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Clinical efficacy of peritoneal perfusion of bevacizumab in combination with venous chemotherapy of paclitaxel and Cis-platinum on the late-stage ovarian cancer and the effect on levels of VEGF, MIF, HE4 and CA125

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ABSTRACT

***Background*:** Often diagnosed at late stages, ovarian cancer is one of the leading causes of global cancer death. Major therapeutic choices include debugging surgery followed by chemotherapy and adjuvant therapy. Bevacizumab is an anti-VEGF medication used to treat various malignancies such as colorectal, lung, and renal cancer. The combination therapy of bevacizumab with other platinum-based medications has proved promising. Thus, researchers sought to evaluate the clinical efficacy of intraperitoneal bevacizumab combined with intravenous paclitaxel and cis-platinum and their subsequent effect on blood levels of VEGF, MIF, and CA125. ***Materials and Methods*:** Ninety patients diagnosed with late-stage ovarian cancer were enrolled. Patients were divided into control and experimental groups receiving intravenous and combination chemotherapy, respectively. Clinical efficacy and alterations in tumor markers blood levels were afterward compared between the two groups. ***Results*:** Combination therapy elicited significantly higher response and total effectiveness rates with a p-value of 0.015 and 0.002, respectively. Both treatments significantly decreased tumor markers blood levels (p-value<0.05), however, combination therapy significantly induced a more profound reduction (p-value<0.01). ***Conclusion*:** Intraperitoneal bevacizumab combination therapy with intravenous paclitaxel and cis-platinum is superior to intravenous chemotherapy alone in treating late-stage ovarian cancer and increases 1- and 2-year survival rates.

INTRODUCTION

Ovarian cancer is the third most common gynecologic cancer worldwide, bearing the highest mortality rate and the worst prognosis among these cancers [1]. Although breast cancer is more prevalent, ovarian cancer mortality rate is three times higher [2]. One study reports that in every 5 patients with ovarian cancer, 4 patients are diagnosed with advanced progressed disease [3]. This high rate of fatality is caused by asymptomatic and latent growth of tumor cells, late onset of symptoms, and a shortage of promising screening tools for early-stage detection programs [4]. Also, cancer could have affected the abdominal cavity at the time of diagnosis, accounting for poor diagnosis and survival expectancy of fewer than six months [5].

Various markers are evaluated for the diagnosis of ovarian cancer and determining the disease stage. Cancer antigen 125 (CA125), human epididymis protein 4 (HE4), and macrophage migrating inhibitory factors (MIF) are among these markers. CA125 is a membrane glycoprotein of the large mucin family. Recently this marker has been found in patients with ovarian cancer [6]. However, the test for this marker is not highly sensitive in early-stage cancers and may also be elevated upon menstruation or endometriosis; hence, other markers such as HE-4 are evaluated for more accurate results. The combined evaluation of these two markers has proved to be more efficacious [7,8]. Recently, a particular MIF isoform has been introduced as a cancer marker and drug target in the colorectal, pancreatic, lung, and ovarian cancers [9,10]. Also, recent efforts to cease tumor angiogenesis have made vascular endothelial growth factor (VEGF) a viable drug target in anti-VEGF drug therapies [11].

The treatment options for ovarian cancer include surgery, chemotherapy, neoadjuvant therapy, and cytoreductive surgery [12]. Several therapy regimens

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have been introduced and suggested for ovarian cancer treatment, among which anti-VEGF therapy in combination with platinum-based chemotherapy plays an important role [13]. Bevacizumab is a recombinant humanized monoclonal antibody that has been indicated for the treatment of various tumors in colorectal, renal, and lung cancers [14]. However, only a few studies have investigated the combination therapy of bevacizumab with paclitaxel and cis-platinum. Therefore, researchers in this study aimed to evaluate the clinical efficacy of intraperitoneal bevacizumab combined with intravenous paclitaxel and cis-platinum chemotherapy and their subsequent impact on the blood levels of VEGF, MIF, HE4, and CA125.

MATERIALS AND METHODS

Study design

The current case-control study was conducted in Weihai Central Hospital, Weihai, China, from March 2017 to September 2018. Clinical data of patients were reviewed regarding inclusion and exclusion criteria summarized in table 1. Subsequently, 90 patients were enrolled and divided into control (n=40) experimental (n=50) groups. The control group received intravenous chemotherapy comprised of paclitaxel and cis-platinum. The experimental group received combination therapy, including intraperitoneal bevacizumab added to the previously defined intravenous chemotherapy.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Patients with the diagnosis of ovarian cancer based on CT, MRI, and pathological test results	Patients complicated with infection or chronic inflammation
Patients younger than 70 years old	Patients with an estimated survival time < 3 months
Patients staged at FIGO III or IV	Patients manifesting significant intolerance to the chemotherapeutics and treatment cycle < 3
Patients with measurable, solid tumors and ascites ≤ 1000mL as indicated by ultrasonic B examination	Ovarian cancer complicated with tumors in other sites
Patients with KPS scores over 70	-

Procedures

Standard examinations were done for all patients. Accordingly, patients rested in bed, received oxygen therapy, sedation, or intensive care for regular treatment, if necessary. All patients were cared for in compliance with the World Medical Association (WMA) Declaration of Helsinki. The ethical committee of Weihai Central Hospital approved this study on 伦理批件号：2017年KT第19号(2017KT19) with the registration number ChiCTR-TRC-13003262.

All patients underwent physical examination and complete blood count (CBC), urinary protein levels, and coagulation tests preceding chemotherapy. Tumor staging was performed for all patients according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [15]. Moreover, the Karnofsky performance score (KPC) was calculated for all patients.

Additionally, one day before and after treatment, fasting venous blood was drawn from all patients. Blood samples were centrifuged at 3000 r/min to isolate the serum and stored at -80°C afterward. Enzyme-linked immunosorbent assay (ELISA) kits were utilized to detect the VEGF (E0080Hu, BT Lab™, China), MIF (E0141Hu, BT Lab™, China), HE4 (E3309Hu, BT Lab™, China), and CA125 (E1662Hu, BT Lab™, China) serum levels [16].

All patients underwent 2 courses of intravenous chemotherapy in 6 weeks. Cis-platinum was given the day after paclitaxel in each intravenous chemotherapy course. Paclitaxel and cis-platinum were delivered through an intravenous drip with a dosage of 60 mg/m^2 and 100 mg/m^2, respectively. Cimetidine (300 mg) and dexamethasone (20 mg) were respectively administered 30 minutes and 6 hours before chemotherapy to prevent gastrointestinal bleeding and allergic reactions [5]. Furthermore, symptomatic treatment was considered using polyene phosphatidylcholine to protect the liver and azasetron to stop vomiting.

The control group patients underwent chemotherapy combined with peritoneal decompression to reduce the ascites (volume ≤500 mL) in two courses with a three-week interval.

The bevacizumab combination therapy group underwent sterilization followed by infiltrative administration of 2% lidocaine in the supine position. Afterward, patients received color doppler ultrasonography-assisted peritoneal catheterization to drain ascites. The viscosity, appearance, and color of the ascites were evaluated. Intraperitoneal hyperthermic perfusion chemotherapy was performed by perfusing warm bevacizumab (Manufacturer: Genentech Inc.; SFDA Approval No.: S20120068) at 43 to 45°C (not surpassing 50°C) at a dosage of 5 mg/kg in 3000 mL of normal saline. Afterward, the perfused liquid was drained once per week.

The efficacy of the treatment was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST);

1. Complete response (CR): Patients with no lesions for 30 days or longer
2. Partial response (PR): Tumor shrinking by 50% or more in the multiply of the maximal diameter and vertical diameter of the tumor
3. Stable disease (SD): Tumor shrinking by less than

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50% in the multiply of the maximal diameter and vertical diameter of tumor, or expanding by less than 25%

4. Progressive disease (PD): Tumor shrinking by more than 25% in the multiply of the maximal diameter and vertical diameter of one or more tumors

Given the definitions provided in the RECIST, the response rate (RR) and total effectiveness rate (TER) were calculated using equations 1 and 2.

$$Response\ rate = \frac{CR + PR}{Sample\ size} \times 100\% \quad (1)$$

$$Total\ effectiveness\ rate = \frac{CR + PR + SD}{Sample\ size} \times 100\% \quad (2)$$

In addition, the WHO toxicity grading system was used to evaluate toxic side effects [17].

Statistical analysis

Researchers used SPSS package version 16.0 to analyze the data. Measurement data were presented in mean ± standard deviation, compared between groups using independent sample *t-test*, and inside one group using pairwise *t-test*. The survival rate was calculated directly. Chi-square test, corrected chi-square test, and Fisher's exact test were used to evaluate the significance of enumeration date differences. Statistical significance was indicated by a p-value less than 0.05.

RESULTS

This case-control study was performed on 90 people divided into experimental (n=50) and control (n=40) groups. The mean±standard deviation age for the experimental and control group was 57.3 (±11.1) and 56.5 (±10.7), respectively. The mean KPS for the experimental group was 76.3 (±4.1) and 75.7 (±3.9) for the control group.

According to the FIGO staging system, 27 and 21 stage III patients were in the experimental and control groups, respectively. Further, stage IV patients in the experimental and control group were respectively counted 23 and 19. The two groups did not significantly differ regarding age, FIGO stage, KSP, and tumor types (p-value<0.05 for all variables).

The RR was calculated for the bevacizumab combination therapy and intravenous chemotherapy at 75.00% and 46%, respectively. Chi-square test indicated a significant difference between the two groups regarding RR (χ^2 = 5.890, P = 0.015). Likewise, the difference between the TER of bevacizumab combination therapy (95.00%) and the control group (66.67%) proved statistically significant (χ^2 = 9.691, P = 0.002; Table 3).

Serum levels of VEGF, MIF, HE4, and CA125 obtained through ELISA tests did not significantly differ between the two groups before the treatment (p-value>0.05). Conversely, both bevacizumab combination therapy and intravenous chemotherapy significantly reduced serum levels of the tumor markers (all p-values, 0.05). However, tumor marker reduction following bevacizumab combination therapy was more pronounced and significantly higher than intravenous chemotherapy (p-value<0.01). Table 3 provides further details on the serum levels of VEGF, MIF, HE4, and CA125.

No significant difference was found regarding the incidence of adverse events and side effects such as bone marrow suppression, nausea, vomiting, diarrhea, liver and kidney dysfunction, peripheral neuritis, and cardiac toxicity between bevacizumab combination therapy and the control group (all p-values > 0.05). Further detail is available in table 5.

The one- and two-year survival rates following bevacizumab combination therapy and intravenous therapy are summarized in table 6. Data analysis shows that bevacizumab combination therapy significantly prolongs both one- and two-year survival rates further than intravenous chemotherapy (p<0.05).

Table 2. Summary of tumor types.

	Control Group n=40 (%)	Experimental group n=50 (%)
FIGO – Stage III	21 (52.5%)	27 (54%)
FIGO – Stage IV	19 (47.5%)	23 (46%)
Serous Tumors	23 (57.5%)	27 (54%)
Mucous Tumors	13 (32.5%)	18 (32%)
Mixed Type Tumors	4 (10%)	5 (10%)
FIGO = International Federation of Gynecology and Obstetrics		

Table 3. Comparison of the clinical efficacy between two groups [n (%)].

Group	N	CR	PR	SD	PD	Response rate [n (%)]	Total effectiveness rate [n (%)]
Experimental group	50	2	35	10	3	40(75.00)	47(94.00)
Control group	40	0	19	8	13	19(47.50)	27(67.50)
χ^2 value						5.893	9.695
***P*-value**						0.014	0.002
***N** = Normal / CR = Complete response / PR = Partial response / SD = Stable disease / PD = Progressive disease							

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Table 4. Comparison of the levels of VEGF, MIF, HE4 and CA125 in serum before and after treatment between two groups (mean ± standard deviation).

Group	Time	N	VEGF (ng/mL)	MIF (ng/mL)	HE4 (pmol/L)	CA125 (U/mL)
Experimental group	Before treatment	50	53.87±9.78	13.62±3.21	274.2±89.7	411.5±188.7
Control group	Before treatment	40	51.18±10.07	14.04±3.69	276.9±92.4	418.9±195.4
***t* value**			1.127	0.511	0.129	0.163
***P* value**			0.263	0.611	0.898	0.871
Experimental group	After treatment	50	22.16±5.97*	4.85±2.21*	79.3±26.2*	69.4±32.6*
Control group	After treatment	40	29.97±7.09*	7.34±2.85*	101.6±32.7*	94.7±46.3*
***t* value**			5.006	4.136	3.179	2.691
***P* value**			0	0.001	0.002	0.009

VEGF = vascular endothelial growth factor / MIF = macrophage migration inhibitory factor / HE4 = human epididimis protein 4 / CA125 = cancer antigen 125

Table 5. Comparison of the incidence rates of the adverse reactions between two groups [n (%)].

Adverse effects	Experimental group (n=50)		Control group (n=40)		χ^2	*P*
	Degree 0 to I	Degree II to IV	Degree 0 to I	Degree II to IV		
Bone marrow suppression	31(62.00)	19(38.00)	29(72.50)	11(27.50)	0.913	0.339
Nausea and vomiting	41(82.00)	9(18.00)	36(90.00)	4(10.00)	0.290	0.589
Diarrhea	42(84.00)	8(16.00)	37(92.50)	3(7.50)	0.500	0.481
Liver damage	48(96.00)	2(4.00)	38(95.00)	2(5.00)	0.073	0.795
Kidney damage	47(94.00)	3(6.00)	40(100.00)	0		0.503
Peripheral neuritis	49(98.00)	1(2.00)	40(100.00)	0		1.000
Cardiac toxicity	49(98.00)	1(2.00)	40(100.00)	0		1.000

Table 6. Comparison of the long-term prognosis between two groups [n (%)].

Group	N	1-year survival rate	2-year survival rate
Experimental group	50	35 (70.00%)	24 (48.00%)
Control group	40	17 (42.50%)	8 (20.00%)
χ^2		5.027	5.649
P		0.023	0.015

DISCUSSION

This study evaluated the efficacy of intraperitoneal bevacizumab combined with intravenous paclitaxel and cis-platinum in the treatment of end-stage ovarian cancer compared with intravenous chemotherapy alone. The response rate and total effectiveness rate of bevacizumab combination therapy were significantly higher than intravenous therapy. Also, a significant decrease was found between the experimental and control groups regarding the serum levels of VEGF, MIF, HE4, and CA125.

Several studies have suggested that traditional chemotherapy combined with monoclonal antibodies is more effective in treating ovarian cancer [18–20]. Among these methods, evaluating the efficacy and effectiveness of intraperitoneal bevacizumab combined with intravenous paclitaxel and cis-platinum has recently been of great interest in the literature. A recent multinational study has investigated the combination therapy of bevacizumab, carboplatin, and paclitaxel in advanced cervical cancer patients. The response rate of this regimen was 61%, and the overall survival was 25 months (ranging from 20.9 to 30.4 months). Also, one - and two-year survival rates were 78% and 52%, respectively [21].

A similar study on 452 patients has compared the efficacy and survival rate of bevacizumab, carboplatin, and paclitaxel chemotherapy alone. The response rate of this combination therapy and chemotherapy alone was 48% and 36%, respectively. Also, the combination of topotecan and paclitaxel was significantly associated with the risk of progression compared with carboplatin and paclitaxel combination therapy. This study also evaluated the life quality of these cancer patients and indicated that bevacizumab did not adversely affect it. The median overall survival rate also increased by 3.7 months in patients with recurrent, persistent, or metastatic cervical cancer [22]. Another review study also indicated that in platinum-resistant ovarian cancer patients, bevacizumab and chemotherapy combination therapy is more safe and effective [14].

A recent systematic review and meta-analysis of 23 studies compared the efficacy and overall survival rates of non-bevacizumab therapies and bevacizumab combined with paclitaxel-cisplatin or paclitaxel-topotecan chemotherapy. A prolonged overall survival rate was found in bevacizumab combination therapies in comparison with non-bevacizumab therapies. Also, bevacizumab combination therapy with paclitaxel and cisplatin was the most efficacious compared to other therapies, with the highest probability of 68.1% [23].

Zhang *et al.* in a similar study investigating the efficacy of bevacizumab-nedaplatin combination therapy, compared pre- and post-treatment serum levels of HE4, MIF, and CA125.

Post-treatment measurements of H£4, MIF, and CA125 serum levels showed a significant decrease compared to pre-treatment levels. This study also

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reported that bevacizumab and nedaplatin combination therapy significantly increases serum immunity indexes such as CD3+, CD4+, CD8+ and NK cells. It concluded that the efficacy of bevacizumab and nedaplatin combination therapy is superior to the controlled group [24].

Bevacizumab is an anti-VEGF monoclonal antibody that was introduced in clinical practice around 20 years ago. However, it has been only recently approved for ovarian cancer treatment in combination with chemotherapy. Several studies reaching consistent results, have reported the efficacy and effectiveness of bevacizumab in attenuating tumor angiogenesis [25–28]. Although few studies have reported VEGF rise in patients treated with bevacizumab [29], a recent study has explained this rise, indicating that the VEGF rise is not a tumor escape mechanism; rather, protein degradation and antibody reactions are the underlying causes of this VEGF rise [30].

CONCLUSION

The combination therapy of bevacizumab with paclitaxel and cis-platinum may significantly decrease serum levels of cancer markers including VEGF, MIF, HE4, and CA125 and accordingly increase one- and two-year survival rates.

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Not applicable.

Ethics approval and consent to participate: The ethics committee of Weihai Central Hospital approved this study. All the patients were fully informed, had complete access to clinical data, and were enrolled in the study only after obtaining signed informed consent. All authors declare that they have consented for publication.

Conflict of Interest: All authors declare no conflict of interest.

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Authors' contributions: All authors contributed equally to the design of the study, data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

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