Impact of the radiotherapy combined with cisplatin plus paclitaxel chemotherapy on the immunologic functions in the patients with esophageal cancer

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Abstract: to study the impact of radiotherapy combined with cisplatin plus paclitaxel chemotherapy on the immunologic functions in the patients with esophageal cancer, from July 2012 to September 2014, 82 patients of esophageal cancer which were receiving treatment in our hospital chose out for this research. Among them, 42 patients received radiotherapy only, as the control group; while the other 40 patients with concurrent cisplatin plus paclitaxel chemo radiotherapy was taken as the observation group. Then the immunologic functions, toxic and side effects were compared between the two groups as well as the survival rates after 3-year-followup-visit, Th level of the total T cells, Th cells and the ratio of Th cells to Ts cells after receiving treatment all increased significantly compared with prior treatment. And the difference was statistically significant ($P<0.05$). After the treatment, the level of T cells, Th cells and the ratio of Th cells to Ts cells of the observation group were all significantly lower than the control group, and the difference was statistically significant ($P<0.05$). While the difference of the ratio of Ts cells to natural killer cells (NK cells) between the two groups were not significant. The toxic and side effects were mainly myelosuppression, decrease leukocyte, esophagit, nausea and vomiting, and it was not statistically significant in the difference between the two groups ($P>0.05$), the survival rates from the first year to the third year in the observation group were respectively significantly higher than the control group, and the difference was statistically significant ($P<0.05$). Radiotherapy combined with cisplatin plus paclitaxel chemotherapy could properly increase the immunologic functions in patients with esophageal cancer, benefiting for the survival rate with a good security. Therefore, it was worth promoting.

Keywords: Radiotherapy; cisplatin plus paclitaxel chemotherapy; esophageal cancer; immunologic function.

INTRODUCTION

Esophageal cancer is a kind of common malignant tumor in clinic, with a high morbidity and lethality, with which the 5-year survival rate in some patients was even less than 10% (Rochigneux *et al*., 2014). To the treatment for esophageal cancer, the combination of the radiotherapy and chemotherapy has been widely used in clinical, with a good application effect, which can effectively improve the survival rates of patients.

In recent studies, it has found that immune cells play a leading role in the cancer immunity, and the change of the T lymphocytes and NK cells is closely related to the progress and diffusion of cancer (Sunpaweravong *et al*., 2014). Therefore, to study the impact of radiotherapy combined with cisplatin plus paclitaxel chemotherapy on the immunologic functions in the patients with esophageal cancer and to verify the safety of this treatment, this paper aims at choosing the best scheme for better treatment for patients with esophageal cancer.

MATERIAL AND METHODS

General information

82 patients with esophageal cancer accepting treatment in our hospital from July 2012 to September 2014 were chose out for the research. The criteria (Selek *et al*., 2014; Suzuki *et al*., 2012): (1) meeting the relevant standards of the treatment for esophageal cancer in WHO; (2) the expected survival time was more than six months; (3) indication of chemotherapy and radiotherapy. Exclusion criteria: (1) patients with other malignant tumor; (2) patients with blood diseases; (3) incomplete laboratory testing data. Among them, 42 cases receiving radiotherapy alone, were classified as control group, in which there were 29 male cases and 13 female cases, with an age of 42years to 68 years (an average age of 55.6±2.4 years), and there were 18 cases of I-II TNM stage and 24 cases III-IV stage; and there were 23 cases of high differentiation and 21 cases of low differentiation. The other 40 patients accepting concurrent chemo radiotherapy, were classified as observation group, in which there were 30 male cases and 10 female cases, with an age of 43 years to 66 years (an average age of 55.4±2.5 years); and there were 19 cases of I-II TNM stage and 21 cases III-IV stage; and there were 22 cases of high differentiation and 18 cases of low differentiation. The baseline data of the two groups was compared and there was no statistically significant difference ($P>0.05$), which was comparable.

Research methods

Both groups were given routine blood biochemical and

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imaging examination before receiving treatment. And the control group were given radiotherapy alone, with the illumination by linear accelerator, parameter of 200 cGy/time, conventional segmentation, and dose of DT60 ~70Gy, ensuring that the injectivity of spinal cord was < 40gy, and lung injectivity was 20Gy with the lung volume <20%. And the radiotherapy lasted for six weeks. While the observation group were given the concurrent chemo radiotherapy, with the same radiotherapy method in the control group, and the chemotherapy methods: 135mg /㎡ taxol was soluble in the normal saline with 500ml, vein drop for 3h, d1; then vein drop cisplatin, 80mg / (m^2*d), d1 - 3, 3 weeks as a course. And the patients were given 2 courses of chemotherapy.

Observation indexes

The immune function, toxic and side effects and the 1-3-year survival rates after 3-year-fowllow-up visit of the two groups were compared. And the detection reagent of immune function were: (1) monoclonal antibody of anti-CD3FITC; (2) anti- CD4 APC; (3) anti-CD8 PE; (4) CD16 + CD56 + PE; (5) red cell lysis buffer produced in the American BD company. The total T: CD3 +; Th: CD3 + CD4 +; Ts: CD3 + CD8 +; NK cells: CD16 + CD56 +. The testing step: EDTA-K2 anticoagulation peripheral blood about 100μL was taken and added into the monoclonal antibody about 20μL and mixed up to be placed away from light at room temperature for 0.5 h to be incubated. Then 2ml Red Blood Cell Lysis Buffer was added into it and mixed up to be placed away from light at room temperature for 10min to split red blood cells. And it was centrifuged for 5min and refused the supernatant. 2ml PBS containing 0.1% sodium azide was added into each tube and mixed up to be centrifuged for 5min and refused the supernatant. And 2mL PBS again was added into each tube to be mixed up to be determined within 2h. 1* 10^4 cells were taken from per tube, using type FACSCalibur flow cytometry instrument and MultiSet software to analyze these data.

STATISTICAL ANALYSIS

SPSS17.0 statistical software was adopted. Measurement data was presented by the ($\overline{x}$ ± s) and x^2 test was applied for comparison of measurement data. And the measurement data was tested by the chi-square and ranked data was tested by the rank sum test to calculate Z value. And the difference was statistically significant (P< 0.05).

RESULTS

Comparison of the immune function between the two groups before and after receiving treatment

The index comparison of the immune function between the two groups prior treatment, the difference was not significant (P>0.05); After receiving treatment, the level of the total T, Th and Th/Ts in both groups increased significantly, and Ts decreased significantly, the difference was statistically significant (P<0.05). In the observation group post treatment the level of the total T, Th and Th/Ts were significantly lower than the control group respectively, the difference was statistically significant (P<0.05). The difference of the ratio of the Ts to NK cells post-treatment in the two groups was not significant (P>0.05) (table 1).

Comparison of toxicity and side effects between the two groups

The toxicity and side effects in patients with esophageal cancer mainly manifested in the myelosuppression, leukocyte decrease, esophagitis and nausea and vomiting. The difference between the two groups was not statistically significant (P>0.05) (table 2).

The comparison of 1 -3 year survival rates between the two groups

The 1 -3 year survival rates in the observation group were respectively significantly higher than the control group, the difference was statistically significant (P<0.05) (table 3).

DISCUSSION

In recent years, in our country esophageal cancer has the trend of the increase morbidity in clinic, having serious effects on human life and health. The main treatment for esophageal cancer is radiotherapy, but after receiving treatment some patients still might suffer local uncontrol and relapse and even distant metastasis (D'amico, 2007). Therefore, comprehensive therapy gradually become one of the clinical research focuses. Some foreign reports have pointed out that (Ohira *et al*., 2015; Zhang *et al*., 2012), cisplatin and paclitaxel combination chemotherapy in the treatment for esophageal cancer has a certain curative effect, and the 3-year survival rate can even reach 30%. And the concurrent chemo radiotherapy is based on this combined chemotherapy, which can further improve the clinical effects (Castadot *et al*., 2011). However, as the patients with cancer have weak immune function, it was not clear whether the concurrent chemo radiotherapy affects it or not, and the relative clinical researches are rather little.

It was founded in this paper that the immune functions in the two groups after receiving treatment have a certain change, in which the level of the total T, Th and Th/Ts were respectively increased significantly, the Ts significantly reduced, indicating that the disease was controlled as well as the relative immune function was improved significantly in the patients with esophageal cancer. The reason might be that the immunosuppressive factor secreted by the cancer cells were almost broken down after receiving treatment. However, the total T, Th and Th/Ts and other indicators in the observation group

Table 1 Comparison of the immune function between the two groups of patients before and after treatment (examples, ± s)

Groups	Total T (%)		Th (%)		Ts (%)		Th/Ts		NK cells (%)	
	Prior treatment	Post treatment	Prior treatment	Post treatment	Prior treatment	Post treatment	Prior treatment	Post treatment	Prior treatment	Post treatment
Observation group (n=40)	58.92±1.42	64.12±0.68*	30.64±1.14	38.11±1.12*	27.75±0.81	25.64±0.14*	1.10±0.47	1.41±0.06*	16.88±0.45	17.64±1.92
Control group (n=42)	59.24±1.93	66.79±0.52*	29.66±1.23	40.66±0.66*	28.31±0.72	25.53±0.62*	1.31±0.08	1.62±0.03*	17.39±0.44	18.29±1.68
T	0.11	2.19	1.11	2.20	0.37	0.10	0.42	2.13	0.42	1.63
P	0.91	0.03	0.26	0.03	0.70	0.91	0.67	0.03	0.67	0.10

Items	Observation group (n=40)					Control group (n=42)					Compared Statistics	
	0 degree	degree	II degree	III degree	IV degree	~ degree	I degree	II degree	III degree	IV degree	Z	P
Myelosuppression	6	16	13	3	2	8	15	14	4	1	0.36	0.42
Leukocyte decrease	4	15	15	3	3	10	16	12	3	1	0.40	0.29
Oesophagitis	12	15	8	5	0	16	15	10	1	0	1.02	0.32
Nausea and vomiting	5	20	12	3	0	7	21	12	2	0	0.29	0.17

Note: Compared with the before treatment, P<0.05

Table 2: Comparison of toxicity and side effects between the two groups

Groups	1-year survival rate	2-year survival rate	3-year survival rate
Observation group (n=40)	34(80.00)	24(60.01)	18(47.50)
Control group (n=42)	22(54.01)	13(29.59)	10(21.43)
x^2	5.91	6.98	6.19
P	0.01	0.01	0.01

were significantly lower than the control group, and the difference of the ratio of the Ts to NK cell compared between the two groups was not significant. It indicated that the single radiotherapy could improve the immune function in the patients with esophageal cancer; while the concurrent chemo radiotherapy might inhibit immune function of the patients. The reason might be it caused worse damage to the body immune function in the patients when it was added chemotherapy to the course of the radiotherapy (Song *et al*., 2015). Therefore, it should take some protection measures when the clinical adopts the concurrent chemo radiotherapy in patients with esophageal cancer, for example, to postpone chemotherapy or to reduce the dosage of the drugs when the immune function was at low level. Foreign reports said that the formation and progress of tumors was closely related to the function change of human T cells, and not a less of patients with cancer suffer a low immune function and a disorder ration of T cell subgroup and other symptoms (Platz *et al*, 2013). T lymphocytes are mainly derived from lymphoid stem cells in the bone marrow, later develop into T cells in the thymus, then play a role of specific cellular immune responses in the lymphatic organization. During the progress, T cells are divided into the T helper cells (Th) and T suppressor cells (Ts) based on the immune functions, the former can help B cells to differentiate and form antibodies in the body and the latter can suppress the synthesis and secretion of the antibody and the proliferation of T cells (Kepp *et al*., 2011; Zhang *et al*., 2015). Some studies have confirmed that cancer cells could form a large number of immunosuppressive factors, which could lead to the increase of Ts cells, and the decrease of the total T cells and Th cells. While the decrease of the ratio of Th to Ts cell eventually made proper conditions for tumor growth and metastasis, which could be confirmed in this paper. NK cells belong to the effect or cells, which can play a certain role in the early stage of the tumor. And they, being the first defensive line do not need to contact with the antigen. Therefore, the NK cells will decrease in the patients with cancer and weak immune function, which was the same as this paper.

In terms of toxicity and side effects, the manifestations were mainly myelosuppression, leukocyte decrease, esophagitis and nausea and vomiting and so on and the difference between the two groups was not statistically significant, indicating that the concurrent chemo radiotherapy was with a high security. Rees *et al*. (2015) and Otowa *et al* (2015) reported that chemo radiotherapy might have a higher incidence of toxicity and side effects, especially in the respect of myelosuppression. It was not found the difference in the myelosuppression in this paper, the reason might be the little samples. In addition, the 1-3-year survival rates in the observation group were all higher than the control group, indicating that the concurrent chemo radiotherapy was with a higher survival rates, the reason might be the combination of chemotherapy and radiotherapy playing the synergistic effect, helping the chemotherapy to enhance the striking force against the tumor, which could kill the microscopic extension and the distant small metastases, therefore, the

survival rates were increased.

CONCLUSION

Radio chemotherapy combined with the cisplatin plus paclitaxel chemotherapy can appropriately enhance the immune function of patients with esophageal cancer, which can improve the survival rate, with a good security, worth promoting.

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