Journal of Hainan Medical University

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Effect of endostar combined with paclitaxel liposome and radiotherapy simultaneously on serum CYFRA21−1, CEA, SCCA, CA125, IL−8 and T lymphocyte subsets in patients with advanced cervical cancer

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ARTICLE INFO

Article history:
Received 4 Jul 2016
Received in revised form 19 Jul 2016
Accepted 11 Jul 2016
Available online 24 Jul 2016

Keywords:
Endostar
Paclitaxel liposome
Radiotherapy
Advanced cervical cancer
T lymphocyte subsets

ABSTRACT

Objective: To study the effect of endostar combined with paclitaxel liposome and radiotherapy simultaneously on serum CYFRA21-1, CEA, SCCA, CA125, IL-8 and T lymphocyte subsets in patients with advanced cervical cancer. **Methods:** A total of 72 patients with advanced cervical cancer in our hospital from January 2014 to February 2016 were enrolled in this study. The subjects were divided into control group (n=36) and experiment group (n=36) randomly. The control group were treated with radiotherapy, the experiment group were treated with endostar combined with paclitaxel liposome and radiotherapy simultaneously. 3 weeks for a period of treatment and the two groups were treated for 4 periods. The serum CYFRA21-1, CEA, SCCA, CA125, IL-8 levels and peripheral blood CD3+, CD4+ and CD8+ cells of the two groups before and after treatment were compared. **Results:** There were no significantly differences of the serum CYFRA21-1, CEA, SCCA, CA125, IL-8 levels and peripheral blood CD3+, CD4+ and CD8+ cells of the two groups before treatment. The serum CYFRA21-1, CEA, SCCA, CA125 and IL-8 levels of the two groups after treatment were significantly lower than before treatment, and that of experiment were significantly lower than control group. The peripheral blood CD3+, CD4+ cells of the two groups after treatment were significantly lower than before treatment, CD8+ cells of the two groups after treatment were significantly higher than before treatment, and that of experiment group were significantly better than control group. **Conclusion:** Endostar combined with paclitaxel liposome and radiotherapy simultaneously can significantly reduce the serum CYFRA21-1, CEA, SCCA, CA125 and IL-8 levels, improve peripheral blood CD3+, CD4+ and CD8+ levels of patients with advanced cervical cancer, and it was worthy clinical application.

1. Introduction

Cervical cancer is a malignant tumor of the female reproductive system, which is made by the gradual progress of precancerous lesions of chronic cervicitis, it has a high incidence rate,and the incidence of cervical cancer is the second only to breast cancer in female malignant tumors in China[1]. With the increasing pressure of living and the changing of women's social roles, cervical cancer incidence increased year by year, which has been a serious threat to the health of women[2]. There is no typical clinical symptoms in the early stage of cervical cancer, the patient often has been in the late stage of cervical cancer diagnosis, so is difficult to treat[3]. At present, the clinical treatment of advanced cervical cancer mainly used radiotherapy[4]. Along with the progress of medical technology, although radiotherapy facilities and technical means have been greatly developed, the effect is still not obvious,and its prognosis is poor, it is prone to local recurrence or distant metastasis[5]. Concurrent chemotherapy and radiotherapy has been widely used in clinical practice[6]. This study was to investigate the effects of endostar combined with paclitaxel liposome and radiotherapy simultaneously on serum CYFRA21-1, CEA, SCCA, CA125, IL-8 and T lymphocyte subsets in patients with advanced cervical cancer.

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Fund program: Wuhan municipal health and Family Planning Commission of clinical medical research projects(WX15D59).

The results are as follows.

2. Informations and Methods

2.1. General information

A total of 72 patients with advanced cervical cancer in our hospital from January 2014 to February 2016 were enrolled in this study. All patients were informed consent and voluntarily signed informed consent to join the study. Case inclusion criteria: (1) patients with advanced cervical cancer who were diagnosed by the examination of the vaginal examination and pathology; (2) Pathological stage for patients with stage III-IV; (3) Expected survival time in 6 months or more; (4) Not received any chemotherapy treatment. Case exclusion criteria:(1) Patients with other malignant tumors; (2) patients with renal dysfunction. (3) patients with contraindications of chemotherapy; (4) patients with abnormal ECG; (5) Pregnant or lactating women.

A total of 72 cases of advanced ovarian cancer were randomly divided into experimental group and control group using random number method, 36 cases in each group. In the control group,patients were aged from 35 to 60 years old,mean age (50.39±8.43) years old;Weight 40-70 kg, mean weight (54.33±10.17) kg; Pathologic type:6 cases of adenocarcinoma,30 cases of squamous cell carcinoma; Pathological stage: 21 cases of stage III, 15 cases of stage IV; Differentiation type:13 cases of highly differentiated type, 21 cases of middle differentiation type, 2 cases of poorly differentiation type.In the experimental group, patients were aged from 34 to 62 years old,mean age (49.48±12.03) years old; Weight 41-71 kg, mean weight (55.88±9.91) kg; Pathologic type: 7 cases of adenocarcinoma, 29 cases of squamous cell carcinoma; Pathological stage: 20 cases of stage III, 16 cases of stage IV; Differentiation type:11 cases of highly differentiated type, 22 case of middle differentiation type, 3 case of poorly differentiation type. There were no significant differences in age, weight, tumor type and pathological stage between the two groups (P>0.05).

2.2. Experimental method

Patients in the control group were treated with radiotherapy alone, and the 6MV-X - ray of the BJ-6B linear accelerator was used to treat the pelvic cavity with the irradiation method, the irradiation range was as follows: Since patients with fourth lumbar vertebral body edge to the lower edge of the obturator,5 times per week, total irradiation dose was 50 Gy/25 f/5 W; The iridium-192 is used to install the therapeutic equipment in the pelvic cavity, and intra cavity irradiation and external irradiation is not synchronized, 1 times a week. The experimental group was treated with endostar combined with paclitaxel radiotherapy and chemotherapy, radiotherapy regimen was the same as control group, and were given endostar (Purchased from Shandong medgenn Simcere bio Pharmaceutical Co., Specification 15mg/branch, Chinese medicine standard word: S20050088) every day from the beginning of radiotherapy, Intravenous infusion, 7.5 mg/m2,once everyday; And gave liposome(Purchased from Nanjing Luye Pharmaceutical Co., Specification 30 mg/bottle, Chinese medicine standard word: H20030357) intravenous infusion at the first day of radiotherapy, 135 mg/m2, 3 weeks for 1 courses. Two groups of patients were treated for 4 courses of treatment.

2.3. Detection index

Two groups of patients were collected before and after the treatment of fasting venous blood 3 mL, serum separation, Isolated serum in a spped of 2 500 rpm centrifuge for 10 min, then the levels of CYFRA21-1, CEA, SCCA, CA125, IL-8 and the ratio of CD3+, CD4+, CD8+ were detected and compared between the two groups before and after treatment.

The detection of serum CYFRA21-1 and CEA levels were used the method of electrochemical luminescence immunoassay (ECLI), the instrument used was Elec-sys1010 automatic electrochemical luminescence instrument produced by the Swiss Roche company. Serum SCCA, CA125 and IL-8 levels were detected by double antibody sandwich enzyme-linked immunosorbent assay (ELISA),and the reagents and test kits were purchased from Shanghai Jiang Lai biotechnology company, all operations were carried out strictly in accordance with the instructions of the kit. Peripheral blood CD3+, CD4+ and CD8+ cells were detected by Backman CytoFLEX flow cytometry. Tumor markers CYFRA21-1, CEA, SCCA and CA125 positive criteria were: CRFRA21-1>3.3ng/mL, CEA>6.0ng/mL, SCCA>1.5ng/L, CA125>35.0U/mL[7-9].

2.4. Statistical method

We carry on data statistics and analysis using SPSS 19.0 software package , mean ± standard deviation (Mean ± sd) represents measurement data, the use of t test was to compare between groups of measurement data and count data, with P<0.05 as a statistically significant.

3. Results

3.1. Comparison of serum CYFRA21-1, CEA and SCCA levels before and after treatment between the two groups patients

Before treatment, the levels of serum CYFRA21-1, CEA and SCCA in the experimental group were (8.15±2.03) ng/mL,

Table 1.
Comparison of serum CYFRA21-1, CEA and SCCA levels before and after treatment between the two groups' patients.

Group	*n*		CYFRA21-1 (ng/mL)	CEA(ng/mL)	SCCA (ng/L)
Control	36	Before treatment	7.85±1.96	14.38±5.14	10.67±2.11
		After treatment	2.77±0.87*	5.16±1.07*	1.28±0.12*
Experimental	36	Before treatment	8.15±2.03	13.96±4.83	9.95±1.45
		After treatment	1.05±0.41*#	2.25±0.75*#	0.39±0.07*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

(13.96±4.83) ng/mL and (9.95±1.45) ng/L, the serum levels of CYFRA21-1, CEA and SCCA in the control group were (7.85±1.96) ng/mL, (14.38±5.14) ng/mL and(10.67±2.11) ng/L, and there was no significant difference in the serum levels of CYFRA21-1, CEA and SCCA between the two groups (P>0.05); After treatment, the levels of serum CYFRA21-1, CEA and SCCA in the experimental group were(1.05±0.41) ng/mL, (2.25±0.75) ng/mL and (0.39±0.07) ng/L, the serum levels of CYFRA21-1, CEA and SCCA in the control group were (2.77±0.87) ng/mL, (5.16±1.07) ng/mL and (1.28±0.12) ng/L, and those levers in the two groups were all significantly lower than that before treatment, meanwhile, the serum levels of CYFRA21-1, CEA and SCCA in the experimental group were significantly lower than those in the control group, the difference was statistically significant (P<0.05). Please look at the table 1.

3.2. Comparison of the levels of serum CA125 and IL-8 before and after treatment in two groups

Before treatment, the levels of serum CA125 and IL-8 in the experimental group were(88.07±10.24) U/mL, (0.34±0.19) ng/mL, the serum levels of CA125 and IL-8 in the control group were (87.41±9.62) U/mL, (0.33±0.16) ng/mL, and there was no significant difference in the serum levels of CA125 and IL-8 between the two groups (P>0.05); After treatment, the levels of serum CA125 and IL-8 in the experimental group were (10.39±4.25) U/mL, (0.10±0.04) ng/mL, the serum levels of CA125 and IL-8 in the control group were (31.19±6.18) U/mL, (0.17±0.08) ng/mL, and those levers in the two groups were all significantly lower than that before treatment,meanwhile, the serum levels of CA125 and IL-8 in the experimental group were significantly lower than those in the control group, the difference was statistically significant (P<0.05). Please look at the table 2.

Table 2.
Comparison of the levels of serum CA125 and IL-8 before and after treatment in two groups.

Group	*n*		CA125 (U/mL)	IL-8(ng/mL)
Control	36	Before treatment	87.41±9.62	0.33±0.16
		After treatment	31.19±6.18*	0.17±0.08*
Experimental	36	Before treatment	88.07±10.24	0.34±0.19
		After treatment	10.39±4.25*#	0.10±0.04*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05

3.3. Comparison of the level of peripheral blood immune cells between the two groups before and after treatment

Before treatment, the ratio of CD3+, CD4+ and CD8+ cells in peripheral blood of patients in the experimental group were (57.96±7.19)%, (45.97±6.12)% and (29.15±4.03)%, the ratio of CD3+, CD4+ and CD8+ cells in peripheral blood of patients in control group were (58.43±6.65)%, (46.51±5.49)% and (28.47±3.62)%, there was no significant difference between the two groups (P>0.05); After treatment, the ratio of CD3+, CD4+ and CD8+ cells in peripheral blood of patients in the experimental group were (40.72±4.33)%, (37.41±4.88)% and (51.66±5.21)%, the ratio of CD3+, CD4+ and CD8+ cells in peripheral blood of patients in control group were (19.75±2.78)%, (26.31±3.26)% and (37.56±4.17)%, and the ratio of CD3+ and CD4+ cells in peripheral blood of the two groups was significantly lower than that before treatment, and the ratio of CD8+ cells was significantly higher than that before treatment. At the same time, the proportion of T lymphocyte subsets in the experimental group was significantly better than that in the control group, and the difference was statistically significant (P<0.05). Please look at the table 3.

Table 3.
Comparison of the level of peripheral blood immune cells between the two groups before and after treatment.

Group	*n*		CD3+	CD4+	CD8+
Control	36	Before treatment	58.43±6.65	46.51±5.49	28.47±3.62
		After treatment	19.75±2.78*	26.31±3.26*	37.56±4.17*
Experimental	36	Before treatment	57.96±7.19	45.97±6.12	29.15±4.03
		After treatment	40.72±4.33*#	37.41±4.88*#	51.66±5.21*#

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05

4. Discussion

At present, the treatment of advanced cervical cancer is mainly treated by radiotherapy combined with chemotherapy. However, different advanced cervical cancer patients with the same pathological characteristics showed different treatment effects for the same kind of chemotherapy drugs. Therefore, it is of great clinical significance to select reasonable chemotherapeutic drugs[10]. Endostatin is a novel recombinant human vascular endothelial inhibin production,has the function to block the formation of tumor blood vessels by inhibiting the proliferation of endothelial cells that form blood vessels, thus blocking the body's nutrition supply to the tumor cells, inhibiting tumor cell proliferation, metastasis and tumor growth[11,12].Liposome is one kind of liposomal paclitaxel, which can inhibit the tumor cell division to play an anti-tumor effect, has the advantage of better water solubility, low adverse reaction, and a relatively long plasma half-life, so it is better than the conventional anti-tumor effect of paclitaxel[13,14]. During the growth of tumor cells, some proteins are released into the blood because of the activation or degradation of the protein,so the detection of these tumor markers is of great significance for the occurrence and development of tumors and the prognosis of the patients[15,16]. CYFRA21-1, CEA, SCCA and CA125 are commonly used in cervical cancer serum tumor markers, detection of the level of serum in the diagnosis and prognosis of the tumor has an important value[17]. CYFRA21-1 is a kind of protein antigen, which is composed of 19 segments of cell keratin[18]. Studies have showed that in more than 67% of cervical cancer patients' serum, CYFRA21-1 has a higher level, and with the occurrence and development of cancer, CYFRA21-1 levels increased significantly[19]. CEA is a broad spectrum of nonspecific tumor markers, and it also has a certain expression in cervical cancer[20]. SCCA is a silk protein, which is lower in the serum of normal condition, when the cells become cancerous, the degradation of SCCA leads to a large number of SCCA into the blood, causing significant increase in the level of SCCA[21]. CA125 is a tumor of the female reproductive system tumor markers, is widely used in the diagnosis and prognosis of cervical cancer[22]. IL-8 is a kind of inflammatory factor, which is closely related to the occurrence and development of cervical cancer[23]. This study was to investigate the effects of endostar combined with paclitaxel liposome and radiotherapy simultaneously on serum CYFRA21-1, CEA, SCCA, CA125, IL-8 and T lymphocyte subsets in patients with advanced cervical cancer, thus providing a clinical basis in advanced radiotherapy in treatment of cervical cancer for the clinical application of Endostar combined liposome..

The results of this study showed that there was no significant difference in serum CYFRA21-1, CEA, SCCA, CA125 and IL-8 levels between the two groups before treatment (P>0.05); After treatment, the serum levels of CYFRA21-1, CEA, SCCA, CA125 and IL-8 in the two groups were significantly lower than that before treatment, At the same time, the serum indexes of the experimental group were significantly lower than those of the control group, the difference was statistically significant (P<0.05). This suggests that Endostar combined paclitaxel concurrent radiotherapy can significantly decreased serum CYFRA21-1, CEA, SCCA, CA125 and IL-8 levels in patients with advanced ovarian cancer. Endostar suppresses tumor angiogenesis by blocking tumor cell proliferation of endothelial cells to nutrient supply, so as to exert anti-tumor effect.And liposome blocked the mitosis of the cells by inhibiting the aggregation of the tumor cells, inhibited differentiation of tumor cells, so as to exert anti-tumor effect. The combination of the two can play a synergistic effect[24,25], which led to a significant decrease in serum levels of CYFRA21-1, CEA, SCCA, CA125 and IL-8 levels in the patients. In addition, the study showed that the effect of irradiation on the two times of oxygen and the radiation sensitivity of the cells was enhanced by using liposome, and the effect of the treatment on tumor cells was increased[26]. In addition, the results of this study showed that there was no significant difference in the ratio of peripheral blood CD3+, CD4+ and CD8+ cells in the peripheral blood of the two groups (P>0.05); After treatment, the ratio of CD3+ and CD4+ cells in peripheral blood of the two groups was significantly lower than that before treatment, and the ratio of CD8+ cells was significantly higher than that before treatment, at the same time, the proportion of T lymphocyte subsets in the experimental group was better than that in the control group, and the difference was statistically significant (P<0.05). This suggests that Endostar combined paclitaxel concurrent radiotherapy can obviously improve the advanced ovarian cancer patients T lymphocyte immune level, enhance the immunity of the body. This may be because that radiotherapy can inhibit the immune function of T lymphocytes in patients to a certain extent,but liposome can activate the body's immune system after entering the body sheets mononuclear devour phagocytic system of endothelial cells ,thus improving the immune function of the patients[27].

In summary, Endostar combined paclitaxel concurrent radiotherapy could significantly decrease the levels of serum CYFRA21-1, CEA, SCCA, CA125 and IL-8 in advanced cervical cancer, improve the level of T lymphocyte subsets, improve the immunity of patients, and it was worthy clinical application.

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