Impact of Adding Bevacizumab to Paclitaxel + Carboplatin for Platinum-Sensitive Recurrent Epithelial Ovarian Cancer: A Propensity Score Matching Analysis

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Purpose: We evaluated whether adding bevacizumab (Bev) to paclitaxel + carboplatin (TC) could improve outcomes, especially progression-free survival (PFS), in patients with platinum-sensitive recurrent ovarian cancer.

Patients and Methods: Among patients with platinum-sensitive recurrent ovarian cancer treated at our hospital from May 2008 to March 2017, PFS was compared between those receiving platinum-based chemotherapy or TC + Bev therapy by propensity score matching analysis.

Results: Nineteen patients received platinum-based chemotherapy and 13 patients received TC + Bev therapy. PFS (the primary endpoint) was 6.31 months in the platinum-based chemotherapy group versus 14.71 months in the TC + Bev group (hazard ratio: 0.304; 95% confidence interval: 0.114−0.8121; p = 0.01752). The safety profile was similar to that expected.

Conclusion: Adding Bev to TC prolonged PFS in patients with platinum-sensitive recurrent ovarian cancer and adverse effects were tolerable.

Key words: Bevacizumab, Ovarian cancer, Propensity score matching analysis, Progression free survival, Safety

INTRODUCTION

In 2013, new epithelial ovarian cancer was diagnosed in 9804 patients in Japan and 4717 patients died of this disease [1]. Epithelial ovarian cancer has a high mortality rate because it is often advanced at the time of diagnosis. Many patients with primary ovarian cancer undergo debulking surgery and receive postoperative platinum-based chemotherapy, but recurrence is frequent. If ovarian cancer recurs at six months or longer after completion of chemotherapy, it is defined as platinum-sensitive recurrence and platinum-based chemotherapy like the previous postoperative chemotherapy is administered again [2−4].

Bevacizumab (Bev) is a monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A), and use of Bev to treat ovarian cancer in combination with other anticancer agents has been covered by health insurance in Japan since 2013.

The international collaborative phase 3 OCEANS study compared the efficacy of chemotherapy alone with chemotherapy + Bev for platinum-sensitive recurrent ovarian cancer. The control arm received gemcitabine + carboplatin (GC) therapy, which was compared with GC + Bev therapy on the basis of progression-free survival (PFS). It was found that PFS, the objective response rate (ORR), and the duration of response were all significantly better with GC + Bev therapy. The median PFS was 12.4 months in the GC + Bev group versus 8.4 months in the control group (hazard ratio [HR]: 0.484; 95% confidence interval [CI]: 0.388−0.605; $p < 0.0001$ by the log-rank test), while ORR was 78.5% vs. 57.4% ($p < 0.0001$) and the duration of response was 10.4 months vs. 7.4 months (HR: 0.534; 95% CI: 0.408−0.698) [5].

Concomitant treatment with paclitaxel and carboplatin (TC therapy) is often employed for platinum-sensitive recurrent ovarian cancer in routine clinical practice because of its high tolerability, but there have been few reports about the combination of Bev with TC therapy (Bev + TC therapy).

Accordingly, we compared Bev + TC therapy with chemotherapy alone by propensity score matching analysis in ovarian cancer patients who developed recurrence at ≥ 6 months after first-line chemotherapy with TC therapy.

PATIENTS AND METHODS

This retrospective observational study investigated patients with platinum-sensitive recurrent ovarian cancer who underwent treatment at Tokai University Hospital. They included 19 patients who received platinum-based chemotherapy (paclitaxel + carboplatin or gemcitabine + carboplatin) from May 2008 to December 2013 and 13 patients who received Bev + TC therapy from May 2014 to March 2017. All of the patients received TC therapy as first-line chemotherapy. We excluded patients who were not eligible to receive Bev according to the criteria of the OCEANS study, such as patients with intestinal obstruction and patients receiving treatment for thrombosis at the time of the recurrence. The median observation period was 4.4

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Table 1 Patient characteristics

	Before matting*				After matting * *			
	without Bev		with Bev		without Bev		with Bev	
	n=19	%	n=13	%	n=13	%	n=13	%
Median age(years)(range)	59(31−82)		63(36−78)		61(53−82)		63(36−78)	
ECOG PS								
0	16	84.2	13	100	10	76.9	13	100
1	3	15.8	0	0	3	13.1	0	0
Primary site								
Fallopian tube	2	10.5	1	7.7	2	15.4	1	7.7
Ovarian	12	63.2	11	84.6	7	53.8	11	84.6
Primary peritoneal	5	26.3	1	7.7	4	30.8	1	7.7
Histology subtype								
Serous	12	63.2	10	76.9	11	84.6	10	76.9
Mucinous	0	0.0	1	7.7	0	0.0	1	7.7
Endometrioid	2	10.5	2	15.4	2	15.4	2	15.4
Clear cell	5	26.3	0	0.0	0	0.0	0	0.0
Serous+Endometrioid	14	73.7	12	92.3	13	100	12	92.3
Mucinous+Clear cell	5	26.3	1	7.7	0	0	1	7.7
Time to recurrence since last platinum-based therapy,month								
6−12	11	57.9	9	69.2	8	61.5	9	69.2
> 12	8	42.1	4	30.8	5	38.5	4	30.8

ECOG PS: the Eastern Cooperative Oncology Group Performance Status
*:Fisher's exact test(no significant differences of background patient characteristics were found between two groups before matting)
* *:McNemar test (no significant differences of background patient characteristics were found between two groups after matting)

months in the chemotherapy group and 14.5 months in the Bev + TC group.

Six cycles of TC therapy were performed. Every three weeks, paclitaxel (175 mg/m^2) was administered intravenously over three hours, followed by carboplatin (area under the curve 5) over one hour, along with a standard antiemetic and hypersensitivity regimen.

Bev (15 mg/kg) was also administered intravenously on Day 1 of each cycle. After completion of TC therapy, Bev was continued until disease progression was detected or unacceptable toxicity occurred.

Six cycles of GC therapy were performed according to the method used in the study conducted by Phisterer *et al*. [3]. Every three weeks, gemcitabine (1000 mg/m^2) was administered on Days 1 and 8, while carboplatin (area under the curve 4) was administered on Day 1.

Assessments

The primary endpoint of the study was PFS, which was defined as the interval from the day of starting chemotherapy to the day of an event (progression or death). Response rates were evaluated by using RECIST ver. 1.1 and safety was evaluated with the Common Terminology Criteria for Adverse Event (CTCAE ver. 4).

Statistical analysis

PFS was calculated by the Kaplan-Meier method and differences of survival rates were assessed by the log-rank test. Differences between the groups with respect to the severity of adverse events were examined with Fisher's exact test.

Factors included in the propensity score were: age at recurrence((< 65 versus ≥ 65 years), time from last platina treatment to recurrence(6 to 12 versus > 12 months), histology subtype(serous / endometrioid versus clear cell / mucinous).

All statistical analyses, including calculation of the propensity scores, were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) [6]. EZR is a modified version of R commander (version 1.6−3) that incorporates statistical functions used frequently in biostatistics.

RESULTS

Patient profile

Clinical characteristics of the patients are summarized in Table 1. There were 32 patients, including 19 patients in the chemotherapy group and 13 patients in the Bev + TC group. The median age was 59 years (range: 31−82 years) in the chemotherapy group and 63 years (range: 36−78 years) in the Bev + TC group (p = 0.44). No significant differences of background characteristics were found between the two groups, including tumor histology and time to relapse.

Outcomes

The response rate was 57.9% (CR, n = 3; PR, n = 8) in the chemotherapy group and 92.3% (CR, n = 9; PR, n = 3) in the Bev + TC group. Median PFS was 6.73 months in the chemotherapy group versus 14.71 months in the Bev + TC group (Fig. 1). According to propensity score matching analysis, PFS was 6.31 months in the chemotherapy group and 14.71 months in the Bev + TC group [HR, 0.304 (95% CI, 0.114−0.8121); p = 0.01752] (Fig. 2).

Safety

Adverse events are summarized in Table 2. All of the patients in both groups experienced at least one adverse event.

Adverse effects that were Grade 3 or more severe included anemia (5.3% in the chemotherapy group and 23.1% in the Bev + TC group), thrombocytopenia

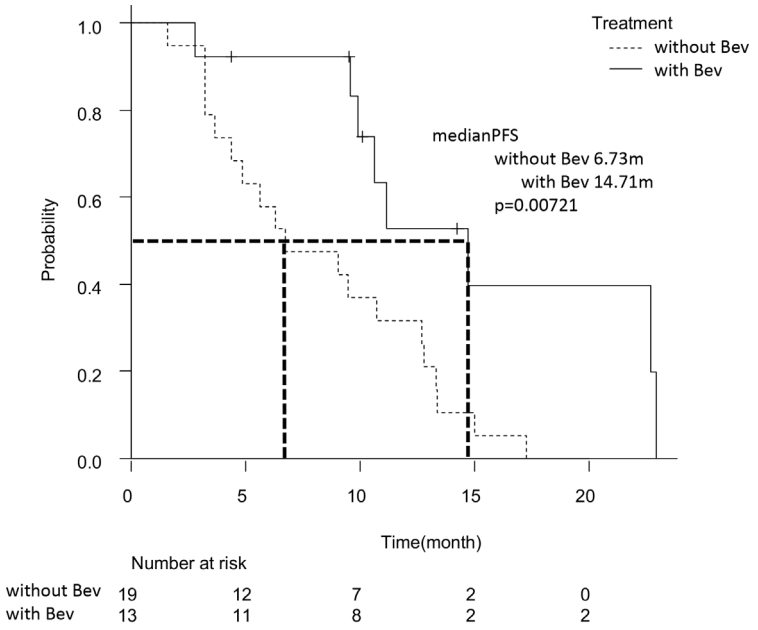

Fig. 1 Progression free survival in patients who received chemotherapy with Bevacizumab or without Bevacizumab before propensity score matting analysis.

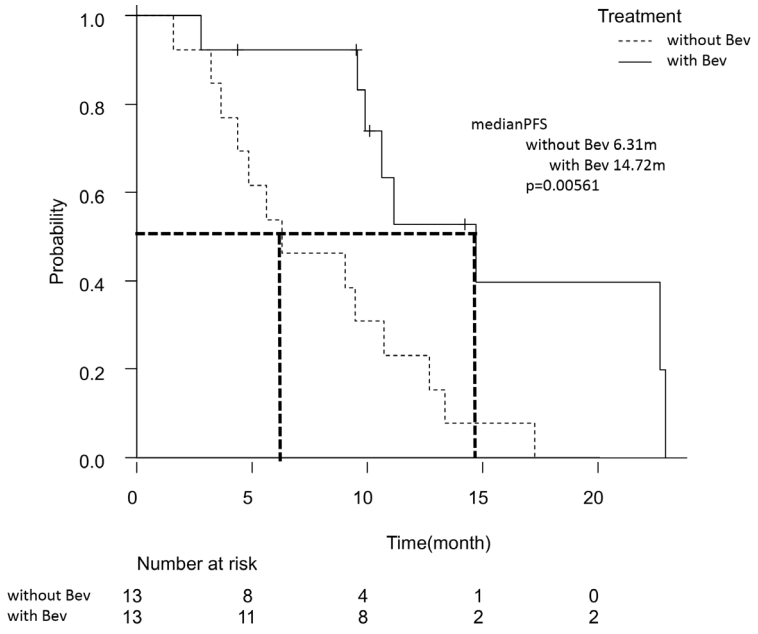

Fig. 2 Progression free survival in patients who received chemotherapy with Bevacizumab or without Bevacizumabafter propensity score matting analysis.

(5.3% and 7.7%), neutropenia (21.1% and 38.5%), and febrile neutropenia (FN; 0% and 7.7%). There were no significant differences in the frequency of adverse events between the two groups. However, the patient with FN died of sepsis. None of the adverse events that were Grade 3 or more severe showed specificity for Bev. The Bev-specific Grade 2 or milder adverse events included hypertension (38.5%), proteinuria (23.1%), epistaxis (53.8%), and thromboembolism (7.7%).

DISCUSSION

It has been reported that Bev combined with chemotherapy was highly effective for advanced recurrent ovarian cancer [5, 8–10]. The OCEANS study (an international, collaborative, phase 3 study) showed that adding Bev to GC therapy achieved marked prolongation of PFS compared to placebo in patients with platinum-sensitive recurrent ovarian cancer (HR, 0.48; 95% CI, 0.388–0.605; log-rank $P < 0.001$) [5]. However, GC therapy has inconvenient administration intervals and gemcitabine often cannot be administered on Day 8 due to adverse events such as anemia. In fact, TC therapy is currently preferred in clinical practice because of its high tolerability and greater convenience for patients [2].

The GOG213 study evaluated addition of Bev to TC therapy in patients with platinum-sensitive recurrent ovarian cancer, as well as assessing the usefulness of secondary debulking surgery (SDS) [11]. The primary endpoint of the study was overall survival (OS) and the secondary endpoint was PFS. Because there were errors in calculating the platinum-free interval (a selection criterion) and SDS was performed before chemotherapy, the actual outcomes of the study differed from the expected outcomes and the expected OS (primary endpoint) was not achieved. However,

Table 2 Safety summary

		without Bev (n=19)				with Bev (n=13)				p value
		Any Grades		Grades 3 to 5		Any Grades		Grades 3 to 5		(Any Grades)
		No.	%	No.	%	No.	%	No.	%	
Hematologic toxicity										
	Anemia	16	84.2	1	5.3	9	69.2	3	23.1	0.401
	Thrombocytpenia	3	15.8	1	5.3	5	38.5	1	7.7	0.219
	Neutropenia	18	94.7	4	21.1	7	53.8	5	38.5	0.0102
	Febrile neutropenia	0	0.0	0	0.0	1	7.7	1	7.7	0.406
non-Hematologic toxicity										
	Alopecia	18	94.7	–		8	61.5	–		0.0289
	Epistaxis	0	0.0	0	0.0	7	53.8	0	0.0	0.00051
	Fatigue	15	78.9	0	0.0	3	23.1	0	0.0	0.00329
	Hoarseness	0	0.0	0	0.0	1	7.7	0	0.0	0.406
	Hypertension	0	0.0	0	0.0	5	38.5	0	0.0	0.00639
	Intestinal obstruction	0	0.0	0	0.0	2	15.4	0	0.0	0.157
	Malaise	0	0.0	–		1	7.7	–		0.406
	Mucositis oral	0	0.0	0	0.0	1	7.7	0	0.0	0.406
	Proteinuria	0	0.0	0	0.0	3	23.1	0	0.0	0.0577
	Sensory	9	47.4	0	0.0	7	53.8	0	0.0	1
	Thromboembolic event	0	0.0	0	0.0	1	7.7	0	0.0	0.406

median OS was 37.3 months in the chemotherapy group and 42.2 months in the chemotherapy plus Bev group (HR, 0.829; 95% CI, 0.683–1.005; p = 0.056). In addition, significant prolongation of PFS was observed in the chemotherapy plus Bev group, with median PFS being 10.4 months in the chemotherapy group versus 13.8 months in the chemotherapy plus Bev group (HR, 0.628; 95% CI, 0.534–0.739; p < 0.0001). Because chemotherapy (GC or TC therapy) was selected by the attending physician, the study did not only assess the usefulness of adding Bev to TC therapy.

In this study, we compared outcomes by propensity score matching analysis between chemotherapy alone and Bev + TC therapy in patients with platinum-sensitive recurrent ovarian cancer treated at our hospital. Comparison between groups of patients with different characteristics should be performed carefully because there may be selection bias or other biases. Propensity score matching analysis is a method that was proposed by Rosenbaum and Rubin to eliminate the effects of confounding factors by combining multiple covariates into a single value called a propensity score [7].

Accordingly, we used propensity score matching analysis in the present study. We found that adding Bev to TC therapy resulted in the prolongation of PFS, which was 6.31 months in the chemotherapy group and 14.71 months in the Bev + TC group [HR, 0.304 (95% CI, 0.114–0.8121); p = 0.01752].

PFS of the Bev + TC group in the present study was comparable to PFS in the OCEANS study and the GOG213 study, so these results suggested that Bev + TC therapy can be effective. Evaluation of OS was incomplete because the number of OS events was insufficient in the Bev + TC therapy group.

Regarding safety, no significant differences of Grade 3 or more severe adverse events were observed between the two groups. However, one patient died of sepsis in the Bev + TC therapy group. In patients receiving chemotherapy, the neutrophil count can be markedly decreased and infections may occur (febrile neutropenia) that result in sepsis. In previous studies of combination therapy with Bev, deaths due to infection were reported in both patients receiving chemotherapy + Bev and those receiving chemotherapy alone [5, 8, 9]. It is possible that sepsis was due to chemotherapy in the patient who died from sepsis in the present study, emphasizing again that close monitoring is required when patients receive chemotherapy. Common Bev-specific adverse events were epistaxis and hypertension, but treatment with Bev was not discontinued in any of the patients developing these events. The profile of other adverse events was similar to that observed in previous studies and these events were tolerable.

The limitations of the present study should be considered. First, it was not a randomized study and the characteristics of the two groups of patients showed some differences. We employed propensity score adjustment to reduce bias with respect to treatment selection, allowing for more accurate comparison. However, without randomization of patients to each treatment, the possibility that unknown confounding variables influenced the results cannot be excluded.

In conclusion, adding Bev to TC therapy improved PFS in patients with platinum-sensitive recurrent epithelial ovarian cancer. To confirm these findings and perform further evaluation, large-scale prospective clinical studies will need to be conducted.

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