Effective Treatment for Malignant Pleural Effusion and Ascites with Combined Therapy of Bevacizumab and Cisplatin

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Abstract. *Objective: To record the efficacy and toxicity of combining bevacizumab with cisplatin in treating malignant pleural effusion and ascites through intrapleural and intraperitoneal infusion. Patients and Methods: Forty-three patients were admitted to the Oncology Department of Yantai Yuhuangding Hospital with confirmed malignant effusion since January, 2011. Twenty of them received intrapleural and intraperitoneal perfusion of 200 mg bevacizumab plus 60 mg cisplatin every three weeks, and 23 patients received 60 mg cisplatin alone after draining effusion as much as possible. Reduction of effusion was determined by type-B ultrasonography. Results: The complete remission rate and effective rate of bevacizumab group was superior to that of the cisplatin group. The quality of life recovery rate of bevacizumab group was superior to that of the cisplatin group. The anhelation and abdominal distention of bevacizumab group was significantly improved. There was no significant difference in level III/IV toxicities and adverse effects between two groups. Conclusion: Bevacizumab significantly improved the objective response rate and quality of life of patients with malignant pleural effusion and ascites, while not causing notable adverse events.*

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Key Words: Bevacizumab, cisplatin, malignant pleural effusion, ascites, intrapleural and intraperitoneal chemotherapy.

Malignant pleural effusion (MPE) and ascites are among the most severe and difficult complications of late-stage malignancy. The incidence of serous effusion during the disease course of patients with late-stage carcinoma is around 50%. Numerous studies have indicated that the tumor burden, pleural and peritoneal effusion quantity, and tumor growth rate are closely related to the life expectancy of patients (1, 2). The occurrence of malignant effusion often indicates late-stage carcinoma with poor prognosis. If not controlled properly, MPE and ascites will severely affect the life quality of patients and are often life-threatening.

At present, chemotherapy is one of the main methods for treating malignant MPE and ascites. However, standard chemotherapy has little specificity for cancer cells and does not concentrate in tumor tissue, leading to low response rate and side-effects. In recent years, the generation of malignant serous cavity effusion was found to be directly related to increased secretion of the vascular endothelial growth factor (VEGF) (3-5). The VEGF family regulates angiogenesis, but as it promotes blood vessel permeability, VEGF is the leading cause of MPE and ascites. Therefore, inhibiting VEGF signaling could reduce the formation of malignant intracavity effusion (6).

Bevacizumab is a humanized monoclonal antibody against human VEGFA. It is able to inhibit proliferation, migration and differentiation of vascular endothelial cells directly (7). It can also promote apoptosis of endothelial cells and suppress VEGF-induced neoangiogenesis and vascular permeability (8). Bevacizumab has been shown to synergize with chemotherapeutic agents to block the accumulation of pleural fluid, thus making it a potential candidate for the clinical management of MPE (9-11). However, intravenous administration of bevacizumab requires a much higher dose to achieve a corresponding effect, the side-effect of which might offset the ability of bevacizumab to diminish effusion

itself (12). Studies have suggested that combination of bevacizumab with other chemotherapeutic drugs resulted in better clinical outcome, for example, combination with carboplatin or paclitaxel (13), and more recently, with cisplatin, for which great improvement in overall survival and quality of life (QOL) in patients with epithelial ovarian cancer and non-small cell lung cancer has been documented (14, 15).

However, these data are far from enough to cover all aspects of tremendous numbers of different types of cancer. Therefore, to further evaluate this combination method, this study retrospectively analyzed 43 cases of late-stage malignant carcinoma accompanied by MPE and ascites. The aim was to compare the efficacy and toxicity of cisplatin treatment with and without bevacizumab.

Patients and Methods

Patients. This study was approved by the Committee Board of Yantai Yuhuangding Hospital (Yantai, China) and written informed consent was obtained from all participants.

Inclusion criteria were: Advanced-stage disease confirmed with histological or pathological examinations; imaging examinations confirmed an increased amount of unilateral or bilateral pleural effusion; there were malignant tumor cells found in the pleural fluid; no anti-neoplastic drugs or hardener was injected intrapleural within one month before the study; Karnofsky score (KPS) >60, age over 18 years at time of recruitment, and a predicted survival time greater than 3 months; no major organ dysfunction, blood cell count, heart rate, liver, and kidney test all resulted within normal range; previous chemotherapy to have been discontinued for more than 6 weeks prior to the study.

The exclusion criteria were: History of allergy to biological agents; current treatment with anti-neoplastic drugs; detectable internal lesions or major organ dysfunctions; metastasis to the central nervous system; pregnancy or breastfeeding; infection; history of refractory psychiatric disease. Patients were withdrawn on the basis of the following criteria: at patient's request; grade III/IV adverse reactions related to bevacizumab therapy; disease progression; patient non-compliance; wound dehiscence or severe bleeding; severe arterial thrombus; hypertension crisis or hypertensive encephalopathy; reversible posterior leukoencephalopathy syndrome; and nephrotic syndrome.

Forty-three patients with cancer with presence of excess levels of pleural fluid were enrolled in this study from January 2011 to July 2013. Patient characteristics are summarized in Table I. All patients received systematic, intrapleural and intraperitoneal chemotherapy of cisplatin alone (n=20) or cisplatin combined with bevacizumab (Avastin, Roche, Inc., Penzberg, Germany) (n=23).

Treatment protocol. After drainage of the pleural fluid by thoracentesis, patients received intrapleural or intraperitoneal administration of either a combination of 60 mg of cisplatin plus 200 mg of bevacizumab (Roche Pharmaceuticals & Chemicals Ltd) or 60 mg of cisplatin monotherapy. After bed rest, patients were asked to turn over every 15 min in order to encourage full access of the delivered drugs to the coelom. Both groups were accompanied by systematic chemotherapy. Supportive treatment such as liver and stomach protection and anti-emesis were administered prior to the infusion. Five milligrams of dexamethasone and 5 ml xylocaine were given before and after the infusion to reduce side-effects. The treatment efficacy was evaluated through type-B ultrasonography at the end of each treatment course every 3 weeks.

Table I. *Comparison of general information, Patient demographics and characteristics. There were no significant differences between the two group regarding characteristics (p>0.05).*

Characteristic	BV/CP, n(%), n=20	CP, n(%), n=23
Median age (y)	51	53
Gender		
Male	11 (55.0%)	13 (56.5%)
Female	9 (45.0%)	10 (43.5%)
Hydrops type		
Hydrothorax	9 (45.0%)	12 (52.2%)
Ascites	11 (55.0%)	11 (47.8%)
Clinical stage		
Stage III	13 (65.0%)	13 (56.5%)
Stage IV	7 (35.0%)	10 (43.5)
Tumor		
NSCLC	7 (35.0%)	9 (39.1%)
Colorectal	5 (25.0%)	5 (21.8%)
Gastric	2 (10.0%)	3 (13.0%)
Cervical	2 (10.0%)	2 (8.7%)
Hepatic	1 (5.0%)	1 (4.3%)
Breast	3 (15.0%)	3 (13.0%)
KPS score		
≥80	16 (80.0%)	19 (82.6%)
60-80	4 (20.0%)	4 (17.4%)
History of systemic treatment		
Yes	13 (65.0%)	14 (60.9%)
No	7 (35.0%)	9 (39.1%)

BV, Bevacizumab; CP, cisplatin.

Evaluation of efficacy. Evaluation of short-term efficacy of bevacizumab was determined according to previous studies (6, 16, 17). Complete remission (CR): accumulated effusion had disappeared and remained stable for at least four weeks; partial remission (PR): accumulated effusion had decreased by 50%, associated with improved symptoms with no increased accumulation of fluid, and remained stable for at least four weeks; remission not obvious (NC): less than 50% of the pleural effusion had disappeared, or then was no noticeable change in symptoms; progressive disease (PD): the amount of accumulated effusion had increased with worsening of symptoms. Total efficacy was calculated by taking the sum of CR and PR. Adverse reactions were evaluated by the Common Toxicity Evaluation Criteria (CTC) according to the National Cancer Institute (NCI) (18). The QOL was assessed by KPS and recorded as apparently improved (increase in KPS by ≥20 post-treatment), improved (increase in KPS by ≥10), stable (no apparent change in KPS score) and reduced (KPS decline of ≤10). Toxicities were classified grade 0-4 according to the WHO toxicity grading criteria (19). All cases were followed-up through outpatient service, telephone or hospitalization until July 2013, with the death of the patient as the end of the follow-up.

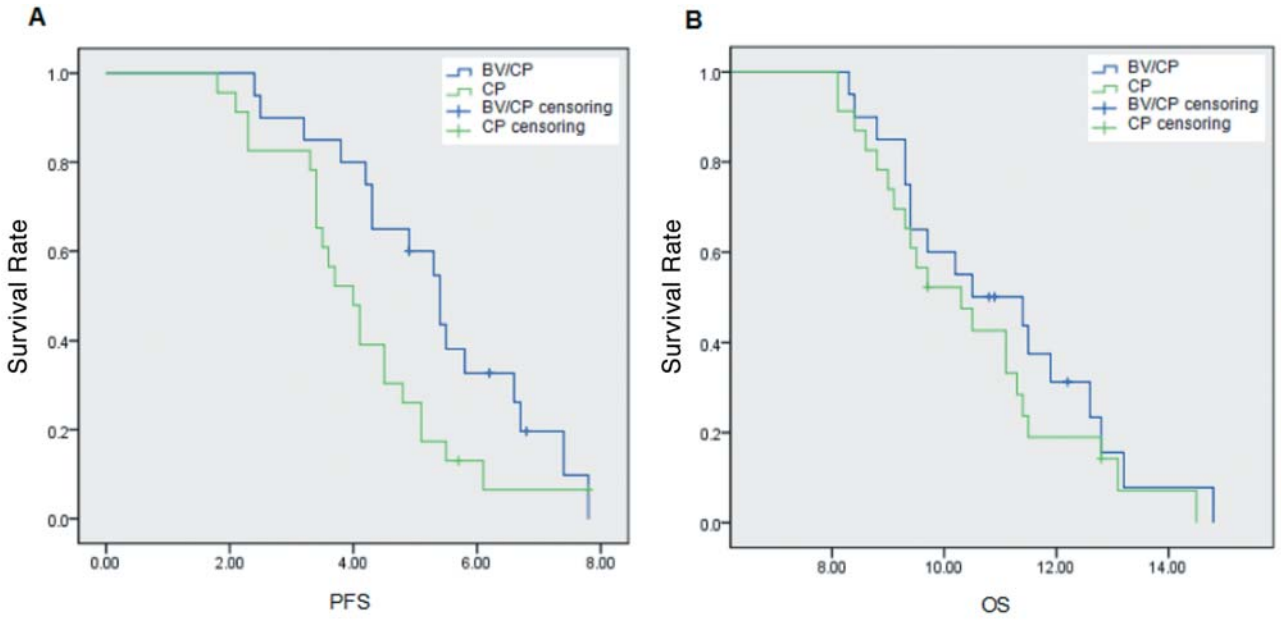

Figure 1. *Comparison of (A) progression-free survivial (PFS) and (B) overall survival (OS) curve between BV/CP and CP alone group.*

Statistical analysis. Collected data were processed and analyzed using SPSS version 17.0 (IBM Crop Armonk, NY, USA). Data were analyzed by the Chi-square test and by the *t*-test. Survival time was analyzed with Kaplan–Meier method, and survival differences were checked by log-rank test. A value of $p<0.05$ was considered statistically significant.

Results

Patients' demographics and characteristics are listed in Table I. Demographic characteristics were similar across the two treatment arms; no significant difference was reported. The patients included 24 males and 17 females with an average age of 52 (range=27-76) years.

Comparison of progression-free survival and overall response rate. The overall response rate (ORR) of patients treated with BV/CP was significantly higher than that of the CP group. The progression-free survival (PFS) was 5.4 months (95% CI was 4.7-6.1 month) in the BV/CP group, and the overall survival rate (OS) was 10.5 months (95% CI was 8.2-12.8 months). In CP alone group, the PFS was 4 months (95% CI: 3.4-4.6 month) and the OS was 10.3 months (95% CI: 9.1-11.9 months). The PFS for BV/CP group was significantly lower than the CP group ($X^2=4.036$, $p<0.05$) while the OS between the two groups was not significantly different ($X^2=0.895$, $p>0.05$) Figure 1.

The 43 patients enrolled in this study had completed at least two cycle courses of treatment. The ORR for the BV/CP group was 80% (CR=7, PR=9, NC/PD=4 out of 20 cases), while that for the CP group was 47.8% (CR=2, PR=9, NC/PD=12 out of 23 cases). The efficacy of BV/CP combined treatment was statistically significantly higher than that of cisplatin monotherapy in treating MPE or ascites ($p=0.03<0.05$).

Comparison of adverse effects. The incidence of hypertension was increased in the BV/CP group, with no other new serious adverse events being identified compared to the CP group (Table II).

Although bevacizumab has possible side-effects such as haemorrhage and hypertension, there was no evidence of significantly increased side-effects from combining bevacizumab with intrapleural and intraperitoneal infusion. Major side-effects, including myelosuppression, nausea, vomiting and diarrhoea, occurred in both groups. However, these symptoms were typical side-effects of chemotherapy, regardless of the introduction of bevacizumab.

The incidence of hypertension was significantly increased in the BV/CP group. However, in all cases, the severity was grade 1 or 2, with only one patient requiring intervention *via* oral administration of hypotensor. In none of the cases did the patient withdraw from the treatment due to intolerable side-effects. No significant difference was observed in the frequency of grade 4 side-effects. Moreover, in the BV/CP group, no serious adverse event such as proteinuria, thrombosis, gastrointestinal or pulmonary haemorrhage was observed.

Table II. *Comparison of toxicity between the groups treated with cisplatin alone and combined with bevacizumab.*

Side-effect	Grade	BV/CP, n% (n=20)	CP, n% (n=23)	*p*-Value
Myelosuppression		65% (13/20)	60.9% (14/23)	
	1-2	11	13	
	3-4	2	1	0.786
Nausea, vomiting		55% (11/20)	60.9% (14/23)	
	1-2	10	13	
	3-4	1	1	0.705
Diarrhea		15% (3/20)	13% (3/23)	
	1-2	3	3	
	3-4	0	0	0.858
Hypertension		30% (6/20)	4.3% (1/23)	
	1-2	6	1	
	3-4	0	0	0.023

BV, Bevacizumab; CP, cisplatin.

Quality of life. In the BV/CP group, the QOL improved in 11 participants, was moderately improved in six, stable in two and worsened in one (improvement rate=85%), which was significantly higher than that of the CP group (improved in four, moderately improved in eight, stable in nine and worsened in two; improvement rate=5.2%) (p=0.022<0.05).

Discussion

Approximately more than half of patients with cancer diagnosed at a relatively advanced stage of the disease present pleural effusion, and life expectancy is usually directly linked to the severity of the effusion (1, 2). Detection of MPE can be a clinical indicator of local invasion or systemic metastasis of advanced-stage cancer. This study discovered that the overall response rate to BV/CP treatment for MPE was significantly higher than that of the CP group. The incidence of hypertension was increased in the BV/CP group, with no other serious adverse event being observed compared to the CP group.

MPE and ascites are leading causes of death among patients with late-stage malignant tumors. Their formation mainly has the following mechanisms: direct invasion of the serosa by tumor cells; increased permeability of the pleuro-peritoneal capillary wall due to tumor-associated inflammation; tumor blocking the blood and lymphatic capillary in the parietal lamina serosa; blockage of lymphatic circulation in lymph nodes due to metastasis. MPE mainly displays as chest distress, suffocation, cough, and dyspnoea. Malignant ascites are primarily characterized by a series of clinical symptoms including abdominal distension and abdominal pain. Both MPE and ascites will severely reduce the patient's QOL. Effective control of pleural and peritoneal fluid is critical in clinical treatment to improve the patient's QOL and prolong their survival.

Current therapy for treating MPE and ascites includes systematic chemotherapy and topical treatment. Despite moderate effect, systematic chemotherapy suffers from the disadvantage of achieving only a low drug concentration and limited distribution in the pleura-peritoneal cavity compared to topical treatment. In 1970, the American Cancer Society first promoted the concept of intracavitary chemotherapy that could maintain an effective drug concentration for a longer period (20). The primary clinical chemotherapeutic drugs for thoracic and abdominal cavity perfusion include cisplatin, oxaliplation, carboplatin, oxaliplatin, bleomycin, adriamycin, mitoxantrone, irinotecan, etoposide and topotecan, *etc*. Cisplatin is a first-generation platinum anticancer drug. Once entering the pleura-peritoneal cavity, cisplatin cannot pass through the chest-peritoneal barrier quickly, thus allowing it to reach an optimal concentration for a longer time. However, even with direct pleura-peritoneal cavity infusion, the penetration capability of cisplatin was only able to reach so far, and the response rate was only as high as 66% (21, 22). The combination of bevacizumab and cisplatin could potentially increase the efficacy of chemotherapy in treating MPE and ascites due to its VEGF-inhibitor function. Bevacizumab has been recommended for the treatment of certain types of metastatic carcinomas, including of the colon, breast and kidney, and glioblastoma (23). Its function in suppressing pleural and peritoneal effusion as monotherapy or in combination with other drugs was appreciated relatively recently (24, 25).

Our results showed that the response rate for bevacizumab/cisplatin combination chemotherapy was 80.0%, that is significantly higher than the 47.8% by cisplatin alone. This result accorded with a recent study by Du *et al*. treating non small cell lung cnacer patients with MPE using 30 mg cisplatin combined with or without 300 mg bevacizumab had a significantly different response

rate of 85.71% and 56.67% (15). The slight difference in response rate between that study and ours was possibly due to differences in the dose administered, with a lower dose of bevacizumab (300 mg *vs*. 200 mg) in this study. It was possibly also due to the fact our study included a number of different types of malignancies rather than focusing on one. In another report, cisplatin combined with bevacizumab and taxol significantly reduced MPE in a 63-year-old patient with lung cancer (25). Similarly, intravenous or intraperitoneal administration of bevacizumab has been demonstrated to effectively treat malignant ascites. Hamilton and colleagues reported that in an 88-year-old patient with ovarian cancer with intractable ascites, intraperitoneal instillation of bevacizumab after peritoneal drainage successfully controlled the formation of ascites and improved the patient's QOL (26). Numnum *et al*. reported on patients with recurrent ovarian cancer and ascites treated with bevacizumab. Following the bevacizumab treatment, the ascites were adequately controlled for up to 6 months (27). El Shami and colleagues also used bevacizumab to treat nine patients with refractory ascites due to colorectal, breast, uterine and ovarian cancer. Long-lasting control of malignant effusions was observed in all cases (28).

Most related studies have mainly focused on ovarian and lung cancer. Our study also addressed the application of bevacizumab and cisplatin in cervical and breast, hepatic and gastric cancer, although with a limited number of cases; a more specialized study with a larger sample size is needed.

In our study, the complete remission rate of patients treated with bevacizumab/cisplatin combined therapy was superior to that of these treated with cisplatin alone. The BV/CP group also demonstrated significant improvement in PFS compared to the group treated with CP alone. Regarding adverse effects, there was no significant difference in grade 3/4 toxicity between the two groups, but with an increased rate of hypertension in the BV/CP group, indicating the relatively good tolerance of patients to this regimen. However, with retrospective studies, the sample size is often restricted and even difficult for multivariate analysis.

In conclusion, cisplatin combined with bevacizumab is reliable, safe and feasible; it provides a novel and efficient method for treating malignant carcinoma with MPE and ascites. More clinical investigations are still required regarding the description of the required dosage of the drugs used with this aim.

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Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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