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ORIGINAL ARTICLE

Efficacy of bevacizumab combined with nedaplatin in the treatment of ovarian cancer and its effects on tumor markers and immunity of patients

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Summary

Purpose: *To study the efficacy of bevacizumab combined with nedaplatin in the treatment of ovarian cancer and its effects on tumor markers and immunity of patients.*

Methods: *A total of 100 ovarian cancer patients treated in our hospital from January 2015 to December 2018 were enrolled and divided into experimental group (n=50) and control group (n=50) using a random number table. Patients in the control group were treated with carboplatin alone, while those in the experimental group were treated with bevacizumab combined with nedaplatin, based on the treatment in the control group. The efficacy, adverse reactions and quality of life (QoL) score of patients were observed. Moreover, the levels of serum human epididymis protein 4 (HE4), alpha fetoprotein (AFP) and macrophage migration inhibitory factor (MIF), tumor markers carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA) and CA19.9, immunity indexes cluster of differentiation 3+ (CD3+), CD4+, CD8+ and natural killer (NK) cells, and serum inflammatory factors interleukin-8 (IL-8), IL-6 and IL-10 were detected before and after therapy.*

Results: *In the experimental group, the efficacy was superior to that in control group ($p<0.05$), and the adverse reactions were significantly reduced ($p<0.05$), while the QoL score was significantly increased ($p<0.05$). Before treatment, there were no significant differences in the levels of HE4, AFP and MIF, tumor markers CA125, CEA and CA19.9, immunity indexes CD3+, CD4+, CD8+ and NK cells, and inflammatory factors IL-8, IL-6 and IL-10 between the two groups ($p>0.05$). After treatment, the levels of HE4, AFP and MIF, CA125, CEA and CA19.9 and inflammatory factors IL-8, IL-6 and IL-10 obviously declined in the experimental group compared with the control group ($p<0.05$), while the levels of immunity indexes CD3+, CD4+, CD8+ and NK cells were clearly increased ($p<0.05$).*

Conclusion: *Bevacizumab combined with nedaplatin has good efficacy in the treatment of ovarian cancer, which can significantly improve the tumor markers, enhance the immunity and ameliorate the QoL of patients, with fewer adverse reactions, so it is worthy of popularization and application.*

Key words: *bevacizumab, nedaplatin, ovarian cancer, tumor markers, efficacy, adverse reactions, immunity*

Introduction

Due to the lack of early characteristic symptoms and effective screening methods, approximately 60% of ovarian cancer patients are definitely diagnosed in the late stages [1]. In the past two decades, cytotoxic chemotherapy, especially carboplatin combined with paclitaxel, has been used

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as a standard treatment. The above cytotoxic drugs have been applied by the gynecologists, and the prognosis of patients is improved by chemotherapy and surgical treatment [2]. However, it is still difficult to radically treat ovarian cancer, especially the progressive ovarian cancer. Among them, epithelial ovarian cancer (EOC) is one of the most deadly tumors in females, causing about 100,000 deaths every year. Advanced ovarian cancer accounts for more than 70% of EOC, and its first therapeutic response is good (platinum drugs mainly used after cytoreductive surgery), but it relapses in almost all cases, because the tumor is no longer sensitive to platinum drugs [3,4]. In recent years, new drugs different from traditional cytotoxic chemicals have been applied in the treatment of ovarian cancer. According to several large-scale prospective studies, bevacizumab (BV) is an anti-angiogenesis humanized monoclonal antibody against vascular endothelial growth factor (VEGF), and VEGF binds to VEGF receptor (VEGFR) expressed on cell membrane to promote cell proliferation, angiogenesis and vascular permeability, which significantly increases the survival of patients with ovarian cancer in adjuvant therapy and treatment of recurrence [5,6]. BV is a molecular targeted drug first applied in ovarian cancer in recent years. When BV binds to VEGF, it prevents VEGF from binding to VEGFR, so BV has an anti-tumor effect [7,8]. Among various types of tumors, ovarian cancer is considered to be highly dependent on angiogenesis factors during progression. In fact, there are reports that VEGF is overexpressed in most ovarian cancers and associated with their prognosis [9]. Based on these characteristics, therefore, the efficacy of BV may be superior in the treatment of ovarian cancer to that in other cancers.

Recently, some studies have reported that the response to tumor neo-epitopes is successfully induced after synthetic peptide vaccination [10,11]. The whole tumor antigen vaccine triggers specific response to tumor neo-epitopes, and the therapeutic effect can be evaluated through detecting the response of immune T cells to autologous tumor cells or autologous tumor lysates [12]. Cluster of differentiation 8+ (CD8+) acts on one or more immune neo-epitopes, and can also induce CD4+, CD3+ and natural killer (NK) cells, which is important for the effective anti-tumor immune response [13]. According to other studies, when the immune markers CD4+ and CD8+ are significantly increased, the survival of patients will be prolonged twice that of the control group, and the production of CD4+, CD8+ and NK cells can also inhibit the excessive production of inflammatory factors interleukin-6 (IL-6), IL-8 and IL-10 to prevent the irreversible damage caused to cells, and stimulate a variety of anti-inflammatory substances to resist the inflammatory injury [14]. Although there are many previous studies, the research results are inconsistent, and no effective therapeutic methods have been obtained for ovarian cancer.

In the present study, therefore, the efficacy of BV combined with nedaplatin in the treatment of ovarian cancer was evaluated, and its effects on tumor markers and immunity of patients were explored.

Methods

Clinical data

This clinical research protocol was approved by the Ethics Committee of Jining no.1 People's Hospital. A total of 100 ovarian cancer patients treated in our hospital from January 2015 to December 2018 were selected as the objects of the study after their signed informed consent was obtained, and they were divided into the experimental group (n=50) and the control group (n=50) using a random number table. In the control group, the patient age was 30-65 years (mean 49±10), and weighed 40-70 kg (mean 45±12.5). In terms of pathological stage, there were 15 cases in stage 1, 20 in stage 2 and 15 in stage 3. In the experimental group, the patient age was 32-64 years (mean 48±12), and weighed 42-71 kg (mean 47±13). In terms of pathological stage, there were 18 cases in stage 1, 20 in stage 2 and 12 in stage 3. No statistically significant differences were seen in this data between the two groups, and subsequent experiments could be performed.

Inclusion criteria: 1) patients diagnosed with ovarian cancer *via* pathological examination and CT; 2) those who received no treatment; 3) those with normal liver and kidney functions; 4) those not allergic to drugs used in the treatment; and 5) those with an expected survival of at least half a year.

Exclusion criteria: 1) patients with severe cardiovascular or cerebrovascular diseases; 2) those resistant to drugs used in the treatment; 3) those with secondary infection complicated with severe liver or kidney dysfunction; or 4) pregnant or lactating patients.

Therapeutic regimens

Treatment in the control group was performed with carboplatin (Qilu Pharmaceutical, H20020181) *via* intravenous infusion (400 mg/m^2), administered at an interval of 21 days. In the experimental group, treatment was performed using BV combined with nedaplatin based on the treatment in the control group, in which BV (Roche, Basel, Switzerland, S20100068) was intravenously injected (7.5 mg/kg) for 90 min, three times a week, and nedaplatin (Qilu Pharmaceutical, H20050563) was administered (85 mg/m^2) at an interval of 21 days. The patients in both groups received 3 courses of treatment.

Observation of clinical efficacy in both groups

Criteria for efficacy: According to the World Health Organization standards, the efficacy is classified into complete response (CR), partial response (PR), stable

disease (SD) and progressive disease (PD). The treatment efficacy in both groups was evaluated, and the number of patients at each kind of response was recorded in detail.

Adverse reactions in both groups

The adverse reactions, such as thrombocytopenia, leukopenia, gastrointestinal reactions and liver and kidney dysfunction in both groups were recorded by at least 3 3 doctors and the specific types of adverse reactions were recorded in detail.

Quality of life (QoL) score

The QoL score was given in both groups by at least 3 doctors using the health scale after care, mainly including the social function, somatic function and cognitive function. The number of patients with each score was recorded in detail. The total score was 100 points, and the higher the score, the higher the patient QoL.

Detection of serum HE4, AFP, MIF, IL-6, IL-8 and IL-10

After treatment, 5 mL of venous blood was drawn from the arm of patients and placed in an Eppendorf (EP) tube containing anticoagulant, followed by centrifugation (2000 g) at room temperature for 15 min. The supernatant was collected to detect the levels of serum HE4, AFP, MIF and inflammatory factors IL-6, IL-8 and IL-10 according to the instructions of enzyme-linked immunosorbent assay (ELISA) kit (Sangon, Shanghai, China). Then, the absorbance in each group was detected using a microplate reader.

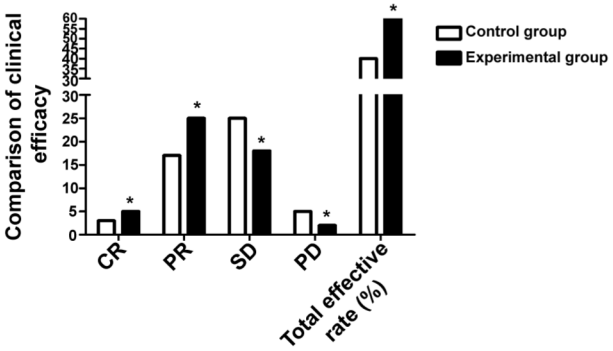

Figure 1. Comparison of clinical efficacy. The CR and PR cases in the experimental group are significantly more than in the control group (p<0.05), while the SD and PD cases are the opposite (p<0.05). *p<0.05 *vs.* control group.

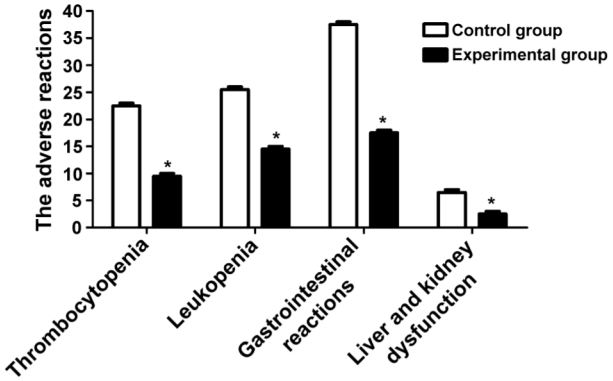

Figure 2. Adverse reactions in patients. The adverse reactions, such as thrombocytopenia, leukopenia, gastrointestinal reactions and liver and kidney dysfunction, are significantly reduced in the experimental group (*p<0.05).

Detection of tumor markers CA125, CEA and CA19.9

The levels of tumor markers CA125, CEA and CA19.9 were detected *via* chemiluminescence immunoassay using the Cobas2000 full-automatic immunoassay analyzer according to the operation program and the instructions of kits. The level of each index was recorded in detail, and their changes were analyzed.

Detection of immunity indexes CD3+, CD4+ and CD8+ and NK cells

After treatment, 5 mL of venous blood was drawn from the arm of patients and placed in an EP tube containing anticoagulant, followed by centrifugation (2000 g) at room temperature for 15 min. The supernatant was collected to detect the serum immunity indexes using the BD full-automatic flow cytometer according to the instructions. The level of each index was recorded in detail, and their changes were analyzed.

Statistics

All raw data obtained in the experiments were statistically analyzed using SPSS 20.0 software (IBM, Armonk, NY, USA), and multiple comparisons were performed. The experimental results were expressed as mean ± standard deviation. P<0.05 suggested that the difference was statistically significant. The bar graph was plotted using GraphPad Prism 7.0.

Results

Clinical efficacy in both groups

As shown in Figure 1, the CR and PR cases in the experimental group were significantly more than those in the control group (p<0.05), while the SD and PD cases were the other way round (p<0.05). The total effective rate in the experimental group (60%) was significantly higher than that in the control group (40%) (p<0.05).

Adverse reactions in both groups

As shown in Figure 2, the adverse reactions, such as thrombocytopenia, leukopenia, gastrointestinal reactions and liver and kidney dysfunction, were significantly reduced in the experimental group (p<0.05).

QoL score

Before treatment, there were no statistically significant differences in the social function, somatic function and cognitive function between the two groups (p>0.05). After treatment, the scores

were significantly higher in both groups than those before treatment, and they were significantly higher in the experimental group than in the control group (p<0.05) (Table 1).

Serum HE4, AFP and MIF

Before treatment, there were no statistically significant differences in the serum HE4, AFP and MIF between the two groups (p>0.05). After treatment, the levels of serum HE4, AFP and MIF were clearly lower in both groups than those before treatment, and they were obviously lower in the experimental group than in the control group (p<0.05) (Table 2).

Serum inflammatory factors

Before treatment, the levels of IL-6, IL-8 and IL-10 had no statistically significant differences between the two groups (p>0.05). After treatment, the levels of IL-6, IL-8 and IL-10 were obviously lower in both groups than those before treatment, and they were obviously lower in the experimental group than in the control group (p<0.05) (Table 3).

Levels of tumor markers CA125, CEA and CA19.9

Before treatment, the levels of tumor markers CA125, CEA and CA19.9 had no statistically significant differences between the two groups

Table 1. Quality of life score

Group	*Social function*	*Somatic function*	*Cognitive function*
Control group			
Before treatment	63.5±1.5	62.4±2.1	61.5±1.4
After treatment	73.2±2.6*	70.5±2.1*	71.5±1.9*
Experimental group			
Before treatment	62.1±1.1	61.7±1.9	63.3±2.9
After treatment	85.7±2.8*#	84.3±1.3*#	85.8±2.6*#

Before treatment, there are no statistically significant differences in the social function, somatic function and cognitive function between the two groups (p>0.05). After treatment, the scores are significantly higher in the experimental group than in the control group (p<0.05). *p<0.05 *vs.* before treatment, *#p<0.05 *vs.* control group in the same period

Table 2. Serum HE4, AFP and MIF

Group	*HE4 (pmol/L)*	*AFP (ng/mL)*	*MIF (μg/L)*
Control group			
Before treatment	270.14±1.52	88.19±2.17	45.49±1.42
After treatment	83.24±2.16*	10.57±2.81*	15.45±1.29*
Experimental group			
Before treatment	272.19±1.17	86.77±1.29	46.39±4.97
After treatment	35.73±2.87*#	4.34±1.31*#	5.83±2.61*#

After treatment the levels of serum HE4, AFP and MIF are clearly lower in both groups than those before treatment, and they are obviously lower in the experimental group than in the control group (p<0.05). *p<0.05 *vs.* before treatment, *#p<0.05 *vs.* control group in the same period. For abbreviations see text.

Table 3. Serum IL-6, IL-8 and IL-10

Group	*IL-6 (pg/mL)*	*IL-8 (pg/mL)*	*IL-10 (ng/L)*
Control group			
Before treatment	62.57±2.96	69.74±2.58	18.45±1.87
After treatment	35.27±2.64*	39.41±2.21*	15.49±1.27*
Experimental group			
Before treatment	61.17±1.23	71.84±1.89	17.79±4.27
After treatment	26.56±2.54*#	32.79±1.91*#	11.78±2.56*#

After treatment the levels of IL-6, IL-8 and IL-10 are obviously lower in both groups than those before treatment, and they are clearly lower in the experimental group than in the control group (p<0.05). *p<0.05 *vs.* before treatment, *#p<0.05 *vs.* control group in the same period

Table 4. Levels of tumor marker CA125, CEA and CA19.9

Group	*CA125 (μ/mL)*	*CA19.9 (μ/mL)*	*CEA (ng/mL)*
Control group			
Before treatment	170.78±1.89	90.54±2.10	33.65±1.47
After treatment	59.25±2.47*	43.03±1.52*	25.63±2.01*
Experimental group			
Before treatment	171.89±1.07	92.42±1.89	32.19±4.40
After treatment	33.56±2.84*#	25.48±2.85*#	11.05±1.81*#

After treatment the levels of CA125, CEA and CA199 are remarkably lower in both groups than those before treatment, and they are clearly lower in the experimental group than in the control group ($p<0.05$). *$p<0.05$ *vs.* before treatment, *#$p<0.05$ *vs.* control group in the same period

Table 5. Immunity indexes CD3+, CD4+, CD8+ and NK cells (%)

Group	*CD3+*	*CD4+*	*CD8+*	*NK*
Control group				
Before treatment	30.24±2.14	15.57±2.31	18.45±1.21	10.78±3.21
After treatment	52.78±2.57*	32.35±1.41*	25.63±2.01*	20.41±2.10*
Experimental group				
Before treatment	31.24±3.14	14.74±1.89	19.24±1.89	10.44±1.85
After treatment	70.52±1.56*#	42.14±2.57*#	36.49±4.77*#	30.98±2.45*#

After treatment the levels of CD3+, CD4+, CD8+ and NK cells are remarkably higher in both groups than those before treatment, and they are clearly higher in the experimental group than in the control group ($p<0.05$). *$p<0.05$ *vs.* before treatment, *#$p<0.05$ *vs.* control group in the same period

($p>0.05$). After treatment, the levels of CA125, CEA and CA19.9 were remarkably lower in both groups than those before treatment, and they were remarkably lower in the experimental group than in the control group ($p<0.05$) (Table 4).

Levels of immunity indexes CD3+, CD4+, CD8+ and NK cells

Before treatment, the levels of serum CD3+, CD4+, CD8+ and NK cells showed no statistically significant differences between the two groups ($p>0.05$). After treatment, the levels of CD3+, CD4+, CD8+ and NK cells were remarkably higher in both groups than those before treatment, and they were remarkably higher in the experimental group than in the control group ($p<0.05$) (Table 5).

Discussion

Ovarian cancer patients are often diagnosed with advanced disease and resistance to conventional (platinum) chemotherapy with poor 5-year overall survival [15]. Due to the extensive vascularization and overexpression of angiogenesis factors in ovarian cancer, inhibiting angiogenesis has been widely studied as a therapeutic strategy [16]. BV is an anti-angiogenesis reagent for VEGF, and when BV binds to VEGF, it prevents VEGF from binding to VEGFR, thus inhibiting the proliferation and metastasis, so BV has an anti-tumor effect. In the present study, the ovarian cancer patients were treated with BV combined with nedaplatin. The efficacy, adverse reactions and QoL score of patients were observed, and the levels of serum HE4, AFP and MIF, serum tumor markers CA125, CEA and CA199, immunity indexes CD3+, etc., and serum inflammatory factors IL-8, IL-6 and IL-10 were detected before and after treatment. According to the observation of clinical efficacy in both groups, the CR and PR cases in the experimental group were significantly more than in the control group, while the SD and PD cases were the opposite. The total effective rate in the experimental group (60%) was significantly higher than in the control group (40%). In addition, the adverse reactions, such as thrombocytopenia, leukopenia, gastrointestinal reactions and liver and kidney dysfunction, were significantly reduced in the experimental group. Concerning the patient QoL it was found that after treatment, the QoL scores were significantly higher in both groups than those before treatment, and they were significantly higher in the experimental group than in the control group. Before treatment, there were no significant differences in the social function, somatic function and cognitive function between the two groups.

The above findings confirm that BV combined with nedaplatin has good efficacy in the treatment of ovarian cancer, with fewer adverse reactions, and the patient QoL is clearly improved, consistent with the results of previous studies [17,18].

Serum CA19.9 was often used as a tumor marker in the diagnosis of pancreatic cancer in the past. However, in recent years, it has been commonly used in the assessment of treatment efficacy of ovarian cancer. Serum CEA is a common tumor marker and CA125 is highly expressed in serous ovarian cancer. Detecting the above three tumor markers in ovarian cancer has important significance [19,20]. In the present study, after treatment, the levels of CA125, CEA and CA19.9 were remarkably lower in both groups than those before treatment, and they were lower in the experimental group than in the control group. In addition, after treatment, the levels of serum HE4, AFP and MIF were obviously lower in both groups than those before treatment, and they were lower in the experimental group than in the control group. Inflammation will further increase the severity of disease, so controlling inflammation is also a good therapeutic approach. IL-6 can stimulate the excessive production of other inflammatory mediators such as IL-10 and IL-8 [21]. In this study, after treatment, the levels of IL-6, IL-8 and IL-10 were obviously lower in both groups than those before treatment, and they were obviously lower in the experimental group than in the control group. CD8+ T cells are potential targets for the immune monitoring of ovarian cancer, and often used to predict the prognosis and overall patient survival. The levels of immune cells after treatment in ovarian cancer patients have been evaluated in some studies, and it was found that CD3+, CD4+ and CD8+ are significantly elevated, and the efficacy is good [22,23]. In a small-scale study, the T cell functions in 21 patients with ovarian cancer were detected at different stages of platinum-based chemotherapy, and the results showed that the clinical tumor response had a strong correlation with the CD8+ and CD4+ cell functions during and after chemotherapy. During the conventional treatment of advanced malignant tumors, monitoring the general functions of T cells can help improve the efficiency of adjuvant chemotherapy [24,25]. In this study, it was found that before treatment, the levels of serum CD3+, CD4+, CD8+ and NK cells showed no significant differences between the two groups. After treatment, the levels of CD3+, CD4+, CD8+ and NK cells were remarkably higher in both groups than those before treatment, and they were remarkably higher in the experimental group than in the control group, which are similar to the results in the above studies. The present study demonstrated that BV combined with nedaplatin has excellent efficacy and fewer adverse reactions in the treatment of ovarian cancer, and can improve the patient QoL, reduce the levels of serum HE4, AFP and MIF, tumor markers CA125, CEA and CA19.9 and serum inflammatory factors IL-8, IL-6 and IL-10, and obviously enhance the immunity indexes CD3+, CD4+, CD8+ and NK cells after treatment. In the future, such an effect can be verified using laboratory animals from multiple levels and perspectives, so as to provide an important theoretical and experimental basis for subsequent research.

Conclusions

In conclusion, BV combined with nedaplatin in the treatment of ovarian cancer can significantly improve the patient QoL, reduce the levels of tumor markers and serum inflammatory factors, and significantly enhance the immunity of patients, with fewer adverse reactions and excellent efficacy. This study provides a theoretical basis for the prevention and treatment of ovarian cancer, as well as new ideas for further research.

Conflict of interests

The authors declare no conflict of interests.

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