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Use of 7.5 mg/kg of bevacizumab to palliate symptomatic malignant ascites in recurrent ovarian cancer

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Summary

Purpose: To investigate the effectiveness of single-agent intravenous bevacizumab (7.5 mg/kg every three to four weeks) for palliating symptomatic malignant ascites caused by recurrent ovarian cancer, the authors examined the cases retrospectively. *Materials and Methods:* Five patients with recurrent ovarian cancer and malignant ascites were treated with bevacizumab. *Results:* A total of 23 bevacizumab infusions were administered for the patients, and the mean inter-infusion interval was 26.1 days (range: 21-35). After one course of therapy, no further paracentesis was required in four patients. However, bevacizumab was not effective in one patient and hence paracentesis had to be repeated. Due to disease progression, treatment was aborted in four patients, who died of their disease within a few months of the bevacizumab treatment (median overall survival period: 3.3 months). *Conclusion:* The intravenous infusion of 7.5 mg/kg bevacizumab at three- to four-week intervals is a promising therapy for malignant ascites caused by recurrent ovarian cancer.

Key words: Bevacizumab; Malignant ascites; Ovarian cancer.

Introduction

Malignant ascites can cause various symptoms such as abdominal swelling/bloating, abdominal pain, nausea, vomiting, anorexia, respiratory distress, fatigue, and loss of appetite and can have a severe impact on quality of life. It is commonly observed in patients with ovarian cancer and is considered to be a major complication of advanced malignancies [1].

Sodium restriction and diuretic drugs are widely used to treat malignant ascites, although there is no consensus regarding their effectiveness [1]. While the use of peritoneovenous shunts has been suggested to be beneficial, it is closely associated with several complications including pulmonary edema and disseminated intravascular coagulopathy [1]. In addition, cell-free and concentrated ascites reinfusion therapy has recently been reported to be effective against malignant ascites; however, it causes patients significant discomfort and has not been compared with other treatments [2]. As most patients with malignant ascites associated with recurrent cancer have already received several rounds of chemotherapy, it cannot be used to treat malignant ascites in such cases without causing severe toxicities. Thus, paracentesis is usually used to relieve malignant ascites; however, it has to be repeated frequently, which results in electrolyte imbalances and the depletion of fluid and proteins [1].

Bevacizumab is a humanized monoclonal antibody that targets all isoforms of vascular endothelial growth factor (VEGF)–A. It has been demonstrated to be effective against various malignancies, including in recent phase III randomized placebo-controlled trials in which it was used to treat ovarian cancer [3]. Bevacizumab was also evaluated as a palliative option in four patients with refractory ovarian carcinoma and symptomatic ascites in a previous study. In the latter study, bevacizumab treatment relieved the patients‘ ascites in all cases without causing any grade 3 or 4 toxicities [4]. Although some case reports have described similar findings, a bevacizumab dose of 15 mg/kg every three weeks was employed in these cases [5, 6], which caused severe adverse effects, and a phase II study of bevacizumab involving patients with platinum-resistant ovarian cancer or peritoneal serous cancer detected an increased incidence of bevacizumab-related gastrointestinal perforation [7].

Here, the authors report the cases of five patients that were treated with 7.5 mg/kg of bevacizumab every three to four weeks with the aim of palliating symptomatic malignant ascites caused by recurrent ovarian cancer.

Materials and Methods

From January to December 2014, five patients with recurrent ovarian cancer and symptomatic ascites were treated with single-agent bevacizumab with palliative intent at the present hospital. All of the patients had significant malignant ascites that required frequent paracentesis. In each case, bevacizumab was administered intravenously and was initiated at a dose of 7.5 mg/kg every three to four weeks. In addition, bevacizumab was specifically employed for symptom palliation and to reduce the need for therapeutic paracentesis. The patients’ clinical data including infor-

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Table 1. — *Summary of the cases of five patients that were treated with bevacizumab.*

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (diagnosis)		54	59	65	64	74
Stage		pT2bN1M0	pT3cN1M0	pT3cN1M0	pT3cNXM0	pT3cN1M1
Histology		Serous	Serous	Serous	Clear cell	Serous
Grade		2	3	3		3
Debulking status		Optimal	Optimal	Optimal	Suboptimal	Neoadjuvant
Chemotherapy	First-line	PTX+CBDCA	PTX+CBDCA	PTX+CBDCA	PTX+CBDCA	PTX+CBDCA
	Second-line	PTX+CBDCA	Weekly PTX	Weekly PTX	Perifosine	PLD
	Third-line	DTX+CBDCA	Gemcitabine	Gemcitabine		Gemcitabine
	Fourth-line	PLD	Nogitecan	PLD		Nogitecan
	Fifth-line	gemcitabine	PLD	Nogitecan		
	Sixth-line		Gemcitabine	PLD		
	Seventh-line		Irinotecan			
	Eighth-line		DTX			
Age (bevacizumab)		59	63	68	65	76
Performance status		2	1	2	1	2
Bevacizumab therapy	Dose (mg/kg)	7.5	7.5	7.5	7.5	7.5
	No. of infusions	12	2	2	5	2
	Interval (days, mean)	27.4	21	21	24.8	28
Response	CA-125	Response	No response	No response	No response	No response
No. of post-bevacizumab paracentesis procedures		0	0	6	0	0
Prognosis		Alive	Dead	Dead	Dead	Dead
Overall survival (months)		10.8	3.3	2.5	3.8	2.2

PTX: paclitaxel, CBDCA: carboplatin, DTX: docetaxel, PLD: pegylated doxorubicin, CA: cancer antigen.

mation about their demographics, cancer stage, surgical history, chemotherapy treatment, physical parameters, cancer antigen (CA)-125 levels, performance status (PS), toxicities, disease status, and survival were collected retrospectively via chart reviews.

The treatment response was analyzed using the Gynecologic Cancer Intergroup (GCIG) CA-125 response criteria. Briefly, the GCIG CA-125 criteria defines responders as patients that exhibit pretreatment CA-125 levels that are at least twice the upper limit of normal on two separate occasions, and a 50% post-treatment reduction in their CA-125 levels [8]. Adverse effects were analyzed according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Overall survival was calculated from the date of the administration of the first dose of bevacizumab to the date of death from any cause; data for patients that were still alive were censored at the date the patient was last known to be alive. The Kaplan–Meier method was used to estimate survival.

Results

The patients' data are summarized in Table 1. At the start of the bevacizumab treatment, their mean age was 66.2 years (range: 59-76), and all of their tumors were considered to be platinum-resistant. The median number of rounds of chemotherapy administered before the bevacizumab treatment was five (range: 2-8). Two patients exhibited baseline Eastern Cooperative Oncology Group (ECOG) PS of 1, while the other patients had ECOG PS of 2. All of the patients suffered from symptomatic malignant ascites caused by carcinomatous peritonitis of recurrent ovarian cancer, and patients 1 and 3 also had symptomatic malignant pleural effusion that required pleurodesis using OK-432.

A total of 23 bevacizumab infusions were administered. While the dose of bevacizumab was not reduced in any case, the inter-infusion interval was changed according to the patients' ascites symptoms. The mean inter-infusion interval was 26.1 days (range: 21-35, median: 28).

After one course of bevacizumab therapy, no further paracentesis was required in four patients. However, bevacizumab was not effective against malignant ascites in patient 3, and so paracentesis was repeated. The ascites collected from patient 3 after the first round of bevacizumab therapy was chylous. While the serum CA-125 level of patient 1 decreased from 1,541.0 U/ml to 311.6 U/ml, those of the other patients did not decrease.

Treatment was aborted due to disease progression in four patients. The major symptoms of disease progression were fatigue in patients 4 and 5, intestinal obstruction in patient 2, and symptomatic ascites in patient 3. Symptomatic ascites also reappeared in patient 1, and so bevacizumab was repeated to prevent a rapid increase in their ascites. While patient 1 was alive with disease at the time of writing, the other patients died of their disease within a few months of receiving bevacizumab (median overall survival period: 3.3 months). None of the patients developed gastrointestinal perforation, deep venous thrombosis, grade 3-4 hypertension, proteinuria, or other severe toxicities.

Discussion

Recently, two studies have shown that anti-VEGF treatment is effective against malignant ascites. Heiss *et al.* found that catumaxomab had a clear clinical benefit in patients with malignant ascites secondary to epithelial cancer [9], and Gotlieb *et al.* reported that blockading VEGF with aflibercept was effective at reducing malignant ascites [10]. These studies demonstrated that the time between successive paracentesis procedures could be extended by blockading VEGF, although it did not result in any improvement in overall survival. Since some studies have shown that bevacizumab can also reduce malignant ascites [7-9], the present authors considered that the effectiveness of bevacizumab for palliating the symptoms of malignant ascites should be studied.

Gastrointestinal perforation is one of the most clinically significant adverse effects of bevacizumab. In a phase II study of bevacizumab treatment for recurrent ovarian cancer, Cannistra *et al.* found that the incidence of gastrointestinal perforation was 11.4% (5/44) [7]. They also reported that patients that had received three or more rounds of chemotherapy prior to bevacizumab treatment or exhibited bowel wall thickening or bowel obstruction on computed tomography scans frequently suffered severe adverse events. Although the incidence of gastrointestinal perforation was much lower in other studies, steps should be taken to prevent it from occurring in patients with recurrent disease and malignant ascites that are treated with bevacizumab as it has a significant adverse effect on quality of life.

Another problem with bevacizumab therapy is the cost. Since its efficacy was demonstrated in phase III randomized placebo-controlled trials, bevacizumab has become a standard treatment for ovarian cancer. However, some studies have questioned its cost-effectiveness [11, 12]. Even if bevacizumab is not cost-effective as a primary curative treatment, we should consider its cost-effectiveness as a salvage treatment that aims to prolong survival and/or as a palliative treatment for relieving patients' symptoms.

Bevacizumab dose reduction during treatment for ovarian cancer has been examined in several studies. In a retrospective study, Emile *et al.* reported their clinical experience of the use of single-agent bevacizumab to treat recurrent ovarian cancer at a dose of 2.5 mg/kg/week [13]. Liu *et al.* found that combination chemotherapy including five mg/kg of bevacizumab every two weeks was effective against recurrent ovarian cancer [14]. Furthermore, in ICON7, a phase III study of primary treatment for ovarian cancer in which a bevacizumab dose of 7.5 mg/kg was administered every three weeks, bevacizumab treatment resulted in prolonged progression-free survival [3].

The present study suggested that the intravenous infusion of 7.5 mg/kg bevacizumab every three to four weeks is effective against malignant ascites caused by recurrent ovarian cancer. While only five patients were evaluable, bevacizumab ameliorated the symptoms of malignant ascites in four cases without causing severe toxicities. Although the median overall survival period was only 3.3 months, patients with recurrent ovarian cancer and malignant ascites exhibit a very poor prognosis. For example, Heiss *et al.* reported that the median overall survival period of such patients was 81 days, whereas Gotlieb *et al.* suggested that it was 16.0 weeks [9, 10].

Conclusion

The intravenous infusion of 7.5 mg/kg bevacizumab every three to four weeks is a promising therapy for palliating symptomatic malignant ascites caused by recurrent ovarian cancer. Based on the present authors' experience, further trials should be performed to confirm the effectiveness of lower dose bevacizumab as a treatment for malignant ascites.

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