IMMUNE MECHANISM AND CLINICAL EFFECTS OF PACLITAXEL/CISPLATIN COMBINED WITH LENTINAN IN THE TREATMENT OF ADVANCED CERVICAL CANCER

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ABSTRACT

Objective*: We compare the immune mechanism and clinical effects of paclitaxel/cisplatin combined with lentinan in the treatment of advanced cervical cancer.*

Methods: *We retrospectively analyzed 46 patients with advanced cervical cancer admitted to our hospital from January 2017 to October 2018. They were divided into two groups (23 cases in each group) according to the treatment they had received. The control group was treated with paclitaxel/cisplatin combined with radiotherapy and chemotherapy; the observation group was treated with lentinan for two cycles. The changes in immune cells, short-term efficacy, and adverse reactions were analyzed and compared between the two groups.*

Results: *After treatment, the activity of CD4, CD4/CD8, and NK cells in the observation group was significantly higher than it had been before treatment (P<0.05). The activity of CD3, CD4, CD4/CD8, and NK cells in the control group was significantly lower than it had been before treatment (P<0.05). The activity of CD4, CD4/CD8, and NK cells in the observation group was significantly higher than in the control group (P<0.05). There were no significant differences in the effective rate between the observation group and the control group (P>0.05). However, the incidence of myelosuppression, nausea, and vomiting was lower in the observation group than in the control group; the difference between the two groups was significant (P<0.05).*

Conclusion: *Paclitaxel/cisplatin combined with lentinan can significantly improve the immune function of patients with advanced cervical cancer. The clinical effect is positive and the side effects are minor, which improves patients' quality of life. This treatment is worthy of clinical application.*

Keywords: *Paclitaxel, cisplatin, lentinan, concurrent radiotherapy and chemotherapy, advanced cervical cancer, immune mechanism.*

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Introduction

Cervical cancer has become the most common malignant tumor in gynecology. For patients who cannot undergo the best treatment option available (surgical operation), paclitaxel/cisplatin synchronous radiotherapy and chemotherapy has become an important treatment plan for cervical, lung, and other cancers; it has good clinical effect[1]. Lentinan (LTN) is a polysaccharide separated and purified from Lentinus edodes. It functions as an immune adjuvant with macrophages and is guided by T cells[2].

With an average molecular weight of ~500 KD, lentinan has strong antitumor activity and can significantly recover and improve the body's immune function. Its auxiliary treatment effect is achieved primarily by using it as a biological response regulator combined with conventional chemotherapy[3]. Therefore, we have systematically evaluated the immune mechanism and clinical effects of paclitaxel/cisplatin combined with lentinan in the treatment of advanced cervical cancer.

Materials and methods

General information

We retrospectively analyzed 46 patients with advanced cervical cancer admitted to our hospital from January 2017 to October 2018, including 18 patients with stage IIB and 28 patients with stage III, aged 40–75 (46.43±9.28) years. According to the treatment plan, they were divided into two groups with 23 cases in each group. The observation group was treated with paclitaxel/cisplatin combined with lentinan, while the control group was treated with paclitaxel/cisplatin combined with radiotherapy and chemotherapy. There was no significant difference in disease stage and age between the control group and the observation group (P>0.05).

Inclusion criteria:

- Advanced cervical squamous cell carcinoma confirmed by pathological biopsy;
- No history of other primary malignant tumors;
- No treatment received at the time of enrollment;
- Complete data and cooperation;
- Informed consent of patients and their families;
- Approved by the ethics committee of the hospital.

Exclusion criteria:

- Previous neoadjuvant chemotherapy;
- Cancer metastasis; drug allergy;
- Severe renal failure;
- Pregnant or lactating;
- Incomplete data or lack of cooperation.

Treatment method

The patients in the two groups were treated with dexamethasone 20mg once at 12h and 6h before chemotherapy and with diphenhydramine 25mg intramuscularly and ranitidine 50mg intravenously 30 minutes before chemotherapy.

In the control group, paclitaxel 135mg/m^{2}dl and cisplatin 75mg/m2dl were infused intravenously for 3 hours. Paclitaxel was dissolved in 500ml normal saline and administered via a polyethylene infusion set, a special rubber tube, and a filter screen.

To reduce the nephrotoxicity of cisplatin, patients were asked to drink more water than usual; heart rate, respiration, and allergic reaction were monitored after the infusion. On the basis of this observation, we used lentinan 2mg + Sodium Chloride Injection 250ml for intravenous drip twice a week. This chemotherapy regimen consisted of two three-week cycles.

Evaluation criteria

Changes in immune cells

The two groups of patients gave 5ml samples of early morning fasting venous blood before and after treatment. The number of CD3, CD4, and CD8 cell subsets and the NK cell activity in patients' peripheral blood were detected by flow cytometry (Beckman Kurt Trading Co., Ltd.); the ratio of CD4/CD8 was calculated. The mean and standard deviation of the changes before and after chemotherapy were compared.

Short term efficacy

The WHO standards for evaluating solid tumor treatment efficacy define several categories of efficacy: complete remission (CR)-100% of the tumor has regressed; partial remission (PR)-tumor volume reduction of ≥50% maintained for more than 4 weeks; stable (SD-tumor volume reduction of <50% or growth of <25%, maintained for more than 4 weeks with no new lesions appearing; ineffective (PD): tumor volume growth of more than 25% with new lesions appearing. CR and PR are effective, and the total is effective.

Adverse reactions

The CTCAE 3.0 defines standards for categorizing adverse events, using grades 1-5. After the treatment, the patients were followed for one year. The adverse reactions were observed by telephone follow-up and reexamination.

Statistical methods

SPSS19.0 statistical software was used for data processing and analysis. The formula $\bar{x}\pm s$ was used to input the measurement data according to normal distribution. The results were analyzed using a t-test. We used 'n (%)' to input the counting data and applied the χ^2 test. Significance was defined as P<0.05.

Results

Comparison of T cell subsets and NK cell activity before and after treatment

There was no significant difference in T cell subsets and NK cell activity between the two groups before treatment (P>0.05). After treatment, the activities of CD4, CD4/CD8, and NK cells in the observation group were significantly higher than they had been before treatment (P<0.05). The activities of CD3, CD4, CD4/CD8, and NK cells in the control

group were significantly lower than they had been before treatment (P<0.05). The activities of CD4, CD4/CD8, and NK cells in the observation group were significantly higher than those in the control group (P<0.05).

Group	Cases	CD3 (%)		CD4 (%)		CD4/CD8		NK (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	23	62.94± 10.01	61.63± 11.52	35.54± 7.49	39.89± 7.07*	1.31± 0.68	1.96± 1.33*	26.34± 7.21	35.75± 8.21*
Control group	23	63.52± 11.37	56.44± 12.75*	35.40± 7.62	29.47± 7.58*	1.42± 0.72	1.01± 0.63*	27.46± 10.37	20.77± 10.53*
T value		0.184	1.580	0.063	4.821	0.291	3.522	0.425	5.380
P value		0.855	0.121	0.950	0.001	0.773	0.001	0.673	0.001

Table 1: Comparison of T cell subsets and NK cell activities between the two groups before and after treatment ($\bar{x}\pm s$).
*Note: Comparison with the values before treatment, *P<0.05.*

Comparison of clinical effects

There was no significant difference in the effective rate between the observation group and the control group (P>0.05). We followed up with all 46 patients in both groups.

Group	Cases	CR	PR	SD+PD	Effective rate (%)
Observation group	23	15(65.22)	4(17.39)	4(17.39)	82.61
Control group	23	12(52.17)	5(21.74)	6(26.09)	73.91
χ^2					0.511
P value					0.475

Table 2: Comparison of clinical efficacy between the two groups [case (%)].

Comparison of adverse reactions

There were no allergic reactions or treatment-related deaths in either group. There was no significant difference in neurotoxicity or rectal reaction between the two groups (P>0.05). The incidence of myelosuppression, nausea, and vomiting was lower in the observation group than in the control group (P<0.05) (Table 3).

Group	Cases	Myelosuppression		Nausea and vomiting		Neurotoxicity		Rectal reaction	
		I~II degree	III~IV degree	I~II degree	III~IV degree	I~II degree	III~IV degree	I~II degree	III~IV degree
Observation group	23	13	1	12	1	1	0	13	2
Control group	23	17	5	19	2	2	0	15	4
χ^2		8.178		5.403		0.357		1.804	
P value		0.004		0.020		0.550		0.179	

Table 3: Comparison of adverse reactions between the two groups [case (%)].

Discussion

As the most common reproductive system malignancy in women, cervical cancer has higher incidence and mortality rates; the incidence rate is younger[4]. The pathogenesis of cervical cancer is not currently clear. It may be influenced by multiple factors, such as the number of deliveries, viral infections, sexual behavior, and other behavioral and biological factors. Early-stage cervical cancer has no obvious symptoms or signs, while late-stage cervical cancer tissue spreads forward and backward in an expanding local invasion range. Therefore, it is difficult to eliminate all potential subclinical lesions and micrometastases[5]. Therefore, radiotherapy and surgery are the primary treatment methods. Although they have a curative effect, these methods are not ideal for the treatment of large tumors in the middle and late stages of cervical cancer. Post-treatment relapse, spread, metastasis, and other complications are common and can occur quickly.

In recent years, the clinical efficacy of concurrent radiotherapy and chemotherapy has been confirmed. One reason for the efficacy of this combination treatment is that chemotherapy drugs exert a sensitization effect on radiotherapy; this can significantly reduce the tumor volume and the distant metastasis rate of advanced cervical cancer, thus improving the efficacy of radiotherapy. Currently, the most commonly used chemotherapy drugs are paclitaxel and cisplatin, which are potent treatments for cervical, lung, and other cancers. Paclitaxel, as a non-cell-cycle-specific and anti-microtubule drug, can inhibit microtubule network recombination by combining the specificity of microtubules, resulting in G2- and M-phase cell division in tumor tissue and inducing apoptosis in tumor cells[6]. The primary mechanism of cisplatin is producing cross-linking within and between chains of DNA. Because it damages DNA and inhibits its replication and transcription, cisplatin has become an essential drug in a variety of cancer treatments[7].

The immune function of the body gradually affects the occurrence and development of the tumor, and the immune function of the patient is inhibited as the tumor grows. T lymphocyte subsets include CD3, CD4, and CD4/CD8, which have a significant impact on the anti-tumor immunity process and help the body resist the invasion of tumor cells[8]. The decrease of CD3+ T cells is seen primarily with immunodeficiency diseases[9]. The CD4 glycoprotein signals inducer and helper T cells. Viral

infectious diseases can reduce the number of CD4+ T cells, while rheumatoid arthritis increases CD4 + T cells[10]. The CD8 molecule signals inhibitor and killer T cells; autoimmune diseases reduce the number of CD8+ T cells, while viral infection and hepatitis increase the number of CD8 + T cells[11]. The CD4+/CD8+ cell ratio fairly accurately reflects changes in immune regulation.

A decreased ratio is common with malignant tumors, AIDS, and some other infectious diseases[12]. NK cells are the primary cells involved in immune surveillance. As the primary defense line against tumors, NK cells can regulate the differentiation of thymocytes, B cells, and bone marrow stem cells; they also secrete IL-2 and other cytokines[13].

Chemotherapy is a primary method for treating advanced tumors, but it may weaken the body's immune-monitoring function due to its cytotoxic effects. Therefore, in the treatment of tumors, it can inhibit tumor cells and rebuild or improve immune function; its importance is the same. Lentinan, as a plant polysaccharide biological-response regulator, can kill tumor cells and enhance immune function. It has been widely used in clinical practice in China and internationally. The results of our study indicate that the activities of CD3, CD4, CD4/CD8, and NK cells in the control group were significantly lower than they had been before treatment ($P<0.05$), demonstrating that concurrent radiotherapy and chemotherapy can inhibit cellular immunity.

After treatment, the activity of CD4, CD4/CD8, and NK cells in the observation group was significantly higher than it had been before treatment ($P<0.05$). The activity of CD4, CD4/CD8, and NK cells in the observation group was significantly higher than their activity in the control group ($P<0.05$). We suggest that the addition of lentinan can overcome the immunosuppression of chemotherapy and improve the body's immune status. Its main function is to kill T cells and help the host induce activated macrophages, enhance NK cell activity, and enhance antibody-dependent macrophage toxicity to play an anti-tumor role. Lentinan can increase the number of CD3+ and CD4+ cells, improve the cellular immune function, and increase the activity of T cell subsets. Therefore, under the combined effect of these cytokines, the immune system can enhance the defense and killing effect on tumor cells.

We found that CD4+ and CD8+ antiserum could block the combined effect of lentinan and IL-2 on lung metastasis, indicating that CD4+ and CD8+ T lymphocytes in antigen-specific regions could mediate the antitumor effect of lentinan. According to relevant research[14], after the immune function of cervical cancer patients is reduced, most of the chemotherapy effect is poor or insensitive. Some patients must stop treatment because they cannot tolerate the chemotherapy reaction. Our results show that there was no significant difference in the effective rate between the observation group and the control group ($P>0.05$), suggesting that the effect of combined lentinan and paclitaxel/cisplatin chemotherapy was similar. There was no allergic reaction or treatment-related death in either group.

The incidence of myelosuppression, nausea, and vomiting in the observation group was lower than in the control group; the difference between the two groups was statistically significant ($P<0.05$). We suggest that paclitaxel/cisplatin combined with radiotherapy and chemotherapy can induce an inflammatory reaction in the tumor, stimulate and enhance the body's anti-tumor immune function, and reduce immunosuppression. The addition of lentinan to the treatment of advanced cervical cancer can enhance the effects of chemotherapy, improve tolerance to radiotherapy and chemotherapy, reduce the toxicity of chemotherapy, and improve patients' quality of life.

Conclusion

In conclusion, the combination of paclitaxel/cisplatin with lentinan in the treatment of advanced cervical cancer patients significantly improved immune function. This combination has a positive clinical efficacy and is significantly better than paclitaxel/cisplatin alone. The side effects are minor and it improves patients' quality of life. Therefore, lentinan with paclitaxel/cisplatin is worthy of clinical application.

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