ORIGINAL ARTICLE

Therapeutic effect of bevacizumab combined with paclitaxel and carboplatin on recurrent ovarian cancer

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Summary

**Purpose:** To observe the clinical efficacy and safety of beva-cizumab (BEV) combined with paclitaxel on recurrent ovar-ian cancer.

**Methods:** A total of 164 patients with recurrent ovarian cancer were selected and randomly divided into two groups: experimental group (n=82, BEV + paclitaxel + carboplatin) and control group (n=82, paclitaxel + carboplatin). The clinical therapeutic effects including objective response rate (ORR), complete response (CR) rate, partial response (PR) rate, stable disease (SD), progressive disease (PD), progression free survival (PFS) and overall survival (OS) were evaluated, together with the adverse clinical reactions and improvement of quality of life (QoL). Immunohistochemistry was used to detect the expression of phosphate and tension homology deleted on chromosome ten (PTEN).

**Results:** The PFS, OS and ORR of patients in the experimen-tal group were significantly higher than those in the control

group (p<0.05). In addition, the incidence rates of allergy, gastrointestinal reactions and leukopenia were significantly lower in the experimental group compared with those in the control group (p<0.05). There was no significant difference in QoL score between the two groups before treatment (p>0.05). However, after treatment, the QoL score in the experimental group was increased significantly compared with the control group (p<0.05). Moreover, the expression of PTEN in PR, SD and PD patients was lower, with significant difference between the two groups (p<0.05).

**Conclusion:** The clinical therapeutic effect of BEV combined with paclitaxel in patients with recurrent ovarian cancer was improved, suggesting it might be beneficial for the treatment of ovarian cancer.

**Key words:** bevacizumab, carboplatin, paclitaxel, recurrent ovarian cancer

Introduction

Ovarian cancer is one of the most common ma-lignant tumors in gynecology. According to recent statistics of the World Health Organization (WHO), the incidence rate of ovarian cancer ranks second among all gynecologic malignancies in the world, followed by cervical cancer [1]. More than 70% of patients are already in advanced stage at the time of first diagnosis [2]. Several studies have found that some chemotherapeutic drugs have therapeu-tic effects on ovarian cancer, but the prognosis is still not satisfactory, with 5-year overall survival about 30% [3,4]. A recent study found that once ovarian cancer patients ceased treatment after be-ing clinically in complete remission, more than 70% of them might develop recurrence and me-tastasis [5].

BEV is a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF)

[6], which binds to VEGF and inhibits proliferation and neovascularization of vascular endothelial cells, thereby exerting anti-tumor effect [7]. BEV has been shown to exert relatively good clinical efficacy in the treatment of various malignancies, including non-small cell lung cancer [8], but the efficacy of its combination with current clinical chemotherapy in the treatment of recurrent ovarian cancer remains poorly understood. This study aimed to evaluate the effectiveness and safety of combined therapy of BEV with chemotherapy in patients with recurrent ovarian cancer.

Methods

Patients

A total of 164 patients with recurrent ovarian cancer who were diagnosed and treated in our hospital from March 2013 to March 2015 were selected and randomly divided into two groups: experimental group and control group. The age of patients in the experimental group ranged from 38 to 70 years, with disease course of 25±9.8 months and time to recurrence of 7-16 months. Patients in the control group were 40-74 years, with disease course of 24±9.5 months and time to recurrence of 8-15 months. The clinical characteristics of patients in these two groups were comparable without statistically significant differences (p>0.05).

Inclusion criteria: Patients were pathologically diagnosed with ovarian cancer, receiving ≥3 weeks of ovarian cancer treatment before recurrence, with complete clinical data, and voluntarily cooperating with the investigators of this study. No patient had significant dysfunction of bone marrow, heart, kidney, liver, respiratory system and gastrointestinal system.

Exclusion criteria: Patients were not pathologically diagnosed, receiving <3 weeks of treatment, severely resistant to platinum drugs, with incomplete clinical data, and repelling the investigation of this study.

This study was approved by the Ethics Committee of our hospital and informed consents were obtained from all participants prior to study entry.

Treatment

Patients in the experimental group were treated with BEV + paclitaxel + carboplatin, and patients in the control group were treated with paclitaxel + carboplatin.

Drugs were administered via intravenous drip and included paclitaxel in normal saline (100 mg/m^2), carbo-

platin glucose solution [area under the curve (AUC) =5] and BEV in normal saline (15 mg/kg). Intravenous drip was performed 3 times a week [9], with 3 weeks defining a course of treatment.

Measurement of carbohydrate antigen 125

Carbohydrate antigen 125 (CA125) was measured using enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Immunohistochemical staining

Recurrent ovarian cancer tissues before and after treatment were paraffin-embedded and cut into 4µm thick sections. Then, sections were dewaxed, hydrated, washed with phosphate-buffered saline (PBS) and blocked for 15 min, followed by primary antibody incubation. Then, sections were incubated with primary antibody solution [phosphate and tension homology deleted on chromosome ten (PTEN) monoclonal antibody] at 4°C overnight, washed with PBS and then incubated with secondary antibody solution for 0.5 h, followed by washing. Next, horseradish peroxidase (HRP)-conjugated secondary antibody was added and incubated at room temperature for 0.5 h, washed and subjected to color development with diaminobenzidine (DAB). Lastly, sections were washed, counterstained with hematoxylin, mounted with neutral gum, and observed.

A field of view was randomly selected to count 100 cells, and the average number of cells with expression of protein was calculated as positive. Scoring of staining intensity: 0 point for no staining, 1 point for weak staining and 2 points for strong staining. Scoring for the positive rate of stained cells: 1-4 point(s) represented the proportions of positive cells (1,25), (26,50), 51,75) and (76,100), respectively. For the final score obtained by multiplying the scores of scoring of staining intensity and scoring for the positive rate of stained cells, 0-2 point(s) meant negative expression, and 3-8 points represented positive expression.

Evaluation methods

According to evaluation criteria of WHO [10], there were 4 kinds of response to therapy: progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR). Overall response rate (ORR)=CR+PR. The adverse reactions of the two groups of patients were recorded and compared. QoL of the two groups of patients was recorded and compared. The follow-up time was 15±5.3 months in the control group and 15.9±51 months in the experimental group.

Table 1. Comparison of efficacy of patients in two groups

Groups	n	CR n (%)	PR n (%)	SD n (%)	PD n (%)	CR+PR %
Experimental group	82	23 (28.05)	42 (1.22)	7 (8.54)	10 (18.19)	79.27
Control group	82	13 (15.85)	23 (28.05)	26 (31.71)	20 (24.39)	43.9
x^2						10.63
p						0.001

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation (SD), and Student's *t*-test was used for comparison of differences. Numerical data were expressed as percents, and x^2 test was used for comparisons. P<0.05 was considered as statistically significant.

Results

Comparison of treatment efficacy

After patients were treated, efficacy evaluation was carried out. The ORR (CR+PR) was 79.27% in the experimental group, which was significantly higher than that in the control group (43.9%; x^2=10.63, p=0.001) (Table 1).

Comparison of adverse reactions during treatment

Adverse reactions during treatment were observed and immediately recorded, including cardiotoxicity, liver function impairment, allergy, gastrointestinal reactions and leukopenia. After analysis, it was found that the incidence rates of allergy, gastrointestinal reactions and leukopenia of patients in the experimental group were significantly lower than those in the control group (p<0.05). However, the incidence rates of cardiotoxicity and liver function impairment of patients showed no signfiicant differences between experimental group and the control group (p>0.05) (Table 2).

Comparison of QoL before and after treatment

Before treatment, the mean QoL scores of the experimental group and control group were 33.25±4.81 and 32.96±5.02, respectively without statistically significant difference (t=0.001, p=0.941). However, after treatment, the mean QoL score was 57.49±8.33 in the experimental group, which was significantly higher than that in the control group (48.42±6.86; t=4.856, p=0.039) (Figure 1).

Serum CA125 expression

CA125 expression in patients with recurrent ovarian cancer was also detected and showed that there was no statistically significant difference between the two groups before treatment (p>0.05). However, its expression in the experimental group was significantly lower than in the control group after treatment (p<0.05) (Figure 2).

Comparisons of progression free survival (PFS) and overall survival (OS)

The mean PFS of patients was 9.3±1.7 months in the experimental group and 6.6±1.2 in the control group without statistically significant differ-
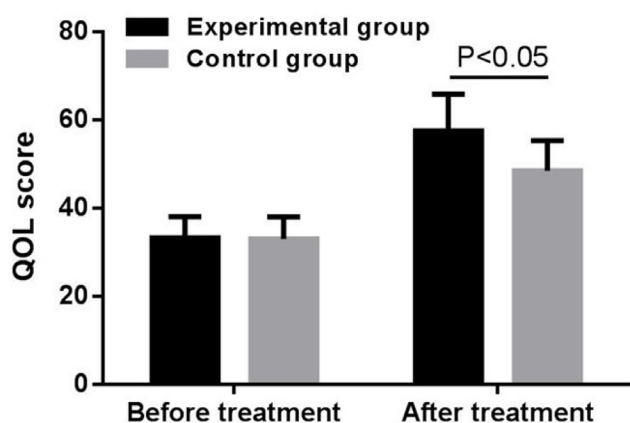

Figure 1. Quality of life (QoL) score of patients before and after treatment.
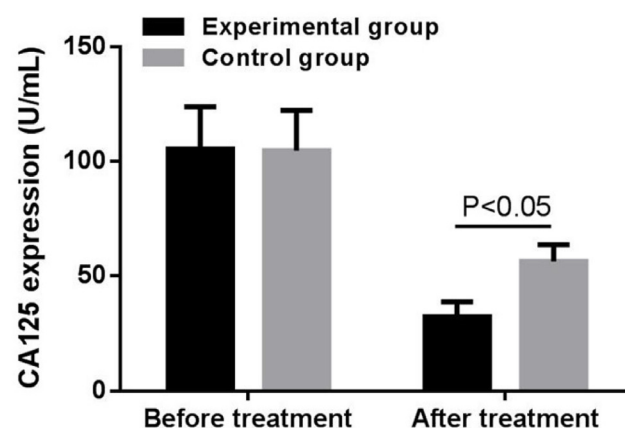

Figure 2. CA125 expression in patients before and after treatment.

Table 2. Comparisons of adverse effects in the two groups of patients during treatment

Groups	n	Cardiotoxicity n (%)	Liver function impairment n (%)	Allergy n (%)	Gastrointestinal reactions n (%)	Leukopenia n (%)
Experimental group	82	4 (4.88)	25 (30.49)	16 (19.51)	30 (36.59)	36 (43.90)
Control group	82	6 (7.32)	28 (34.15)	47 (57.32)	68 (82.93)	75 (91.46)
x^2		0.361	0.274	6.749	4.287	4.252
p		0.573	0.595	0.014	0.043	0.038

Table 3. PTEN expression

Groups	Adjacent tissue n (%)	CR n (%)	PR n (%)	SD n (%)	PD n (%)
Experimental group	82 (100)	21 (91.30)	31 (73.81)	4 (57.14)	5 (50.00)
Control group	82 (100)	12 (92.31)	12 (52.17)	10 (38.46)	4 (20.00)
x^2	-	0.005	5.472	4.352	3.572
p	-	0.857	0.033	0.041	0.048
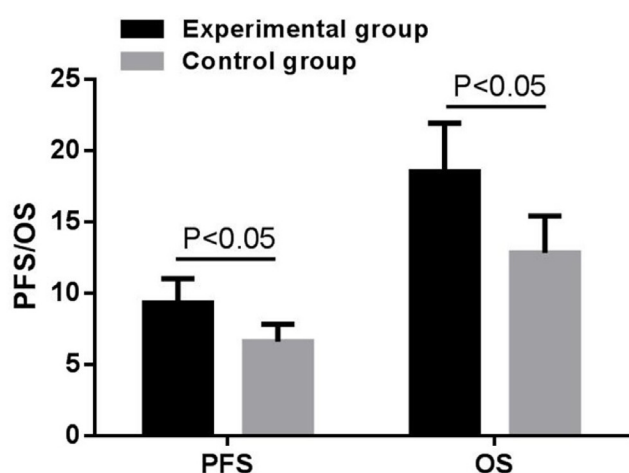
Figure 3. Progression-free survival (PFS) and overall survival (OS) in patients from experimental and control group.

ence (t=8.34, p=0.026). Interestingly, the OS in the experimental group (18.5±3.4 months) was significantly higher than in the control group (12.8±2.6, t=7.12, p=0.031) (Figure 3).

PTEN expression

The results of immunohistochemistry showed that PTEN protein expression was detected in cancer adjacent tissues, and the positive expression rate was 100%. There was no difference in the positive rate of PTEN in tumor tissues of CR patients (p>0.05), while significant differences were found in PTEN expression in tumor tissues of PR, SD and PD patients between the two groups (p<0.05) (Table 3).

Discussion

As one of the most common malignant tumors in women, ovarian cancer ranks high in terms of mortality. Because patients have no signs or symptoms in the early stage, it is easy to miss the presence of cancer, and patients are often in advanced stages at the time of first diagnosis [11]. Currently, radiotherapy, chemotherapy and surgical treatment are the commonly used treatment methods in clinical practice with high treatment efficiency, but the probability of recurrence in patients within

3 years is also very high, being more than 60% [12]. Usually, the perspectives of recurrent ovarian cancer patients are worse than that after primary treatment, with lower clinical curability. Therefore, treatment of recurrent ovarian cancer is usually aimed at prolonging survival of recurrent patients as long as possible and improves their QoL.

The preferred regimen for the clinical treatment of ovarian cancer is paclitaxel and carboplatin. It is reported that when applying paclitaxel and carboplatin in the treatment of ovarian cancer, the efficiency is up or above 70% [13]. In case of recurrent ovarian cancer, patients often have drug resistance, and it is difficult to control the disease further if the same treatment method is used again, which is a big challenge in clinical practice. Neovascularization is one of the foundations of tumor occurrence and development [14], in which VEGF, as a promoting angiogenesis factor, is usually overexpressed in tumor tissues [15]. *In vitro* studies demonstrated that inhibition of VEGF expression can slow down or even arrest the growth of tumor cells [16]. BEV is a recombinant monoclonal antibody against VEGF, which shows excellent clinical treatment efficacy in a large variety of cancers, such as lung cancer [17], colorectal cancer [18] and gastric cancer [19]. Numerous randomized controlled clinical trials have found that patients with recurrent ovarian cancer, no matter whether they are sensitive or resistant to carboplatin, have significantly improved PFS and OS after BEV treatment, and the survival status also has obvious improvement [20]. This is closely related to the fact that BEV inhibits neovascularization and reduces distant metastasis and recurrence of tumor cells.

In this study, patients in the experimental group were treated with BEV, paclitaxel and carboplatin, and patients in the control group were treated with paclitaxel and carboplatin alone. After treatment, the response rates, adverse reactions and survival rates of patients were evaluated and showed that the response rate of patients in the experimental group was significantly higher than that in the control group. However, the incidence rates of allergy, gastrointestinal reactions and leukopenia of patients in the experimental group were

significantly lower than those in the control group. In addition, the QoL score of patients after treatment in the experimental group was significantly higher than that in the control group, indicating that the combined application of BEV, paclitaxel and carboplatin can significantly improve the QoL of patients with recurrent ovarian cancer. Moreover, the PFS and OS after treatment in the experimental group were also higher than those in the control group (p<0.05), suggesting that combined treatment with BEV prolonged the survival of patients with recurrent ovarian cancer with higher treatment effectiveness.

PTEN, as a tumor suppressor gene, acts by inhibiting the growth of tumor cells *in vivo* with phosphatase activity [21], differentiation and promotes apoptosis [22,23]. Lai et al [24] found that PTEN expression is decreased in epithelial ovarian cancer tissues, and this decrease is more obvious with increased disease grade. In this study, measuring the expression of PTEN in tumor and paracancer tissues, we found that there were sig-

nificant differences in PTEN expression in tumor tissues of PR, SD and PD patients between the two groups (p<0.05), which was consistent with a previous study conducted by Shafiee et al [25].

In summary, the combined application of BEV, paclitaxel and carboplatin showed a promising treatment efficacy in patients with recurrent ovarian cancer, with fewer side effects. In addition, the survival of patients was significantly improved after treatment, suggesting that this combination might be beneficial for the treatment of recurrent ovarian cancer.

Acknowledgements

Conflict of interests

The authors declare no conflict of interests.

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