The Efficacy of Bevacizumab in Ovarian Cancer and Its Influence on the Levels of Serum CA125, HE4, CEA and TPA

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Abstract: This paper aims to study the virtue of bevacizumab in the therapy of epithelial ovarian cancer and its impact on the levels of blood serum carbohydrate antigen 125 (CA125), tissue polypeptide antigen (TPA), human epididymis protein 4 (HE4) and carcinoembryonic antigen (CEA). Methods: To analyze the medical records of 60 patients with ovarian cancer who were hpspitalized in the First Hospital of Shanxi Medical University from April 2023 to April 2024 retrospectively. The sick persons were randomly divided into two groups: observs (n=30) with controls (n=30) based on the seperate treatment drugs. The control sick persons were treated with the TC regimen of paclitaxel and carboplatin, while the observe sick persons were treated in combined treatment with bevacizumab. The treatment course was 6 cycles. The efficacy, immune function, and changes in serum CA125, HE4, CEA, and TPA levels were compared between the two seperate groups, and the occurrence of toxic side effects during the treatment period was recorded. Results: The total effective rate and immune function levels of the observes after treatment were higher than those of the control sick persons, and the levels of CA125, HE4, CEA, and TPA in the blood serum were lower than those of the control sick persons ($P<0.05$); there was statistically meaningless in the total incidence of toxic side effects between the observs with controls during the treatment period ($P>0.05$). Conclusion: Bevacizumab has a oustanding therapeutic effect on ovarian cancer, effectively improving immune function and reducing the expression of serum CA125, HE4, CEA and TPA.
***Keywords*:** Ovarian cancer; Bevacizumab; Paclitaxel and carboplatin; Tumor markers; Tissue polypeptide antigen

1. Introduction

Carcinoma of ovary ranks as the 7th leading cause of death among all malignancy in women worldwide, seriously endangering women's health. It is also a familiar malignant tumor in the female genital system and has the highest rate for gynecological tumors deaths[1].Over the years, with the improvement of diagnostic and therapeutic techniques, although some progress has been made in the therapy of carcinoma of ovary, currently, tumor maximal resection and paclitaxel, platinum-based combined chemotherapy are the first-line treatment options for ovarian cancer patients. Whereas, the 5-year survival rate of carcinoma of ovary remains very low, approximately 25-30%. Due to the insidious onset of carcinoma of ovary, most clinical cases are discovered at a late stage, and surgery cannot completely remove the tumor[2]. Many cases fail to achieve the satisfactory tumor reduction after surgery.Generally, autoimmune functions play an vital part in the mechanisms of tumorigenesis.The sick persons with carcinoma of ovary also show abnormal immune functions, which all affect the progression of the disease and seriously endanger the health and life of women[3].Bevacizumab is a mono-clonal antibody that it inhibits vascular endothelial growth factor (VEGF). Clinically, it is used to treat various types of cancers. It mainly works by specifically binding to the HER2 receptor on the surface of tumor cells, thereby inhibiting the growth and spread of cancer cells. It can also reduce the generation of tumor microvessels and inhibit the progression of metastatic foci by inhibiting the biological activity of VEGF. At the same time, it can enhance the efficacy of chemotherapeutic drugs[4]. Carbohydrate Antigen 125 (CA125) is a large molecule glycoprotein belonging to the mucin family. It is mainly used as a tumor marker for epithelial carcinoma of ovary. The CA125 level of carcinoma of ovary patients is significantly elevated. After surgery and chemotherapy, the CA125 level drops rapidly. If there is recurrence, the increase in CA125 can occur before clinical symptoms[5].CA125 is commonly used for the medical diagnosis of ovarian tumor and for judging whether there is recurrence after surgery.Human epididymal protein HE4: It was first discovered in the distal epithelial cells of the epididymis. However, subsequent studies revealed that the HE4 expression was detected in separate malignant tumor tissues,for instance ovarian tumor, transitional cell carcinoma of the urinary system, and lung cancer, among others. Among them, the expression of HE4 in ovarian tumor is particularly significant. As a tumor biomarker for carcinoma of ovary, HE4 has a high detection sensitivity because it not only can be used for the early diagnosis but also monitoring of ovarian tumor[6].The joint examination of HE4 ,CA125 provides a more accurate method for the early diagnosis of ovarian tumor. Meanwhile, it is as well applicable for the detection during postoperative treatment of ovarian tumor and the judgment of

recurrence. These biomarkers can all assist in diagnosis, monitor disease progression and evaluate treatment effects[6]. Carcinoembryonic antigen (CEA) is a glucoprotein produced by colorectal tumor tissues. It is widely present in digestive system cancers originated from endoderm, as well as in normal embryonic digestive tract tissues. Trace amounts of CEA can also be found in normal human serum. It is a broad spectrum tumor biomarker. The antigenic determinant of CEA is a glycoprotein, and the infiltration,metastasis of tumor cells are all related to the glycosylation changes of cell membrane glycoproteins. It can reflect the existence of separate tumors and it is a better tumor biomarker for estimating the therapeutic effect of multiple malignancies[7].Tissue Polypeptide Antigen (TPA) consists of three subunits: B1, B2 and C. TPA is present in placenta and various tumor tissues, including ovarian cancer, colorectal cancer and multiple malignancies[8].The detection rate of serum TPA is considered positive when it exceeds 130 U/L. In the serum of patients with malignant tumors, its detection rate can be as high as 70% or even higher. Moreover, its increase has a relatively high sensitivity in observing the therapeutic effect of tumor treatment[8].The purpose of this research is to explore the efficacy of bevacizumab in treating carcinoma of ovary and its influence on the levels of blood serum CA125, HE4, CEA and TPA.

2. Materials and Methods

2.1 General Information

To analyze the medical records of 60 patients with carcinoma of ovary who were hpspitalized in the First Hospital of Shanxi Medical University from April 2023 to April 2024 retrospectively. Inclusion criteria: ①The patients' pathological examination met the clinical diagnosis of ovarian cancer; ②Recurrence after surgery and initial treatment; ③ Adequate understanding of the treatment plan and recovery measures; ④All sick persons signed the informed consent form without protest;⑤Physical examination and imaging examinations showed no metastasis to other vital organs such as the heart, liver, brain. Exclusion criteria: ① History of mental illness and inability to communicate; ②Concurrent other malignant tumors; ③ Severe allergic reactions to the treatment drugs; ④Liver and kidney dysfunction; ⑤Severe ovarian cancer with cachexia and serious metastasis threatening life; ⑥Poor compliance and poor cooperation.

2.2 Therapeutic Approaches

Based on the different treatment methods, 60 patients were divided into the observation group (n=30) and the control group (n=30). The patients in the observation group were aged 35 to 75 (54.25 ± 8.07) years old, with a BMI value ranging from 28 to 30 (28.68 ±1.43) kg/m^2. According to the surgical and pathological staging criteria of the FIGO, 40 cases were in stage III and 20 cases in stage IV. The control sick persons were aged 34 to 77 (55.06 ± 8.75) years old, with a BMI value ranging from 28 to 31 (29.14 ± 1.35) kg/m^2. There were 38 cases in stage III and 22 cases in stage IV in the control sick persons. There was statistically meaningless in the clinical data between the two groups ($P > 0.05$).

Treatment method: The control group was given chemotherapy with paclitaxel and carboplatin.[Paclitaxel specification: 30mg/5ml, purchased from Hainan Pharmaceutical Co., Ltd.][The specification of carboplatin for injection: 10ml, 0.1g. Purchased from Qilu Pharmaceutical Co., Ltd.]. The observe sick persons was further treated with bevacizumab injection on this basis.[Bevacizumab specification: 100mg: 4ml, purchased from Qilu Pharmaceutical Co., Ltd.].One course of treatment lasts for 3 weeks. Both groups of the sick persons received 6 courses of treatment. This study was approved by the ethics committee.

2.3 Observation Indicators

①Therapeutic Effect: Clinical therapeutic outcome and total effective rate: marked improvement, disappearance of lesions and ascites; effective, reduction of lesions and improvement of ascites by more than 50%; ineffective, no improvement of clinical symptoms. ②Cellular Immune Function: Before and after treatment, collect 5 ml of venous blood from the sick persons in the morning on an empty stomach, centrifuge and extract serum, and detect the levels of CD3+, CD4+, CD8+, and NK using an automatic flow cytometer. ③Serum CA125, HE4, CEA, TPA: Before and after treatment, extract serum for detection from patients in both groups, and detect the levels of CA125, HE4,CEA, and TPA using electrochemiluminescence method.④Safety: Record toxic,side effects, and observe the occurrence of severe adverse reactions during treatment.

2.4 Statistical methods

Statistical analysis was conducted using SPSS 27.0 software. Measurement data were expressed as (±s), and independent sample t-test was used for comparison. Chi-square test was employed for comparison of count data. $P < 0.05$ was considered statistically significant.

3. Result

3.1 Comparison of therapeutic effects between the two sick persons groups

In the observation group, 18 cases showed marked improvement, 6 cases were effective, and 6 cases were ineffective; in the control group, 12 cases showed marked improvement, 7 cases were effective, and 11 cases were ineffective. The total effective rate in the observation sick persons (22 cases, 76.6%) was higher than that in the control sick persons (19 cases, 63.3%).

3.2 Comparison of immune function levels between the two sick persons groups

After treatment, CD3, CD4 and NK levels in both groups decreased, while CD4/CD8 ratio slightly increased. However, the levels in the observe sick persons were higher than those in the control sick persons (all $P < 0.05$). See Table 1,Table 2.

Table 1. Comparison of Immune Function Levels(CD3+, CD4+)Before and After Treatment between Two Groups of sick Persons (Mean±SD, %)

Group	Number of cases	CD3+		CD4+	
		Before treatment	After treatment	Before treatment	Before treatment
The observation group	30	75.15±8.05	67.26±4.25	38.27±4.20	33.20±3.15
The control group	30	75.07±8.08	61.15±4.12	38.14±4.12	28.20±3.07
t-value		0.038	5.654	0.121	6.226
p-value		0.969	0.000	0.904	0.000

Table 2. Comparison of Immune Function Levels(NK, CD4+/CD8+) Before and After Treatment between Two Groups of sick Persons (Mean±SD, %)

Group	Number of cases	NK		CD4+/CD8+	
		Before treatment	After treatment	Before treatment	Before treatment
The observation group	30	28.25±3.10	25.15±2.90	1.18±0.21	1.72±0.25
The control group	30	28.14±3.12	22.34±3.08	1.19±0.20	1.46±0.28
t-value		0.137	3.638	-0.189	3.794
p-value		0.892	0.001	0.851	0.000

Note: Compared with the baseline of this group, ① $P < 0.05$

3.3 Comparison of serum tumor marker levels between the two groups

After treatment, CA125, HE4, CEA and TPA levels in both groups decreased, and those in the observe sick persons were lower than those in the control sick persons (all $P < 0.05$). See Table 3 and Table 4.

Table 3. Comparison of serum tumor marker levels(CA125, HE4)between the two groups of sick persons

Group	Number of cases	CA125(U/ml)		HE4(pmol/L)	
		Before treatment	After treatment	Before treatment	Before treatment
The observation group	30	475.15±50.05	167.26±20.25	238.25±34.20	33.20±10.15
The control group	30	465.15±60.05	211.15±35.12	225.14±30.12	75.20±17.12
t-value		0.701	-5.930	1.576	-11.558
p-value		0.486	0.000	0.121	0.000

Table 4. Comparison of serum tumor marker levels(CEA, TPA) between the two groups of sick persons

Group	Number of cases	CEA(ug/L)		TPA(U/L)	
		Before treatment	After treatment	Before treatment	Before treatment
The observation group	30	29.25±4.10	2.25±0.80	71.18±22.21	29.20±10.25
The control group	30	28.14±4.24	4.14±1.12	72.35±25.20	47.35±15.28
t-value		1.031	-7.521	-0.191	-5.403
p-value		0.307	0.000	0.849	0.000

Note: Compared with the baseline of this group, ① $P < 0.05$

3.4 Comparison of toxic and side effects between the two groups

There was no statistically significant difference in the total incidence of toxic and side effects between the two groups during the treatment period (P > 0.05), See Table5.

Table 5. Comparison of toxic and side effects between the two groups

Group	Number of cases	Decreased platelet count	Decreased white blood cell count	Liver insufficiency	Gastrointestinal reactions
The observation group	30	20	22	20	22
The control group	30	22	23	22	20
Chi-square test		1.063	1.053	1.063	1.511
p-value		0.303	0.301	0.303	0.310

4. Discussion

Carcinoma of ovary is a familiar malignant tumor in the female genital system, accounting for approximately 4% of all malignancy in women. On account of occult onset of carcinoma of ovary, most clinical cases are diagnosed at an terminal stage, leading to a high mortality rate. It arrays first among gynecological tumors and causes a serious threats on women's lives. The tumor cells of ovarian cancer have high invasiveness, and 70% of patients have already developed to an advanced stage when diagnosed. For such patients, simple surgical treatment alone cannot effectively cure the disease. Clinically, multiple methods need to be combined for treatment. Chemotherapy is one of the postsurgical treatment alternative for carcinoma of ovary, especially the TC regimen (paclitaxel combined with carboplatin) is the most common method. It is widespread used in the postsurgical treatment alternative for carcinoma of ovary and has significant effects. Some research have linked that the occurrence of carcinoma of ovary is also connected with the weakened or reduced immune function of the body, which is a related factor for the onset of ovarian cancer. There are multiple components of innate immunity in the body, including phagocytes, T cells, B cells, NK cells, etc. T lymphocytes mature in the thymus, being the main functional group of cellular immunity in the body's immune system. They fully participate in the cellular immune response process according to different functions and can be divided into several different subgroups. CD3 is composed of 6 peptide chains, which binds closely with TCR to form a TCR-CD3 complex containing 8 peptide chains. CD3 can fully reflect the overall function and number of T cells. CD4 is an important surface molecule of immune cells, mainly expressed on T lymphocytes , and participates in the activation and differentiation of T cells, playing an considerable regulatory role in the body's immune response. CD4 cells are also the main target of HIV virus attack, thereby causing the occurrence and development of diseases such as AIDS and immune system disorders. CD8 is a subgroup of T lymphocytes, called cytotoxic T cells, which further differentiate and proliferate after activation to become effector cells, called cytotoxic T lymphocytes. CD8 and other types of T cells originate from the bone marrow and mature in the thymus. CD8 recognizes specific antigens presented by the MHCI class molecules through TCR. It is a surface marker molecule of cytotoxic T cells. NK cells are also known as natural killer cells and are important immune cells in the body. They not only participate in anti-tumor, anti-viral infection, and immune regulation, but even participate in the occurrence and progression of hypersensitivity reactions and autoimmune diseases in certain cases. Because NK cells have some differentiation antigens of T cells, such as 20-30% of NK cells CD3 and 30% of NK cells CD8, it is generally believed that NK cells have a close relationship with the development of T cells. Studies have shown that T lymphocytes are the main participants in cellular immune responses in the body. The sick persons with carcinoma of ovary, the immune function is low. This experiment detects the immune function level of ovarian cancer patients after treatment, which has very important clinical significance for further evaluating the efficacy of treatment for patients[10].Bevacizumab is a mono-clonal antibody that it inhibits VEGF. Its mechanism of action is to interfere with the binding of VEGF to its vascular endothelial receptors, thereby achieving the purpose of inhibiting tumor angiogenesis. It can slow down tumor growth and delay the spread of the disease, playing a significant role.Last several years, it has been widespread used in clinical therapeutics for diverse tumor patients. Bevacizumab is used to cure diverse tumors, including carcinoma of ovary, gastric cancer, rectal cancer, and other malignancy[11].In the treatment of ovarian cancer, especially in cases of advanced or recurrent ovarian cancer, the combination of bevacizumab, paclitaxel, and carboplatin chemotherapy drugs is quite common. Bevacizumab works by inhibiting angiogenesis and promoting the degeneration of blood vessels within and around the tumor, thereby slowing or controlling the proliferation and spread of malignancy cells, enhancing the efficacy of chemotherapy and thus enabling better prolongation of the lifetime period of the sick persons with carcinoma of ovary.

This experiment research shows that both the observe sick persons and the control sick persons experienced a decline in

immune function after chemotherapy. However, the immune function indicators of the observe sick persons were significantly higher than those of the control sick persons. This might indicate that the combination of bevacizumab, paclitaxel, and carboplatin chemotherapy for the sick persons with carcinoma of ovary can reduce the impact of chemotherapy drugs on their immune function[12]. This might be because chemotherapy drugs kill tumor cells while also killing some immune-active cells, thereby affecting the body's immune function. Studies have shown that bevacizumab significantly inhibits the VEGF pathway, inhibits tumor cell growth, and effectively reduces tumor-induced immunosuppression, improving the immune function of the sick persons with carcinoma of ovary[13].The results of this research show that the observe sick persons treated with bevacizumab and the combination of paclitaxel, carboplatin chemotherapy have a higher total effective rate than the control sick persons in treating ovarian cancer. Analyzing the bevacizumab combined with paclitaxel and carboplatin chemotherapy, the utilization rate of chemotherapy drugs was improved, and the combined treatment of the two drugs significantly enhanced the therapeutic effect of carcinoma of ovary. The levels of CA125, HE4, CEA, and TPA in the blood serum of the observe sick persons were lower than those of the control sick persons. After treatment, the levels of CD3, CD4, and NK in both groups decreased, while CD4/CD8 slightly increased. However, the levels in the observation sick persons containing bevacizumab were higher than those in the control sick persons. This suggests that the combination of bevacizumab, paclitaxel, and carboplatin chemotherapy for the sick persons with carcinoma of ovary can enhance the immune function of patients, lower the levels of tumor markers, and better exert the anti-tumor effect.

In conclusion, bevacizumab combined with paclitaxel and carboplatin has a remarkable therapeutic effect on ovarian cancer. It can effectively improve the immune function of patients and reduce the expression levels of serum CA125, HE4, CEA and TPA.

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