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Original Article

Effect of bevacizumab plus paclitaxel and carboplatin regimen on prognostic survival of ovarian cancer patients

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Abstract: Objective: To investigate the efficacy of bevacizumab, paclitaxel and carboplatin in the treatment of ovarian cancer (OC) and the impact on patients' prognosis. Methods: A total of 90 patients with OC treated at our institution were enrolled in this retrospective analysis. Among them, 30 patients treated with bevacizumab plus paclitaxel and carboplatin regimen were classified as an observation group (OG), and 60 other patients who received paclitaxel and carboplatin were assigned as a control group (CG). The changes of carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA) and carcinoembryonic antigen 242 (CA242) were observed before and after treatment in both groups. The clinical efficacy was observed, and the patients were followed up for 3 years to observe their survival and the adverse effects. Independent factors affecting patient's prognosis were evaluated by Cox regression analysis. Results: After treatment, the objective remission rate and disease control rate were markedly higher in the OG than those in the CG ($P<0.05$). The serum CA199, CEA and CA242 levels of patients in the OG were dramatically lower than those in the CG after chemotherapy ($P<0.05$). There was no statistically significant difference in the incidence of leukopenia, hemoglobin reduction, neutropenia, gastrointestinal reactions, abnormal renal function and abnormal liver function between the two groups ($P>0.05$). Cox regression analysis identified that the degree of differentiation, International Federation of Gynecology and Obstetrics stage, CA199 and treatment regimen were independent factors affecting the prognosis of patients ($P<0.05$). Conclusion: Combined treatment of bevacizumab plus paclitaxel and carboplatin improved the treatment outcome and reduced the levels of CA199, CEA and CA242 in OC without increasing the incidence of adverse events.

Keywords: Bevacizumab, paclitaxel, carboplatin, ovarian cancer

Introduction

Ovarian cancer (OC) is one of the three major malignancies of the female reproductive system. It has the highest death rate among gynecologic malignancies, which seriously threatens women's health and life [1]. Globally, approximately 239,000 new cases of OC are detected each year, accounting for 3.6% of all cancer cases, and 152,000 OC deaths from OC each year, accounting for 4.3% of all cancer deaths [2]. Additionally, data show that the 5-year survival rate for OC ranges from 47% for all stages to only 29% for patients at advanced stages (III-IV) [3]. Surgery is the optimal treatment for OC, but patients are usually not diagnosed at early stage. The ovaries are deep in the pelvis and do not cause significant signs and symptoms in the early stages, so approximately 75% of patients are diagnosed at an advanced stage (International Federation of Gynecology and Obstetrics (FIGO) stage III-IV) [4]. The efficacy of radical surgery for advanced OC is not ideal and is prone to recurrence after surgery, and surgery also causes greater trauma to patients and slows postoperative recovery [5]. Furthermore, chemotherapeutic drugs have high toxicity and low clinical remission rates. Therefore, searching for a treatment that is superior to chemotherapy and a combination of chemotherapy that patients can tolerate has become the main direction of OC treatment at this stage.

Paclitaxel combined with carboplatin regimen is usually chosen for the clinical treatment of

patients with OC in the advanced stage of chemotherapy [6]. But the uncertain efficacy in recurrent OC may be related to the drug resistance in tumor cells secondary to genetic mutations [7]. Recently, a large number of studies and clinical trials have provided more possibilities for OC treatment, among which molecular targeted therapy has become an important treatment option other than surgery and chemotherapy [8]. The most common and effective molecular target drugs available are vascular endothelial growth factor (VEGF) inhibitors [9]. Bevacizumab is a type of monoclonal antibody, which targets VEGF and has been found to be clinically effective in the treatment of lung cancer. Also, carboplatin has a tumor-controlling effect by binding to DNA molecules and thus inhibiting their function [10]. However, further studies are needed to determine whether bevacizumab can improve the clinical outcomes of patients with paclitaxel and carboplatin regimen.

The purpose of this study was to analyze the efficacy of bevacizumab plus paclitaxel and carboplatin regimen in treatment of OC patients, and to evaluate the factors affecting the prognosis of OC by Cox regression analysis, so as to provide a reference for the clinical treatment regimen for OC.

Methods and materials

Clinical data

A total of 90 patients with OC who underwent treatment at the PLA Navy Anqing Hospital from February 2014 to February 2018 were enrolled in this retrospective analysis. Sixty patients treated with paclitaxel and carboplatin served as a control group (CG), and the other 30 patients, who received additional bevacizumab, served as an observation group (OG). This study was conducted with the approval of our medical ethics committee, Ethical lot number LL201783.

Inclusion and exclusion criteria

Inclusion criteria: Patients who were diagnosed with epithelial carcinoma of the ovary by clinical, imaging, and pathological tests; patients with FIGO stage III or IV; patients between 18 and 70 years old; patients who received chemotherapy for the first time for this disease; patients received post-operative tumor cytoreductive surgery; patients who were informed and signed an informed consent form.

Exclusion criteria: patients with secondary OC; patients who were unable to tolerate chemotherapy treatment; patients with primary organ insufficiency, with coagulation dysfunction or other malignancies; patients with mental disorders or other reasons for poor compliance; patients with a history of chemotherapy treatment; patients with an expected survival of less than six months; patients in pregnant or locating; patients who were intolerant to the chemotherapy drugs.

Treatment options

Patients in the CG were given paclitaxel + carboplatin chemotherapy regimen. Paclitaxel injection (China, Jiangsu, JiuXu Pharmaceutical Co., Ltd., SFDA Approval No. H20067715) was given on day 1, and the drug dose was calculated according to 175 mg/m^2 and diluted using 0.9% sodium chloride injection (China, Zhejiang, Wepon Pharmaceutical Holding Group Co., Ltd., SFDA Approval No. H20093657) to prepare a concentration of 0.3-1.2 mg/mL for an over-3-h intravenous injection. On day 2, carboplatin injection (Jinan, China, Qilu Pharmaceutical Co., Ltd., SFDA Approval No. H200-20180) was given intravenously for 1 h, and the dose was calculated according to 400 mg/m^2 and diluted into 0.5 mg/mL mixture using 5% glucose solution (Zhejiang, China, Wepon Pharmaceutical Holding Group Co., Ltd., SFDA Approval No. H20093657). Chemotherapy was administered once every 21 d for 6 months. Patients in the OG were given bevacizumab plus paclitaxel and carboplatin chemotherapy regimen. The drug type and dosage of paclitaxel injection and carboplatin injection were the same as those in the CG. Besides, bevacizumab (Roche Pharma (Switzerland) Ltd., SFDA Approval No. S20120069) was administered at a dose of 15 mg/kg, diluted with 0.9% sodium chloride solution, and administered intravenously to patients 1 d before the start of chemotherapy, with the first intravenous dose lasting 90 min and the second intravenous dose lasting 60 min if well tolerated. The first IV drip time was 90 min, and the second IV drip time was shortened to 60 min if well tolerated. Chemotherapy was administered once every 21 d for 6 months.

Serological tests

Peripheral blood was collected from patients before and after treatment, left to stand for 30 min, and centrifuged at 1500 g for 10 min. The supernatant was collected by SIEMENS ADVIA Centaur CP fully automated chemiluminescence immunoassay, and carbohydrate antigen 199 (CA199) (SFDA Approval No. 20193400446), carcinoembryonic antigen (CEA) (SFDA Approval No. 20173402240) and carcinoembryonic antigen 242 (CA242) (SFDA Approval No. 20193400846) levels were examined by chemiluminescence immunoassay. The instruments and reagents were operated strictly according to the instructions.

Outcome measures

Main outcome measures: The clinical efficacy was observed after treatment in both groups. Patients were considered to be in complete remission (CR) if they were completely free of disease manifestations, with disappearance of lesions and no tumor metastasis after treatment. Patients were in partial remission (PR) if they showed marked improvement in disease manifestations after treatment, with 50% or more reduction in lesion size and no tumor metastasis within 1 month after treatment. Patients were considered stable disease (SD) if the disease manifestations improved after treatment, the lesions became smaller but reduced less than 50%, and no tumor metastasis occurred within 1 month after treatment. Disease progression (PD) was considered if the disease did not improve after treatment, and the lesion size did not decrease or even increase, or with tumor metastasis. The objective remission rate (ORR) of both groups: number of (CR+PR) cases/total number of cases × 100%. To observe the changes in serum levels of CA199, CEA and CA242 before and after treatment. Patients' 3-year survival was counted in the electronic medical records with outpatient follow-up records.

Secondary outcome measures: The differences in clinical data and the adverse reactions between both groups were compared.

Statistical methods

The data collected in this study were assessed via SPSS 20.00 software, and the images were visualized via GraphPad Prism 8 software. The counting data were expressed as percentages (%) and compared using chi-square tests. The measurement data were represented as mean ± standard deviation, and independent t-test was used for inter-group comparison, and paired t-test was for intra-group comparison. Ranked data were tested using the rank sum test and expressed as Z. Survival analysis was performed using the Kaplan-Meier (K-M) method to plot survival curves, calculate survival rates and perform Log-rank tests. The independent factors affecting the patient prognosis were assessed via Cox regression. Statistical differences were indicated at $P<0.05$.

Results

Comparison of clinical data

Comparison of clinical data between both groups revealed no statistical differences in patient age, BMI, degree of differentiation, tissue type and FIGO stage ($P>0.05$, **Table 1**).

Clinical efficacy analysis

The ORR of patients in the CG was dramatically lower than that of those in the OG ($P<0.05$, **Table 2**).

Changes in tumor markers before and after treatment

In this study, we also compared the changes in tumor marker levels between both groups, and patients' serum levels of CA199, CEA and CA242 were dramatically lower after treatment compared with those before treatment ($P<0.05$). Further comparison revealed that the serum levels of CA199, CEA and CA242 were dramatically lower in the OG than those in the CG after treatment ($P<0.05$, **Figure 1**).

Statistics of adverse reactions in both groups

There was no statistical difference in the incidence of leukopenia, hemoglobin reduction, neutropenia, gastrointestinal reactions, abnormal renal function and abnormal liver function ($P>0.05$, **Table 3**).

Cox regression analysis

At the end of the study, we counted the 3-year survival of patients. Univariate Cox regression

Table 1. Comparison of clinical data

Factor	Observation group (n=30)	Control group (n=60)	*P* value
Age (year)	61.60±4014	62.20±4.08	0.515
BMI (kg/m^3)	21.68±2.16	21.48±2.10	0.674
Degree of differentiation			0.570
Highly differentiated	5	16	
Moderately differentiated	11	19	
Poorly differentiated	14	25	
Type of tissue			
Serosity	20	38	0.755
non-serous	10	22	
FIGO stage			
Stage III	24	45	0.597
Stage IV	6	15	

Table 2. Comparison of clinical efficacy

Groups	CR	PR	SD	PD	ORR
Control group (n=60)	8	20	18	14	28 (46.67)
Observation group (n=30)	9	12	6	3	21 (70.00)
X^2/Z value		-2.379			4.390
P value		0.017			0.036

Note: CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease; ORR: objective Response Rate.

analysis was performed and found that the degree of differentiation, FIGO stage, CA199 and treatment regimen were prognostic factors (P<0.05, **Table 4**), whereas multifactorial Cox regression analysis found that the degree of differentiation, FIGO stage, CA199 and treatment regimen were independent factors affecting the prognosis of patients (P<0.05, **Table 5**).

Discussion

As a common gynecologic malignancy, OC has insidious early symptoms and is characterized by rapid growth, easy metastasis and high infiltration capacity. About 70% of patients are already in an advanced stage of cancer when they first seek medical attention, missing the most effective treatment timing, which inevitably increases the difficulty of clinical treatment [11, 12]. Currently, chemotherapy is the main treatment for advanced OC. The treatment regimens have evolved from single chemotherapy to combination therapies, which now may be with addition of targeted therapies.

It has been pointed out that the combination of paclitaxel and carboplatin is the first-line chemotherapy regimen for the treatment of advanced OC. It has a desirable efficacy, but its efficacy in recurrent OC is inaccurate, which may be related to the development of drug resistance in tumor cells secondary to genetic mutations [13]. Bevacizumab, the first anti-tumor angiogenic drug for the treatment of metastatic colon cancer, not only inhibits tumor growth via blocking the binding of VEGF to its receptor, but also remodels aberrant tumor vessels and improves the chances of drug uptake by tumor cells, thereby reducing the risk of tumor metastasis [14, 15]. However, whether bevacizumab plus paclitaxel and carboplatin regimen plays a role in enhancing clinical outcomes for treatment of OC needs to be further investigated. To this end, we analyzed the clinical role of this protocol and found that the ORR was effectively increased and clinical efficacy was improved in the OG after treatment. This is possibly due to the reason that bevacizumab enhances the anti-angiogenic effect of paclitaxel and carboplatin and improves the utilization of chemotherapeutic drugs by remodeling tumor blood vessels, thus enhancing the anti-tumor effect.

We also compared the changes in serum levels of CA199, CEA and CA242 in both groups of patients. CEA is a broad-spectrum tumor marker that is highly expressed in OC [16]. CA199, a glycolipid on the cell membrane, has a high positive expression rate in mucinous OC epithelial tissue [17]. CA242 is a sialylated glycoantigen with a highly positive rate in malignant epithelial-like tumors [18]. In a study by Sun et al. [19], a PARP inhibitor combined with bevaci-

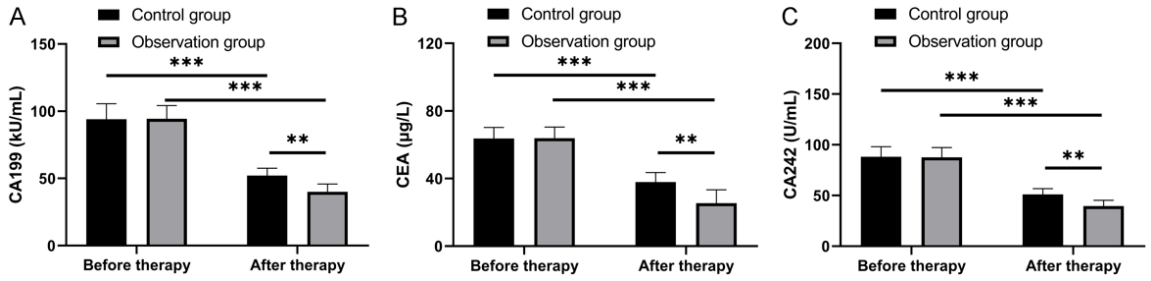

Figure 1. Changes in tumor markers before and after treatment. A. Comparison of changes in serum CA199 before and after treatment. B. Comparison of changes in serum CEA before and after treatment. C. Comparison of changes in serum CA242 before and after treatment. Note: ***P<0.001. CA199: Carbohydrate Antigen 199; CEA: Carcinoembryonic Antigen; CA242: Carcinoembryonic Antigen 242.

Table 3. Statistics of adverse reactions

Groups	Leukopenia	Hemoglobin reduction	Neutropenia	Gastrointestinal reactions	Abnormal renal function	Abnormal liver function
Control group (n=60)	20	9	14	22	20	15
Observation group (n=30)	11	7	12	10	13	8
X^2 values	0.098	0.950	2.704	0.096	0.861	0.029
P value	0.753	0.329	0.100	0.755	0.353	0.864

Table 4. Univariate Cox regression analysis

Predictive factors	β	Standard error	X^2 values	*P* value	HR value	95% CI	
						Lower part	Upper part
Age	-0.052	0.038	1.856	0.173	0.950	0.881	1.023
BMI	0.077	0.073	1.123	0.289	1.080	0.937	1.245
Degree of differentiation	0.814	0.199	16.647	<0.001	2.256	1.526	3.336
Type of tissue	-0.538	0.314	2.933	0.087	0.584	0.316	1.081
FIGO stage	1.138	0.347	10.777	0.001	3.121	1.582	6.159
CA199	0.059	0.016	14.236	<0.001	1.060	1.029	1.093
CEA	-0.008	0.023	0.109	0.741	0.992	0.948	1.039
CA242	-0.016	0.015	1.199	0.274	0.984	0.956	1.013
Treatment regimens	1.648	0.378	19.008	<0.001	5.195	2.477	10.897

Note: BMI: Body Mass Index; FIGO: International Federationof Gynecologyand Obstetrics; CA199: Carbohydrate Antigen 199; CEA: Carcinoembryonic Antigen; CA242: Carcinoembryonic Antigen 242.

Table 5. Multifactorial Cox regression analysis

Predictive factors	β	Standard error	X^2 values	*P* value	HR value	95% CI	
						Lower part	Upper part
Degree of differentiation	0.686	0.187	13.544	<0.001	1.987	1.378	2.863
FIGO stage	1.053	0.326	10.470	0.001	2.867	1.515	5.428
CA199	0.053	0.015	12.767	<0.001	1.055	1.024	1.086
Treatment regimens	1.505	0.356	17.851	<0.001	4.505	2.241	9.056

Note: FIGO: International Federationof Gynecologyand Obstetrics; CA199: Carbohydrate Antigen 199.

zumab was found to be effective in the treatment of platinum-resistant recurrent ovarian epithelial cancer, and the levels of tumor markers CA125 and CA199 were reduced in patients. This suggests that the changes in tumor markers can be used as an outcome measure to assess the efficacy in patients. In this study, we found that the serum levels of CA199, CEA

and CA242 decreased in patients after treatment, and the decrease in the OG was more remarkable than that in the CG. Our results suggested that bevacizumab plus paclitaxel and carboplatin could reduce the level of tumor markers. Besides, we discovered that there was no statistical difference in adverse reactions between both groups, suggesting that co-administration of bevacizumab does not increase the adverse reactions and has a higher safety profile. We also concluded analyses of prognostic factors in patients. It was found that degree of differentiation, FIGO stage, CA199 and treatment regimen were prognostic factors for patients. Zhao et al. [20] found that age and FIGO stage, as shown by Cox regression analysis, were independent factors affecting overall and disease-free survival of patients, suggesting that the degree of pathological classification differentiation was not associated with patient's survival. Nevertheless, this is inconsistent with our findings, which we believe may be due to the small sample size. Zhu et al. [21] confirmed that elevated postoperative CA19-9 was found to be an independent risk factor for recurrence-free and overall survival in patients with normal postoperative CA-125 levels, which is consistent with our findings, suggesting that CA19-9 can be used as a prognostic indicator for patients with early versus late OC. This study first found that 3-year survival rates were markedly higher in patients treated with bevacizumab plus carboplatin and paclitaxel regimen than in those treated with paclitaxel and carboplatin. This suggests that the regimen including bevacizumab can improve patients' prognosis.

Nevertheless, the present study still has some limitations. First, this is a retrospective study, so our results may be biased. Second, this study was unable to conduct long-term follow-up of patients. Thus, we hope to conduct prospective studies in future to refine our findings.

In summary, bevacizumab plus paclitaxel and carboplatin could improve the efficacy and reduce the levels of CA199, CEA and CA242 in OC patients without increasing the incidence of adverse reactions.

Disclosure of conflict of interest

None.

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