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ORIGINAL ARTICLE

Efficacy of bevacizumab combined with albumin-bound paclitaxel in the treatment of platinum-resistant recurrent ovarian cancer

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Summary

Purpose: *To investigate the efficacy and safety of bevacizumab (BEV) combined with albumin-bound paclitaxel (ABP) in the treatment of platinum-resistant recurrent ovarian cancer.*

Methods: *Eighty-six patients with platinum-resistant recurrent ovarian cancer admitted to our hospital from March 2014 to March 2016 were enrolled and randomly divided into two groups: BEV+ABP group (n=43, treated with BEV combined with ABP) and ABP group (n=43, treated with ABP alone). The clinical objective response rate (ORR), changes in serum carbohydrate antigen 125 (CA125) level and adverse reactions were compared between the two groups. Additionally, the progression-free survival (PFS) and overall survival (OS) were evaluated after treatment.*

Results: *The clinical ORR and disease control rate (DCR) were 86.0% (37/43) and 93.0% (40/43) in BEV+ABP group and 62.8% (27/43) and 79.1% (34/43) in ABP group, respectively. The clinical ORR of patients exhibited a statistically significant difference between two groups (p=0.025), which was overtly higher in the BEV + ABP group than in ABP group, while the DCR had no statistically significant difference between two groups (p=0.117). The serum CA125 level was evidently decreased in both groups after treatment (p<0.05) compared with that before treatment, but without significant difference between two groups after treatment (p=0.220). The major adverse reactions were myelosuppression, gastrointestinal reactions, alopecia, rash, fatigue and peripheral neurotoxicity. There was no statistically significant difference in the incidence rate of adverse reactions between two groups (p>0.05). All patients were followed up for 6-29 months. The median OS was 16.3 and 12.6 months in BEV + ABP group and ABP group, respectively, clearly longer in BEV + ABP group than in ABP group (p=0.007). The median PFS in BEV + ABP group was clearly longer than in ABP group (8.9 vs. 6.7 months, p=0.028).*

Conclusions: *In comparison with ABP alone, BEV combined with ABP in the treatment of platinum-resistant recurrent ovarian cancer improves the clinical efficacy, PFS and OS, with good tolerance, and is worthy of popularization and application in clinical practice.*

Key words: *recurrent ovarian cancer, bevacizumab, albumin-bound paclitaxel, platinum-resistance*

Introduction

Ovarian cancer is the 9th malignancy among women in China, with 41,516 new cases in the registered areas in 2010 [1]. Since there is a lack of effective screening methods, 70% of patients with ovarian cancer are already in advanced stage at presentation [2]. Currently, cytoreductive surgery and platinum-based chemotherapy have achieved a relatively high remission rate, but high recurrence rate and platinum-resistance still severely affect the prospective life span and quality of life of patients [3,4].

Paclitaxel, an anticancer drug, has been widely applied in clinical practice and achieves a good therapeutic effect in various malignant tumors like

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breast cancer, non-small cell lung cancer and ovarian cancer [2]. Albumin-bound paclitaxel (ABP), a novel paclitaxel preparation with albumin as a solvent, has stronger anti-tumor ability, has less toxic effects because hematological toxicity and severe anaphylaxis are lower compared with traditional paclitaxel preparations [5,6]. ABP shows obvious efficacy in the treatment of platinum-sensitive or platinum-resistant recurrent ovarian cancer, peritoneal cancer and fallopian tube cancer, with tolerable adverse reactions [7,8]. Studies have proved that vascular endothelial growth factor (VEGF) is highly expressed in ovarian cancer tissues, which is closely correlated with the recurrence and metastasis of ovarian cancer. Studies have also demonstrated that bevacizumab (BEV), a monoclonal antibody against VEGF, represses VEGF activity and slows tumor growth, recurrence and metastasis in a model of ovarian cancer [9,10]. Currently, the role of BEV in combination chemotherapy for various tumors has been widely studied, but the efficacy of BEV combined with existing chemotherapy regimens in the treatment of platinum-resistant recurrent ovarian cancer is unclear [11].

This study compared and analyzed the safety and efficacy of BEV combined with ABP and ABP alone in treating patients with platinum-resistant recurrent ovarian cancer, to provide a reference for the therapeutic regimens of such patients.

Methods

General data

Eighty-six patients with platinum-resistant recurrent ovarian cancer treated in our hospital from March 2014 to March 2016 were studied.

Inclusion criteria

Patients definitely diagnosed with ovarian cancer via imaging and pathology, with clear histological type and tumor-node-metastasis (TNM) stage, those having recurrence within 6 months after discontinuation when clinical complete remission (CR) was achieved with platinum-based chemotherapy after cytoreductive surgery combined with sufficient and regular chemotherapy, those with acceptable general condition, with Eastern Cooperative Oncology Group (ECOG) score ≤1, and those with positive VEGF expression in immunohistochemistry examination.

Exclusion criteria

Patients with severe cardiovascular or cerebrovascular diseases or diseases of other systems, those treated with paclitaxel, ABP or other anthracycline anticancer drugs previously, or those allergic to ABP and/or BEV.

The study was approved by the Ethics Committee of the hospital and signed informed consent was provided by the patients and their families. These 86 patients were divided into BEV + ABP group (n=43) and ABP group (n=43) using a random number table. No statistically significant differences were detected in basic data of patients including age, menopausal status, histological type, tumor stage, ECOG score and first-line treatment between two groups (p>0.05) (Table 1).

Therapeutic methods

BEV + ABP group: The ABP for injection (Abraxis Bioscience, Summit, NJ, USA, NMPN: JX20060230, 100 mg) was dissolved in accordance with the instructions (135-175 mg/m^2) and intravenously infused for 30 min, once a day. BEV (Roche Pharmaceuticals, Basel, Switzerland, batch number: $20100023) was intravenously infused for 90 min, with the dose calculated based on the body weight of patients (7.5 mg/kg). Tropisetron was routinely administered to prevent vomiting and other symptoms. During chemotherapy the patients were exposed to ECG-monitoring. Three weeks were regarded as one course, and six consecutive courses of chemotherapy were to be administered. Before each cycle of treatment, ECOG scoring was assessed. Routine blood, urine, and stool tests, liver and renal functions, coagulation, tumor marker carbohydrate antigen 125 (CA125), and cardiopulmonary function were evaluated.

ABP group: the patients were treated with ABP alone for a total of six continuous courses, with every three weeks representing one course.

Observation indicators

At the end of 6 courses of chemotherapy, the efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1) [12]: CR: complete disappearance of the originally enhanced opacification of lesions in the arterial phase on enhanced CT images; partial remission (PR): a decrease over 30% in the diameter of the originally enhanced opacification of lesions in the arterial phase compared with that before treatment; stable disease (SD): a decrease of less than 30% or no increase in the diameter of the originally enhanced opacification of lesions in the arterial phase compared with that before treatment; and progressive disease (PD): an increase of 20% in the diameter of the originally enhanced opacification of lesions in the arterial phase compared with that before treatment or appearance of new lesions. The objective response rate (ORR) = CR + PR, and the disease control rate (DCR) = CR + PR + SD.

The adverse effects of BEV combined with ABP chemotherapy were graded as per the Common Toxicity Criteria of the National Cancer Institute (NCI) (Version 3.0). In each cycle after receiving BEV-combined chemotherapy, the toxic and side effects of patients were evaluated. Blood pressure monitoring and electrocardiogram (ECG) were employed to assess cardiovascular toxicity, blood routine examination was carried out to judge hematological toxicity, liver function tests were adopted to assess liver toxicity, and urine routine and renal function examinations were used to evaluate the toxicity of urinary system. The toxicity was graded as 0, 1, 2, 3 and 4.

Serum CA125 level was recorded and compared at 1 week before treatment and 4 weeks after treatment. The patients were followed up to record tumor recurrence, median progression-free survival (PFS) and median overall survival (OS). The follow-up was ended in March 2019.

Statistics

SPSS 22.0 was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation, and *t*-test was employed for the comparison between two groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison among groups. P<0.05 suggested that the difference was statistically significant. Survival curves were plotted by Kaplan-Meier method. Log-rank test was applied to compare the survival rate between groups, and p<0.05 suggested a statistically significant difference.

Results

General information of patients

As to pathological type of ovarian cancer, there were 22 (51.2%) and 26 (60.5%) cases of serous cystadenocarcinoma, 18 (41.9%) and 14 (32.6%) cases of mucinous cystadenocarcinoma, 2 (4.6%) cases and 1 (2.3%) case of endometrial carcinoma, and 1 (2.3%) case and 2 (4.6%) cases of undifferentiated carcinoma in the BEV + ABP group and ABP group, respectively. Besides, the majority of these patients was in TNM stage III and IV, with 27 (62.9%) patients and 29 (67.5%) patients in stage III, and 12 (27.9%) patients and 9 (20.9%) patients in stage IV in BEV + ABP group and ABP group, respectively. ECOG score: 25 (58.1%) patients and 18 (41.9%) patients got 0 point and 1 point in BEV + ABP group, respectively. In ABP group, 21 (48.8%) patients and 22 (55.2%) patients got 0 point and 1 point, respectively. The time of first-line treatment received by patients was 5.24±2.63 months and 5.86±2.52 months in BEV + ABP group and ABP group, respectively. There were no statistically significant differences in age, pathological type, TNM stage, ECOG score, menopausal status and first-line treatment between the two groups (p>0.05) (Table 1).

Clinical efficacy

In BEV + ABP group, there were 23 cases with CR, 14 cases with PR, 3 cases with SD and 3 cases with PD, with clinical ORR of 86.0% (37/43) and DCR of 93.0% (40/43). In ABP group, there were 16 cases with CR, 11 cases with PR, 7 cases with SD and 9 cases with PD, with clinical ORR of 62.8% (27/43) and DCR of 79.1% (34/43). The clinical ORR of patients displayed a statistically significant difference between two groups (p=0.025), which was overtly higher in the BEV + ABP group than in ABP group, while the DCR of patients had no statistically significant difference between the two groups (p=0.117) (Table 2).

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*Bevacizumab+ABP group (n=43) n (%)*	*ABP group (n=43) n (%)*	*p value*
Age, years, mean±SD	47.46±8.83	46.61±8.39	0.648
Histology			0.682
Serous cystadenocarcinoma	22 (51.2)	26 (60.5)	
Mucinous cystadenocarcinoma	18 (41.9)	14 (32.6)	
Endometrioid carcinoma	2 (4.6)	1 (2.3)	
Undifferentiated carcinoma	1 (2.3)	2 (4.6)	
ECOG score			0.387
0	25 (58.1)	21 (48.8)	
1	18 (41.9)	22 (55.2)	
TNM stage			0.683
I	2 (4.6)	1 (2.3)	
II	2 (4.6)	4 (9.3)	
III	27 (62.9)	29 (67.5)	
IV	12 (27.9)	9 (20.9)	
Menopause			0.289
Yes	32 (74.4)	36 (83.7)	
No	11 (25.6)	7 (16.3)	
First-line treatment (months), mean±SD	5.24±2.63	5.86±2.52	0.144

ABP: albumin bound paclitaxel, ECOG: Eastern Cooperative Oncology Group, TNM: tumor, node, metastasis

Comparison of serum CA125 level

At 1 week before treatment, the CA125 level of patients was measured and recorded. It was 673.41±67.39 kU/L and 654.38±50.68 kU/L in two groups, respectively, displaying no statistically significant difference (p=0.143). At 4 weeks after treatment, the CA125 level of two groups of patients was recorded again. It was decreased to 22.76±22.80 kU/L and 28.54±20.52 kU/L in two groups, respectively. Compared with that before treatment, the serum CA125 level was evidently lowered in both groups after treatment (p<0.05). Such a decline was greater in the BEV+ABP group than in the ABP group after treatment, but there was no statistically significant difference in the serum CA125 level between two groups after treatment (p=0.220) (Table 3).

Adverse reactions and complications

The major adverse reactions of patients were myelosuppression, gastrointestinal reaction, alopecia, rash, fatigue and peripheral neurotoxicity. As to myelosuppression, grade III-IV granulocytopenia occurred in 4 (9.3%) and 2 (4.7%) patients in the

Table 2. Comparison of tumor response of patients in the two studied groups

Responses	*Bevacizumab+ABP group (n=43) n (%)*	*ABP group (n=43) n (%)*	*p value*
Complete response (CR)	23 (53.5)	16 (37.2)	
Partial response (PR)	14 (32.6)	11 (25.6)	
Stable disease (SD)	3 (7.0)	7 (16.3)	
Progressive disease (PD)	3 (7.0)	9 (20.9)	
ORR (CR+PR)	37 (86.0)	27 (62.8)	0.025
DCR (CR+PR+SD)	40 (93.0)	34 (79.1)	0.117

ABP: albumin bound paclitaxel, ORR: objective response rate, DCR: disease control rate

Table 3. Comparison of serum CA125 level of patients in the two groups (mean±SD)

Cerum CA125 levels	*Bevacizumab+ABP group n=43*	*ABP group n=43*	*p value*
CA125 (kU/l)			
Pretreatment	673.41±67.39	654.38±50.68	0.143
Posttreatment	22.76±22.80	28.54±20.52	0.220

ABP: albumin bound paclitaxel, CA 125: carbohydrate antigen 125

Table 4. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Bevacizumab+ABP group Grade III-IV*		*ABP group Grade III-IV*		*p value*
	n (%)	*n (%)*	*n (%)*	*n (%)*	
Fever	14 (32.6)	0 (0)	12 (27.9)	0(0)	0.815
Fatigue	35 (81.4)	2 (4.7)	31 (72.1)	1 (2.3)	0.461
Erythema	21 (48.8)	0 (0)	16 (37.2)	0 (0)	0.384
Alopecia	33 (76.7)	0 (0)	27 (62.8)	0 (0)	0.240
Neutropenia	28 (65.1)	4 (9.3)	23 (53.5)	2 (4.7)	0.380
Thrombocytopenia	30 (69.8)	5 (11.6)	26 (60.5)	2 (4.7)	0.498
Anemia	14 (32.6)	0 (0)	17 (39.5)	0 (0)	0.654
Nausea, vomiting	34 (79.1)	8 (18.6)	29 (67.4)	5 (11.6)	0.330
Diarrhea	10 (23.2)	0 (0)	7 (16.3)	0 (0)	0.605
Liver dysfunction	9 (20.9)	0 (0)	6 (13.9)	0 (0)	0.589
Renal dysfunction	7 (16.3)	0 (0)	5 (11.6)	0 (0)	0.549
Peripheral neuropathy	23 (53.5)	2 (4.7)	20 (46.5)	1 (2.3)	0.667
Hypertension	4 (9.3)	0 (0)	3 (7.0)	0 (0)	1.000

ABP: albumin bound paclitaxel

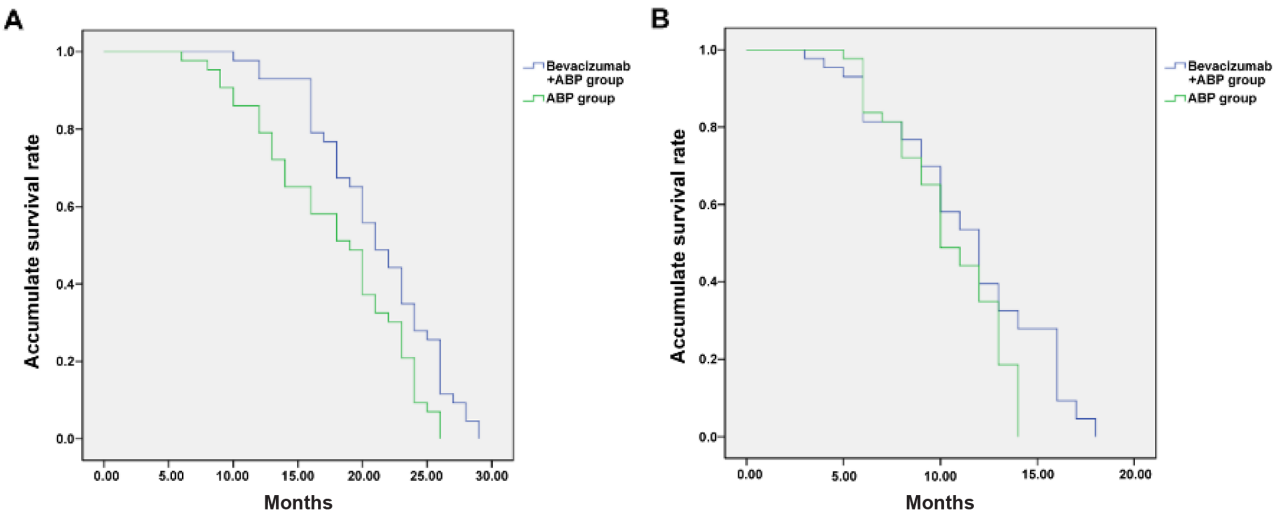

Figure 1. Kaplan-Meier survival curve of patients in the two groups. **A:** Overall survival rate of patients in the Bevacizumab+ABP group was significantly higher than that of the ABP group (p=0.007). **B:** Progression-free survival rate of patients in the Bevacizumab+ABP group was significantly higher than that of the ABP group (p=0.028).

BEV + ABP group and ABP group, respectively, and grade III-IV thrombocytopenia in 5 (11.6%) and 2 (4.7%) patients. In addition, grade III-IV nausea and vomiting were found in 8 (18.6%) patients and 5 (11.6%) patients in the BEV + ABP group and ABP group, respectively. Besides, there were 2 (4.7%) cases of fatigue and 1 (2.3%) case of peripheral neurotoxicity in both groups. Other adverse reactions were mostly grade I-II reactions, within patient tolerance. There were no treatment-related deaths. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups (p>0.05) (Table 4).

Patient survival

All patients were followed-up for 6-29 months, without cases dropping out. The median OS of patients was 16.3 months (1-29 months) in BEV + ABP groups and 12.6 months (1-26 months) in ABP group, with statistically significant difference (p=0.007). Moreover, it was obviously longer in BEV + ABP group than in ABP group. The median PFS of patients was 8.9 months (1-18 months) in BEV + ABP group and 6.7 months (1-14 months) in ABP group, with a statistically significant difference (p=0.028). The PFS of patients was also notably longer in BEV + ABP group than in ABP group. Survival curves were plotted by Kaplan-Meier method. Log-rank test revealed that the OS and PFS of patients had statistically significant differences between two groups (Figure 1).

Discussion

Ovarian cancer is one of the malignancies originating from the ovarian epithelium. In China, there are more than 400,000 new cases of ovarian cancer every year, and most patients tend to be diagnosed at middle or advanced stage in the examination on admission to hospital for the first time since there are no obvious clinical symptoms in the early stage of ovarian cancer [13,14]. For the treatment of ovarian cancer, there are many non-platinum chemotherapeutic drugs, but the total response rate is less than 30%, and the efficacy is worse, especially in recurrent, drug-resistant and refractory ovarian cancer [15]. Based on the time of ovarian cancer recurrence, platinum-resistant recurrent ovarian cancer refers to ovarian cancer recurring within 6 months after discontinuation of platinum-based chemotherapy, and platinum-sensitive recurrent ovarian cancer refers to ovarian cancer recurring after 6 months after discontinuation of therapy [16]. As to the treatment of recurrent ovarian cancer, the paclitaxel/cisplatin (PC) regimen is the most commonly used one at present, but its improvement in PFS is not significant [17]. As a result, finding out new drugs and methods controlling the progression of tumors to improve the quality of life and survival of patients is an important issue in the clinic.

ABP is a new preparation bound to human albumin. Compared with conventional paclitaxel preparations, ABP has a relatively large volume of distribution after intravenous injection and is more widely distributed outside the blood vessels and/or in tissues. In addition, ABP achieves a high total clearance and a remarkably lowered incidence rate of treatment-related adverse reactions in comparison with conventional paclitaxel injection [18]. As the pathogenesis and treatment of ovarian cancer continue to be understood in

depth, molecular targeted therapy has become a research hotspot in the field of ovarian cancer treatment. BEV blocks the binding of VEGF to receptors and suppresses the proliferation of vascular endothelial cells and angiogenesis, thus inhibiting tumor growth and achieving the goals of targeted therapy [19]. Moreover, BEV is able to promote normalization of blood vessels and facilitate the delivery of chemotherapeutic drugs in tumor tissues, thereby exerting a more effective anti-tumor effect [20]. It has been widely applied in malignant tumors such as lung cancer (including non-small cell lung cancer and small cell lung cancer), gastric cancer, breast cancer and cervical cancer, where it has achieved good therapeutic effects and can distinctly prolong the OS and PFS of patients, with adverse reactions within the tolerance of most patients [21,22]. Phase II clinical trials of BEV in the treatment of recurrent ovarian cancer and phase III clinical trials of BEV as the first-line treatment drug in adjuvant therapy of ovarian cancer (including GOG-218 and ICON7) have proved that BEV used in traditional chemotherapy can effectively prolong the PFS and OS of patients with ovarian cancer [23,24]. According to reports of Richardson et al [25], the clinical response rate of BEV combined with gemcitabine+cisplatin in the treatment of 35 patients with recurrent ovarian cancer was 78%.

In this study, it was found that the ORR in the BEV + ABP group was significantly higher than in ABP group [86.0% (37/43) *vs.* 62.8% (27/43), p=0.025], suggesting that the combination of BEV and ABP evidently increases the sensitivity of patients with platinum-resistant recurrent ovarian cancer to chemotherapy. Meanwhile, the PFS and OS of patients were remarkably higher in BEV + ABP group than those in ABP group, indicating that BEV combined with ABP overtly improves the anticipated survival of patients. The above results are similar to the findings of the study (in which, 84 patients with platinum-resistant recurrent ovarian cancer were studied) conducted by Tillmanns et al [26].

During chemotherapy, adverse reactions are important safety factors, which affect the treatment process of patients and even lead to the termination of chemotherapy. Gastrointestinal reaction, neutropenia, proteinuria and hemorrhage are common adverse reactions of BEV and paclitaxel used in chemotherapy. The mechanism of action is related to the dysfunction of vascular endothelial cells after VEGF inhibition. When applied, monitoring of blood pressure, coagulation and lower extremity blood vessels should be strengthened, and early targeted treatment should be conducted, thereby reducing the discontinuation of the medication due to relevant adverse reactions [27]. The results of this study revealed that the number of adverse reactions in BEV + ABP group was greater than in the ABP group, but the total incidence rate of adverse reactions exhibited no statistically significant difference between two groups (p>0.05).

There are still some shortcomings in this study: the number of subjects was relatively small, the follow-up was not comprehensive, and the effect of combination therapy on the quality of life of patients was not evaluated. Therefore, further multi-center randomized controlled clinical trials with a large sample size are needed to verify the conclusions.

Conclusions

In comparison with ABP alone, BEV combined with ABP applied in the treatment of platinum-resistant recurrent ovarian cancer markedly improves the clinical efficacy, PFS and OS of patients, with patient good tolerance, which is worthy of popularization and application in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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