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Lentinan combined with cisplatin and paclitaxel in the treatment of patients with ovarian cancer with ascites 腹水 卵巢癌

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Summary

Objective: To observe the clinical efficacy of lentinan combined with cisplatin and paclitaxel in the treatment of ovarian cancer with ascites. *Materials and Methods:* Two hundred and twelve cases of patients with epithelial ovarian cancer (EOC) and ascites were retrospectively analyzed. Patients were divided into TP (taxinol + platinol) group and TP + lentinan group according to the chemotherapy regimen. *Results:* The effective rate (CR + PR) in TP group (98 cases) was 31.6% and disease control rate (CR +PR + SD) was 80.6%. The effective rate in TP + lentinan group (114 cases) was 50.9% and the disease control rate was 88.6%, with statistical difference compared with TP group. The control of ascites in TP + lentinan group was better than TP group. The common adverse reactions of chemotherapy in TP + lentinan group was relative mild with reduced incidence. *Conclusion:* Lentinan combined with chemotherapy could enhance the efficacy of chemotherapy and control of the ascites.

Key word: Epithelial ovarian cancer; Lentinan; Taxinol; Platinol; Therapeutic effect.

Introduction

Ovarian cancer is the fifth most common cause of cancer deaths in women; though it is fairly uncommon, it often goes undetected until it has reached the advanced stages of the disease [1]. Each year about 200,000 women are diagnosed with ovarian cancer worldwide, and 125,000 women died of the disease [2]. This rate is increasing year by year and the incidence population is younger. The incidence of ovarian cancer in China is about 6.0/10 million, which ranked in the middle level of the world. However, the high fatality rate of ovarian cancer made it become one of the malignant tumors that threatens most the health of women [3]. Malignant ovarian tumors can occur in women of any age. Germ cell tumors is a common type occur in age under 20 years and epithelial ovarian cancer (EOC) is more common in women older than 50 years [4].

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Ovarian cancer is prone to metastasis and leads to the occurrence of ascites. Peritoneal metastasis is the key factor affecting the curative effect and prognosis of ovarian cancer [5]. For patients with advanced ovarian cancer, the occurrence of metastasis results in rendering the surgery opportunity very slim. Chemotherapy is the main treatment method in patients with advanced ovarian cancer. The National Comprehensive Cancer Network (NCCN) (2014 edition) pointed out that there are a variety of chemotherapy options, including chemotherapy, intraperitoneal chemotherapy combined with intravenous chemotherapy, and other chemotherapy regimen in clinical trials [6]. Taxinol and platinol (TP) is the internationally accepted method for treatment of advanced ovarian cancer. Chemotherapy damages normal cells while kills tumor cells. It especially damages normal epithelial cells, gastrointestinal mucosa, and bone marrow cell. The adverse reactions of chemotherapy such as nausea, vomiting, diarrhea, constipation, and loss of hair. Leukopenia 白細胞減少症 causes patients to suffered greatly. Some patients cannot tolerate the adverse reactions to discontinue chemotherapy, which seriously affects treatment [7, 8].

Lentinan, the backbone of β-[1,3]-glucan with β-[1,6] branches, is one of the active ingredients purified from shiitake mushrooms and has been approved as a biological response modifier for the treatment of multi-cancer in China. As a biological response modifier, lentinan has no direct cytotoxic effect, and compelling studies show the mechanism of lentinan is related with activation of macrophages, stimulate the natural killer (NK) cells, and the antibody dependent macrophage cytotoxicity [9, 10]. Some researches indicated that lentinan can directly kill tumor cells, induce apoptosis of tumor cells by changing the cell membrane, and regulate intracellular signal transduction pathway of tumor cells, thus playing a role in antitumor activity [11, 12]. Oba *et al.* [13] also indicates that the addition of lentinan to standard chemotherapy offers a significant advantage over chemotherapy alone in terms of survival for patients with advanced gastric cancer. The organ function of ovarian cancer patients is often poor and many patients encounter difficulty in tolerating chemotherapy. In practi-

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cal clinical application, the authors found that lentinan could improve patient tolerance to adverse reaction of chemotherapy. This study retrospectively analyzed the impact of lentinan on ovarian cancer patients that received chemotherapy.

Materials and Methods

The retrospective study was approved by the ethnic committee of the present hospital. The ethics committee approved relating screening, treatment, and data collection of these patients. Patients were fully informed of the treatment plan, all subjects (or legal representative) signed written informed consent form. All works were undertaken following the provisions of the Declaration of Helsinki.

Patients with EOC who received treatment from March 2012 to December 2014 in the present hospital were included in the study. The patients were confirmed to have ovarian cancer according to their medical case. The inclusion criteria were: 1) patients were pathologically diagnosed as primary ovarian cancer, 2) patients were diagnosed of ascites by ultrasound, and the medical case recorded the changes of ascites, 3) patients with age of under 75 year and ≥ 50 years, 4) patient had FIGO surgical staging ≥ Stage III A, 5) patients who had not received platinum chemotherapy before recruitment, 6) patients who had received chemotherapy regimen of TP with or without lentinan injection, and 7) patients with complete case information.

The ascites was extracted as far as possible in these patients. Routine anti-allergy treatment was performed before administration of paclitaxel. The administrated paclitaxel (135 mg/ (m^2 body surface area d) was added in 500 ml sodium chloride injection and injected in for three hours. ECG monitoring was performed during treatment. Adequate hydration and antiemetic treatment were performed in symptomatic with injection of cisplatin (75 mg/ (m^2 body surface area. d), added in 500 ml sodium chloride injection). A cycle of TP was performed 21 days and continued for three to six cycles. Lentinan was injected intravenously 1 mg each time, two times in a week and three weeks for a cycle. Lentinan was injected intraperitoneally at the first day of administration. The treatment cycle of lentinan was administered simultaneously with chemotherapy treatment. In addition, quality of life evaluation results was collected in partial selected cases according to collected Karnofsky score before and after the treatment.

The recruited cases were divided into two groups according to whether or not they were treated with lentinan: TP group and TP + lentinan group. The demographic data including age, histopathological type, laboratory measured index, adverse reactions and progression free survival, and two-year survival after treatment were collected for comparison. The occurrence of adverse reactions in two groups were recorded and graded according to WHO standard for common adverse reactions of anticancer drugs [14].

According to the Response Evaluation Criteria in Solid Tumors (RECIST) standard, the curative effect is divided into: 1): complete response (CR): the lesions disappeared, the duration > 4 weeks, 2) partial response (PR): the maximum diameter of tumor reduced more than 30%, the duration > 4 weeks, 3) stable disease (SD): the maximum diameter of tumor reduced <30% or increased ≤20%, and 4) progressive disease (PD): the maximum diameter of tumor increased > 20% or the discovery of new lesions. The short-term effective rate = (CR cases + PR cases) / total cases ×100%. The short-term disease control rate = (CR cases + PR cases + SD cases) / total cases ×100%.

The control of ascites was defined as: CR: no ascites was detected by ultrasound examination, and the duration >4 weeks; PR: ascites reduced >50% and the duration >4 weeks; SD: ascites reduced <50%, but >20% and no drainage was performed in four weeks; PD: ascites has not been effectively controlled or worse, drainage was performed within four weeks. The short-term effec-

Table 1. — *Demographic data of included patients.*

	TP group	TP + lentinan group	*p* value
Case number	98	114	--
Age (mean ± SD, years)	58.46±5.33	60.75±5.87	0.04
Family medical history	2	3	0.36
Metastatic site			0.31
Pelvic cavity	63	71	
Liver, kidney and lung	31	40	
others	18	19	
Histopathological type (n)			0.98
Mucinous cystadenocarcinoma	15	17	
Serous cystadenoma	14	13	
Endometrioid carcinomas	7	9	
Clear cell carcinoma	5	8	
Squamous cell carcinoma	5	6	
Mixed epithelial carcinomas	3	4	
FIGO staging			0.47
III a	14	11	
III b	17	19	
III c	16	21	
IV	2	6	

Table 2. — *Short term therapeutic effect comparison.*

	TP group	TP + lentinan group	*p* value
Case number	98	114	--
Complete response (CR)	3	10	0.084
Partial response (PR)	28	48	0.041
Stable disease (SD)	48	43	0.099
Progressive disease (PD)	19	13	0.106
Effective rate	31.6% (31/98)	50.9% (58/114)	0.0046
Disease control rate	80.6% (79/98)	88.6% (101/114)	0.105

Table 3. — *Short-term ascites control comparison.*

	TP group	TP + lentinan group	*p* value
Case number	98	114	--
Complete response (CR)	5	3	0.347
Partial response (PR)	29	49	0.044
Stable disease (SD)	50	52	0.432
Progressive disease (PD)	14	10	0.207
Effective rate	(34/98)	(52/114)	0.106
Disease control rate	(84/98)	(104/114)	0.958

Table 4. — *Comparison of adverse reactions after treatment.*

Adverse reactions	Group	Cases	Grade 0	Grade I	Grade II	Grade III	Grade IV
Gastrointestinal reactions	TP	98	0	40	26	32	0
	TP + lentinan	114	0	76*	27	11*	0
Myelotoxicity	TP	98	12	37	30	8	2
	TP + lentinan	114	21	29	27	3	0
Neurotoxicity	TP	98	53*	20	6*	2	0
	TP + lentinan	114	81	11	4	0	0
Nephrotoxicity	TP	98	60*	19	2	0	0
	TP + lentinan	114	82	11	0	0	0
Hepatotoxicity	TP	98	61	18	3	0	0
	TP + lentinan	114	79	20	0	0	0
Allergic reaction	TP	98	66	16	0	0	0
	TP + lentinan	114	87	20	0	0	0

* *$p<0.05$ compared with TP group.*

Table 5. — *Sub-group comparison of Karnofsky score improvement in the two groups.*

	Case number	Before treatment	After treatment	*p* value
TP group	69	61.11±5.65	66.43±8.09	<0.01
TP + lentinan group	94	60.09±6.90	77.15±8.60	<0.01
p value		0.464	<0.01	

tive rate and disease control rate of ascites were calculated same as described above.

SPSS 22.0 statistical software was used for statistical analysis. Measurement data in the two groups were expressed as mean ± SD and compared using *t*-test or Wilcoxon/Mann-Whitney rank sum test. The proportion of count was expressed as percentage and compared using Chi-square analysis. Kaplan-Meier analysis and Log-rank test were used for survival analysis and PFS comparison. $p < 0.05$ was considered as statistically significant.

Results

A total of 212 cases' information was included successfully. Ninety-eight cases received standard TP treatment and 114 case received TP + lentinan treatment. The collected demographic data is listed in Table 1. Analysis showed that the average age of patients receiving TP + lentinan treatment were slightly higher than patients receiving TP treatment (60.75 ± 5.87 *vs.* 58.46 ± 5.33 years, $p = 0.040$). FIGO stage and histopathological type showed no statistical difference between the two groups.

Compared with standard chemotherapy (TP) alone, the short-term therapeutic effect lentinan + TP had better short-term effective rate and disease control rate (31.6% *vs.* 50.9%, $p < 0.05$ and 50.9% *vs.* 88.6%, Table 2). The PR and effective rate in patients received lentinan + TP were obviously better than patients received TP treatment ($p = 0.041$ and $p = 0.0046$ respectively).

When adding lentinan on the standard TP chemotherapy, the short-term control effect of ascites in patients receiving TP + lentinan was better than patients receiving TP alone. The short-term PR in TP + lentinan group has statistical difference with TP group ($p = 0.044$). While the CR, SD, and PD, short-term effective rate and disease control rate showed no statistical difference (Table 3).

The common gastrointestinal adverse reactions in two groups were nausea, vomiting, diarrhea, and mucositis; the occurrence rate in the two groups was 100%. Most gastrointestinal adverse reactions were grade I in TP + lentinan group. The incidence rate of grades I and III gastrointestinal adverse reactions showed a statistical difference in two groups (Table 4), the gastrointestinal adverse reactions in TP + lentinan group decreased obviously. The myelotoxicity was mainly the decrease of white blood cells and platelets, and improved after treated with granulocyte colony-stimulating factor. The grade 0 myelotoxicity was lower in TP + lentinan group and grade III myelotoxicity was higher ($p <0.05$ compared with TP group. The neurotoxicity was mainly manifested as acroanesthesia, aggravated cold stimulation. There was no grade III and IV hand foot syndrome occurring in two groups. The neurotoxicity in TP lentinan group was significantly reduced (Grade 0, $p < 0.05$). The neurotoxicity mainly manifested as elevated creatinine and uric acid. The hepatotoxicity mainly manifested as elevation of aminotransferase. Although the grade of adverse reaction in TP + lentinan group was relatively mild, the incidence rate of nephrotoxicity, hepatotoxicity, and allergic reactions showed no statistical difference between the two groups (Table 4).

The collected data showed 163 cases completed Karnofsky score evaluation before and after the treatment: 69 cases were in TP group and 94 in TP + lentinan group. Results showed that there was no statistical difference in Karnofsky score before treatment, and the average Karnofsky score all increased after treatment in both groups, but

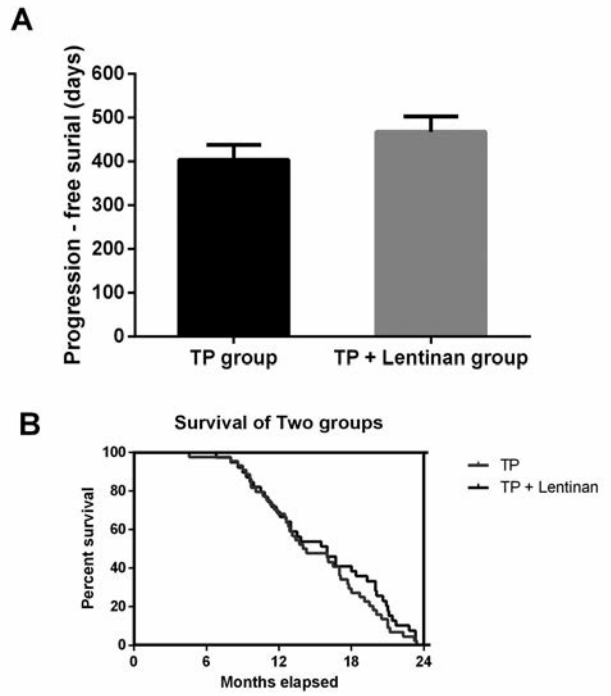

Figure 1. — Comparison of short-term survival of patients in two groups. A) Progression free survival time in TP group and TP + lentinan group. B) Two-year survival in the two groups.

the score was significantly higher in TP + lentinan group ($p < 0.01$, compared with TP group) (Table 5), which demonstrated the quality of life improved in patients received TP + lentinan group treatment.

According to the patient's medical record and telephone follow-up results, the authors compared the PFS and the two-year survival in TP group and TP + lentinan group. The PFS times were 403.25 ± 34.68 and 467.32 ± 35.64 days in TP group and TP + lentinan group, respectively ($p > 0.05$) (Figure 1A). The two-year survival in the two groups showed no statistical difference ($p > 0.05$) (Figure 1B).

Discussion

Ovarian cancer is a common malignant tumor occurring in women; because non-specific symptoms could be observed at early stage, it is difficult to arouse the attention of patients [15]. In addition, lacking of early diagnosis and screening methods, most of the patients are diagnosed in a late stage, and lose the opportunity for surgery [16]. Peritoneal metastasis is important pathologic and biological characteristics of patients with advanced ovarian cancer [17]. Peritoneal metastasis seriously affects the curative effect and prognosis of patient. Massive ascites causes abdominal distension, dyspnea, and significantly reduce patients' quality of life. For patients with advanced ovarian cancer, chemotherapy is an important measure for comprehensive treatment; paclitaxel combined with cisplatin is the standard first-line chemotherapy in advanced ovarian cancer [18, 19]. However, the adverse reactions of chemotherapy is difficult to be ignored, as some patients could not tolerate the serious adverse reaction and must even interrupt chemotherapy, which seriously affects the treatment compliance of the patients. Patients with cancer are plagued by disease and adverse reactions caused by clinical treatment. Their physical function and quality of life are seriously affected. The goal of clinical treatment is not only prolonging the life of patients, but also improving the patients' quality of life. The earlier clinical curative effect indicators focus on the survival rate, the recurrence rate and mortality. Currently, the quality of life has been adopted as an important index for evaluation of clinical treatment prognosis in patients with cancer.

Lentinan is a macromolecule glucan extracted from raw material of mushroom fruit body. Studies have showed that lentinan can inhibit the growth and prevent the transfer of multiple tumors, including gastric cancer, liver cancer, lung cancer, nasopharyngeal carcinoma, colorectal cancer, and breast cancer [12, 20]. Sun *et al.* [21] reported that lentinan reduces tumor progression by enhancing gemcitabine chemotherapy in urothelial bladder cancer. Studies also demonstrated that lentinan combined chemotherapy significant increases the objective response rate and decreases the chemotherapy-related toxicity [22]. A domestic research in China also indicated that lentinan could reduce malignant pleural effusion in patients with lung cancer [23]. In this study, the authors compared the curative effect of TP and TP + lentinan in advanced ovarian cancer with ascites; the results showed that chemotherapy has obvious curative effect for patients with advanced ovarian cancer. Regular chemotherapy significantly reduces solid tumors; the ascites is effectively controlled, and patients' quality of life is improved. On the basis of standardized treatment, lentinan could improve partial therapeutic effect of TP for ovarian cancer and ascites. Combining using lentinan and TP is superior than using TP alone. The Karnofsky score in the two groups showed statistical difference. TP + lentinan treatment could improve the anti-tumor effect and patients' quality of life. In addition, TP + lentinan treatment has better effect on controlling ascites.

Chemotherapy is an important part of the comprehensive treatment for ovarian cancer. It prolongs the survival time of patients; however the occurrence of adverse reactions, such as myelotoxicity, gastrointestinal reaction, and liver and kidney toxicity affect patients' quality of life. For patients with cancer, good quality of life is equally important to longer survival. The present authors observed the adverse reactions in the two groups and the results showed the grade I gastrointestinal adverse reactions were more common in TP + lentinan treatment. On the whole, lentinan effectively reduce the adverse reactions caused by TP, which indicates that the combined use of lentinan might in-

crease the compliance of patients on chemotherapy. Yoshino *et al.* [24] also showed orally taken lentinan could improve the quality of life and prognosis in patients with advanced gastric cancer. In addition, cancer cachexia was markedly attenuated in these patients.

So far, the antitumor mechanism of lentinan is not well explained. The literature review results [25-27] showed its anti-tumor mechanism may be related with: 1) anti-angiogenesis, 2) inhibiting the expression of multi-drug resistant gene, 3) inhibiting proliferation of tumor cell by influencing phosphorylation of ERK1/2 protein kinase, and 4) enhancing immune function, enhancing anti-tumor effect, and reducing the adverse reaction. Polysaccharides are often used in combination with other chemotherapeutic agents in clinical practice. They could stimulate the maturation and differentiation of immune cell to improve immune function for the treatment of cancer. Fucoidan combined with paclitaxel cisplatin and tamoxifen could enhance the antitumor activity to breast cancer cells MCF-7 and MDA-MB-231 [28]. Lentinan combined with 5-fluorouracil can significantly inhibit the growth of H22 cell [29], a hepatocarcinoma cell. Inconsistent with these researches, the present research demonstrated that lentinan combined with TP could control the short-term the development of tumor and ascites of ovarian cancer and especially improve the adverse reaction and quality of life at the same time for the patients receiving TP treatment. However, due to the limited sample size of this retrospective case analysis, its conclusion still requires large-scale and strictly designed clinical research to verify it further.

Conclusions

In summary, the present study shows that lentinan combined with TP could enhance the efficacy of chemotherapy for patients with advanced ovarian cancer with ascites. The combined treatment improves patients' quality of life and alleviates adverse reaction of chemotherapy. Further randomized controlled trials and trials with larger numbers of patients, and with longer follow-up periods, are needed to verify these results.

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