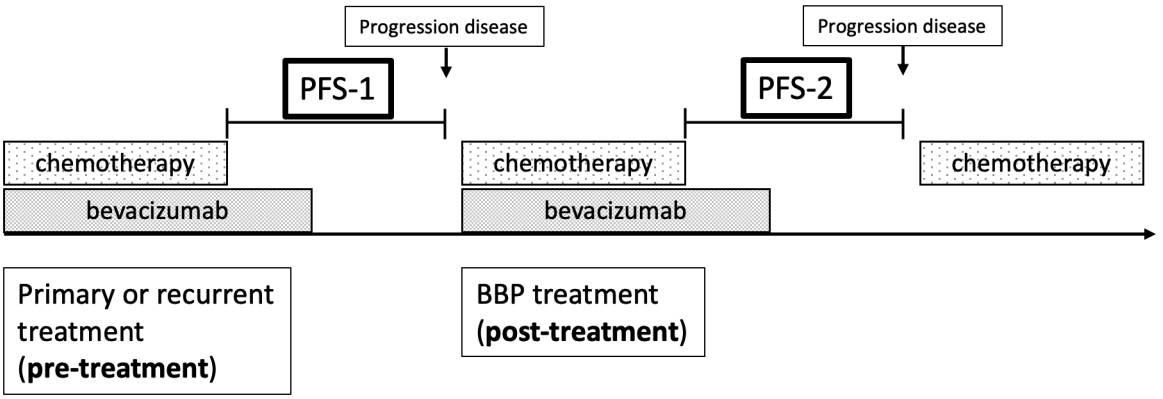

Figure 1. *Definition of progression-free survival and treatment period.*

the end of chemotherapy and did not include bevacizumab maintenance therapy. PFS from primary or recurrent treatment (pre-treatment) to disease progression was defined as PFS-1, and PFS after BBP treatment (post-treatment) was defined as PFS-2 (Figure 1). Furthermore, PFS was evaluated separately for platinum-resistant (defined as PFS <6 months) and platinum-sensitive (defined as PFS ≥6 months) relapses. Tumor measurements and assessments were performed according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) using computed tomography or [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (9). The intervals at which imaging was performed were at the discretion of the attending physician. Tumor markers were also used as references to assess the effects of treatment. Adverse events were evaluated by Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) (10).

Bevacizumab policy. The treatment policy for bevacizumab at our hospital is as follows: For first-line treatment, bevacizumab is used in combination with adjuvant chemotherapy for epithelial ovarian cancer classified as stage III or above and is not used in combination with preoperative chemotherapy; for treatment of recurrent cancer, the decision to use bevacizumab in combination with chemotherapy is made by a cancer board comprising a gynecologist, oncologist, radiologist, pathologist, nurse, and pharmacist.

Statistical analysis. Data are presented as the median (range). Survival analysis was performed using the Kaplan-Meier method. The Fisher's exact test was used to analyze the differences in the frequency of PFS prolongation before and after BBP treatment in platinum-resistant and platinum-sensitive relapses. A p-value<0.05 was considered statistically significant. Statistical analyses were performed using the R software package [R Core Team (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria].

Results

Patient characteristics. A total of 39 patients were recruited in this study. Of these, six were excluded due to hospital transfer, receiving fewer than three courses of chemotherapy, and changing to poly (ADP-ribose) polymerase inhibitor (olaparib) administration during treatment. A final total of 33

Table I. *Characteristics of the study population.*

	Values (n=33)
Age (years)	55 [36-78]
Origin	
Ovary	28 (84)
Fallopian tube	5 (15)
Peritoneal	0 (0)
Clinical stage	
I/II	2 (6)
III	22 (67)
IV	9 (27)
Histology	
Serous carcinoma	26 (79)
Endometrioid carcinoma	2 (6)
Clear cell carcinoma	3 (9)
Other	2 (6)
Period from previous chemotherapy to recurrence	
<6 months	20 (61)
≥6 months	13 (39)
Period from previous bevacizumab administration to recurrence	
Recurrence during bevacizumab treatment	22
<6 months	8
≥6 months	3
Number of treatments with platinum	
1	15
2	15
≥3	3
Number of cycles with bevacizumab in the pre-treatment	13 [3-21]
Number of cycles with bevacizumab in the post- treatment	5 [1-19]

Data are presented as mean [range] or number of patients (%). BBP: Bevacizumab beyond disease progression.

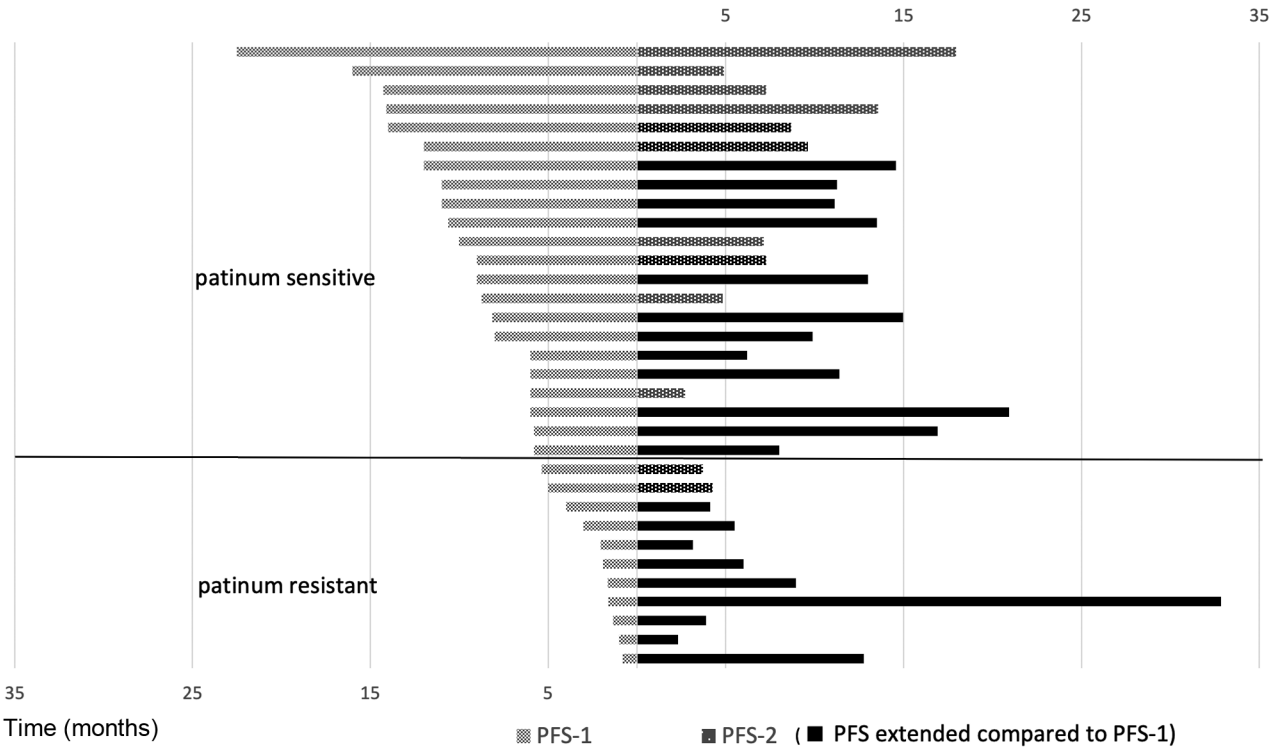

Figure 2. *Comparison of PFS-1 and PFS-2 in platinum-resistant and platinum-sensitive recurrence. Progression-free survival (PFS) from primary or recurrent treatment (pre-treatment) to disease progression was defined as PFS-1, and PFS after BBP treatment (post-treatment) was defined as PFS-2.*

patients were considered for inclusion. Table I details the characteristics of the study population.

Treatment. The median number of pre-treatment bevacizumab cycles was 13 (range=3-21). The median number of post-treatment bevacizumab cycles was 5 (range=1-19). The median duration of treatment was 7 months. Fifteen patients (45%) received bevacizumab maintenance therapy.

Chemotherapy regimens were as follows: platinum combination therapy was carboplatin plus paclitaxel or gemcitabine, docetaxel, or doxorubicin; and single-agent chemotherapy was paclitaxel, doxorubicin, nogitecan, or docetaxel. In the post-treatment, 19 patients (58%) received platinum combination therapy, and 14 (42%) received single-agent chemotherapy. The median number of chemotherapy courses was 6 (range=2-19).

Efficacy. The median follow-up was 20.9 months (range=3.1-43.9 months). The median PFS was 8.7 months [95% confidence interval (CI)=5.5-11] (Figure 2). The median PFS was 4.8 months (95%CI=3.2-11.4) for platinum-resistant recurrent ovarian cancer and 11.1 months (95%CI=7.1-13.5) for platinum-sensitive recurrent ovarian cancer.

A comparison of platinum-sensitive and platinum-resistant recurrence showed that PFS-2 was more prolonged than PFS-1 in platinum-resistant recurrence (50% *vs*. 85%, p=0.06) (Figure 3).

All patients were evaluated for a response. Ten patients had a complete response (30%), and ten patients had a partial response (30%). Stable disease was observed in five patients (15%), and progression of disease was observed in eight patients (24%). The disease control rates were 75%.

Safety. The predominant hematological event with a severity of grade 3 and above was neutropenia. However, neutropenia appears to be an adverse event of chemotherapy. Among the non-hematologic toxicities of grade 3 or above, the predominant event was proteinuria, which was observed in ten patients (30%). Surgery was effective for patients who suffered gastrointestinal perforation, and bevacizumab treatment was terminated thereafter. Treatment was discontinued due to adverse events in one patient (3%). Table II details the adverse events.

Discussion

We investigated the efficacy and safety of continuous bevacizumab administration after disease progression, and a longer PFS was observed among patients with platinum-resistant recurrent ovarian cancer.

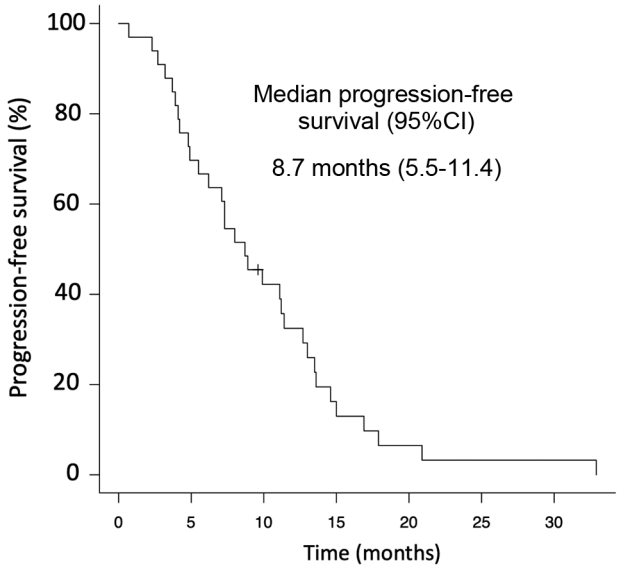

Figure 3. *Kaplan-Meier curves for progression-free survival. CI: Confidence interval.*

Table II. *Adverse events of all grades.*

	Values (n=33)	
Adverse event	All Grades	Grade ≥3
Hypertension	16 (48)	4 (12)
Proteinuria	17 (51)	10 (30)
Gastrointestinal perforation	2 (6)	2 (6)
Hemorrhage	8 (24)	1 (3)
Thrombosis	1 (3)	0 (0)
Neutropenia	26 (78)	24 (72)
Anemia	20 (60)	3 (9)
Thrombocytopenia	22 (66)	5 (15)
Febrile neutropenia	2 (6)	2 (6)

Data are presented as number of patients (%). BBP: Post-progression disease treatment with bevacizumab.

Several studies have reported the benefits of continuous administration of angiogenesis inhibitors. Bagri *et al.* reported that continuous suppression of VEGF was efficacious in a xenograft model, which has tumor cells implanted into a transgenic mouse (11). In addition, the preclinical study by Mancuso *et al.* demonstrated the occurrence of tumor revascularization after cessation of anti-VEGF therapy (12).

The duration of response to chemotherapy in recurrent cancer does not exceed that of initial chemotherapy (13). Treatment options for platinum-resistant recurrent ovarian cancer are limited, and the therapeutic effect is often insufficient. The AURELIA study reported that PFS for platinum-resistant recurrent ovarian cancer improved by the addition of bevacizumab to chemotherapy (chemotherapy only *vs.* bevacizumab combination: 3.4 *vs.* 6.7 months) (14).

The risk of developing resistance to bevacizumab is low, even with continuous administration (15). In addition, bevacizumab reduces the elevated interstitial pressure found in tumor tissues by suppressing vascular permeability, allowing anticancer drugs to be easily transferred to the tumor tissue (16). Therefore, bevacizumab may be effective when combined with chemotherapy in platinum-resistant recurrent ovarian cancer, which is more resistant to chemotherapy.

Continuous administration of bevacizumab after progression of colorectal, lung, and breast cancer has been shown to be beneficial. An observational study revealed that bevacizumab, which continued to be administered from a first- to second-line treatment after disease progression of colorectal cancer, extended the overall survival (BBP group, overall survival=31.8 months *vs.* no-BBP group, 19.9 months; hazard ratio 0.49; 95%CI=0.41-0.58; p=0.001) (3). A subsequent phase III study confirmed the increase in overall survival (11.2 months BBP *vs.* 9.8 months no-BBP, hazard ratio 0.81, 95%CI=0.69-0.94, p=0.0062) (4). The effect of continuous administration of bevacizumab has also been investigated for other carcinomas, and prolongation of PFS in recurrent lung cancer and breast cancer has been reported (5, 6).

Clinical trials are currently underway to investigate the effects of continuous administration of bevacizumab in ovarian cancer. The MITO16/MaNGO trial involves patients with platinum-sensitive recurrent ovarian cancer, and preliminary results were reported at the American Society of Clinical Oncology in 2018 (7). In Japan, a clinical study is currently underway to investigate the effects of bevacizumab beyond disease progression in platinum-resistant recurrent ovarian cancer (8).

In this study, the incidence of grade 3 or higher proteinuria was 30% and that of intestinal perforation was 2%. In a study investigating the effect of bevacizumab in platinum-sensitive recurrence (the OCEANS trial), the frequency of proteinuria that was grade 3 or higher was 9.7% (17); the frequency of intestinal perforation in that trial was 6% in the bevacizumab-treated group and 0% in the placebo group. In a clinical trial investigating the effect of bevacizumab on the primary treatment of ovarian cancer, the frequency of gastrointestinal perforation was 2.6-2.8% (18). Prolonged administration of bevacizumab may be associated with an increased frequency of proteinuria.

Our study has some limitations. The sample size is small and the study is retrospective. Furthermore, the small number of patients results in an insufficient power of statistical analysis. For a single-center study, however, the number of

patients is considered large. The strength of this study is that it determines the criteria for selecting patients.

This study demonstrates the benefits and safety of bevacizumab in patients undergoing post-disease progression treatment; prolonged PFS was noted in patients with platinum-resistant recurrent ovarian cancer.

In conclusion, continuous administration of bevacizumab may have clinical utility in the treatment of recurrent ovarian cancer. The results of ongoing phase III trials may clarify the value of this approach.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

TT conceived the study, designed the analysis, evaluated the date, and drafted the article. NT conceived the study. MO, YA, SN, HN and SO performed acquisition of date. KO and MM performed analysis and interpretation of date. MY and HK performed drafting and revising the article. All Authors read and approved the final article.

Acknowledgements

The Authors would like to thank Editage (www.editage.com) for English language editing.

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Received July 13, 2020
Revised July 21, 2020
Accepted July 22, 2020