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Clinical Efficacy of Zhongjiefeng Injection in the Treatment of Patients with Advanced Esophageal Cancer and Its Effect on the Serum VEGF and S100A4 Levels*

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Abstract Objective: To investigate the curative effect of Zhongjiefeng Injection in the treatment of advanced esophageal cancer and its effect on the serum vascular endothelial cell growth factor (VEGF) levels and S100A4 levels. **Methods:** Sixty one patients with advanced esophageal cancer admitted to our hospital from December 2015 to December 2018 were selected. The patients were divided into two groups by the random number table method. Patients in the control group were given chemotherapy with TP, while patients in the observation group were given Zhongjiefeng Injection on the basis of control group. The clinical efficacy, symptom score, quality of life score, changes of serum VEGF and S100A4 and adverse reactions before and after treatment were compared between the two groups. **Results:** After treatment, the total effective rate and disease control rate in the observation group were 93.55% and 87.1%, respectively, which were significantly higher than those in the control group (70%, 60%, $P<0.05$). The symptom scores, serum VEGF and S100A4 levels of the two groups of patients after treatment were significantly lower than those before treatment, and the above indicators in the observation group were significantly lower than those in the control group ($P<0.05$). The quality of life score of patients in the control group decreased significantly after treatment, which showed no significant changes in the observation group before and after treatment, but it was significantly higher than that in the control group ($P<0.05$). There was no significant difference in incidence of adverse reactions including leukopenia, thrombocytopenia, anemia, nausea and vomiting, and liver and kidney dysfunction between two groups ($P>0.05$). **Conclusion:** Zhongjiefeng Injection combined with chemotherapy can significantly improve the clinical efficacy and quality of life of patients with advanced esophageal cancer, which may be related to its effective reduction of

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serum VEGF and S100A4 levels.

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Introduction

Esophageal cancer is one of the common malignant tumors of the digestive tract in our country, and with changes to people's living environment and dietary habits, the morbidity of esophageal cancer increases year by year, and increases with aging. The mortality of esophageal cancer ranks the second among mortalities of malignant tumors in China [1-3]. The early clinical symptoms of esophageal cancer are not apparent, and most patients suffer from advanced esophageal cancer with metastasis when they go to see the doctor and thus missing the best period for surgery as well as the opportunity for a radical cure of esophageal cancer [4, 5]. Patients with middle-term or advanced esophageal cancers have difficulties in eating and drinking with electrolyte metabolic disturbance and extremely weak body conditions, which seriously affect the health and quality of lives of patients [6,7]. A great number of studies at home and abroad were conducted on pathogenesis of the esophageal cancer, which is currently considered to be related to synergistic effects of multiple factors, such as smoking, excessive intake of nitrite, insufficient intake of trace elements, heavy drinking and nutritional factors [8-10].

At present, advanced esophageal cancer is mainly treated with chemotherapy, aiming at extending the survival duration of the patients and improving their qualities of life [11-43]. Studies showed that [14, 15] the treatment with TP could inhibit spread of focus in patients with esophageal cancer and had good efficacy. However, the adverse reactions of the chemotherapy were obvious patients had poor tolerance to it and the compliance to treatment was low [16, 17]. Chinese traditional medicine classified esophageal cancer to the category of "dysphagia" with pathogenesis of mutual knotting of qi, blood and phlegm in the esophagus, and mutual obstructing of phlegm and qi are seen in the early course of disease, the mutual knotting of sputum and silt is seen in the middle and advanced stages. The mutual obstructing of phlegm and qi as well as inner coagulating of congestion are the main symptoms of patients suffering from esophageal cancer. The phlegm resolving and blood stasis dissipating method is the basic prescription in the traditional Chinese medicine therapy, because the traditional Chinese medicines have many targets and cause little adverse reactions, and have an effect-enhancing and toxicity-reducing role when administered in combination with western medicines [18, 19]. This study mainly investigated the efficacy of Zhongjiefeng Injection in adjuvant treatment of advanced esophageal cancer and its effect on VEGF and S100A4 levels, with the intention of providing more references for clinical medication targeting at esophageal cancer.

1. Information and methods

1.1 General information

Sixty one patients with advanced esophageal cancer admitted to our hospital from December 2015 to December 2018 were selected, and all patients conformed to the diagnostic criteria for advanced esophageal cancer as mentioned in *Expert Consensus on Screening of Early Esophageal Cancer and Corresponding Endoscopic Diagnosis and Treatment in China*. The inclusion criteria: ① All patients were diagnosed by gastroscopy, esophageal X ray with barium

meal and CT examination; ② The patients were 40~75 years old; ③ The KPS score was >70; ④ Patients who were ineligible or not willing to receive a surgery. Exclusion criteria: ① Patients concurrently suffering from key organ function disorders such as heart, liver and kidney; ② Patients concurrently suffering from mental and nervous system diseases; ③ Patients who were allergic to drugs used in this study; ④ Patients who did not receive other medications recently. The patients were divided into two groups by the random number table method. There were 30 patients in the control group, with 17 males and 13 females, 41~72 years old with an average of 52.35 ± 3.57 years old; TMN stage: there were 22 cases in stage III and 8 cases in stage IV; Pathological types: there were 12 patients suffering from adenocarcinoma, 10 patients suffering from squamous carcinoma and 8 patients suffering from small cell cancer. There were 31 patients in the observation group, with 16 males and 15 females, 42~74 years old with an average of 53.64 ± 3.96 years old; TMN stage: there were 21 cases in stage III and 10 cases in stage IV; Pathological types: there were 13 patients suffering from adenocarcinoma, 9 patients suffering from squamous carcinoma and 9 patients suffering from small cell cancer. The general information were comparable and there were no statistical significant differences in general information between the two groups ($P>0.05$).

1.2 Treatment methods

All the patients were given vitamin B6, vitamin C, amino acids, glutathione and cimetidine, etc., for symptomatic treatment. The patients in the control group underwent chemotherapy with TP, where 150 mg/(m²·d) of pzaclitaxel was intravenously infused on Day 1 and 75 mg/m² of cisplatin was intravenously infused on Day 1, Day 2 and Day 3, with 21 days as a cycle of chemotherapy. The observation group was given Zhongjiefeng Injection, 4 ml/time and 1 time/day on the basis of control group. Both groups were continuously treated for 2 cycles.

1.3 Observation indicators

① The clinical efficacy between both groups was compared. ② The scores of clinical symptoms and quality of life were compared between the groups and were evaluated in both groups before and after treatment. ③ The VEGF and S100A4 levels before and after treatment in both groups were compared. 5ml of venous blood from each patient on fasting in both groups were drawn before and after treatment, and the VEGF and S100A4 levels were tested by ELISA method (the kits were provided by Shanghai Kemin Biotechnology Co., LTD.). ④ The incidence of adverse reactions between both groups was compared.

1.4 Evaluation of efficacy and criteria for scoring symptoms and quality of life

Evaluation of efficacy: Complete response (CR): all lesions disappear; partial response (PR): the sum of long diameters of the lesions is shortened by $\geq 30\%$; stable disease (SD): the sum of long diameters of the lesions is shortened by $< 30\%$, but does not reach the criteria for PD; progression of disease (PD): the sum of long diameters of the lesions increases by $\geq 20\%$, or new lesions appear. The overall response rate for treatment = $(CR+PR)/\text{total cases} \times 100\%$. The criteria for scoring symptoms: the criteria for scoring of dysphagia established by referring to *Guidance on Clinical Trials for New Traditional Chinese Medicine (Trial)*, i.e., 0 point: no obvious symptom of dysphagia; 1 point: intermittent and slight dysphagia, for rough food or gollop; 2 points: hard to swallow common food while semiliquid diets could be swallowed; 3 points: hard to swallow semiliquid diets while liquid food could be swallowed; 4 points: hard to swallow liquid food and difficulty in drinking water; 5 points: the symptom was not improved or aggravated. Scoring quality of life: The Karnofsky performance status (KPS) scoring criteria were adopted; 0 point means death, 100 points means normal and the higher the score, the better the patients' quality of life.

1.5 Methods for statistical analysis

The study data were statistically analyzed using SPSS16.0, and the enumeration data were expressed as rate (%). The groups were compared using the chi-square test, and the measurement data were expressed as ($\bar{x} \pm s$). The groups were compared using the t-test and there were statistically significant differences ($P < 0.05$).

2. Results

2.1 Comparison of clinical efficacy between two groups

The overall response rate and disease control rate were 93.55% and 87.1%, respectively, higher than those in the control group (70% and 60%, $P < 0.05$). See Table 1.

Table 1 Comparison of the clinical efficacy between two groups [n (%)]

Groups	Cases	CR	PR	SD	PD	Total effective rate	Disease control rate
Control group	30	9 (30.00)	9 (30.00)	3 (10.00)	9 (30.00)	18 (60.00)	21 (70.00)
Observation group	31	19 (61.29)	8 (25.81)	2 (6.45)	2 (6.45)	27 (87.10)	29 (93.55)
X^2						5.785	5.720
P						0.016	0.017

2.2 Comparison of symptoms and quality of life before and after treatment between two groups

After treatment, the scores of symptoms of patients in both groups were lower than those before treatment, and the scores in the observation group were significantly lower than those in the control group ($P < 0.05$). After treatment, the scores of quality of life in the control group were significantly decreased while there was no change to those in the observation group, which were significantly higher than those in the control group ($P < 0.05$). See Table 2.

Table 2 Comparisons of the symptom and KPS score between two groups before and after treatment ($\bar{x} \pm s$, score)

Groups	Cases	Symptom score		KPS score	
		Before treatment	After treatment	Before treatment	After treatment
Control group	30	4.22 ± 1.15	3.02 ± 0.85*	75.68 ± 18.61	61.34 ± 12.73*
Observation group	31	4.13 ± 1.02	1.51 ± 0.41*	73.58 ± 17.33	70.65 ± 15.23
t		0.324	8.791	0.452	2.586
P		0.747	<0.001	0.653	0.012

Note: Compared with before treatment, * $P < 0.05$.

2.3 Comparisons of serum VEGF and S100A4 levels between groups before and after treatment

Before treatment, there were no statistically significant differences in the serum VEGF and S100A4 levels between groups ($P > 0.05$). After treatment, the serum VEGF and S100A4 levels decreased significantly compared with before treatment and the above-mentioned indicators in the observation group were significantly lower than those in the control group ($P < 0.05$). See Table 3.

Table 3 Comparisons of the serum VEGF and S100A4 levels between groups before and after treatment ($\bar{x} \pm s$)

Groups	Cases	VEGF (ng/L)		S100A4 (ug/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	30	77.25 ± 20.31	55.64 ± 15.36*	6.54 ± 2.01	4.32 ± 1.54*
Observation group	31	75.33 ± 18.27	34.28 ± 10.12*	6.69 ± 2.03	2.63 ± 0.66*
<i>t</i>		0.388	-6.392	-0.290	-5.539
<i>P</i>		0.699	<0.001	0.773	<0.001

Note: Compared with before treatment, * $P < 0.05$.

2.4 Comparison of the incidence of adverse reactions between groups

There was no significant difference in incidence of adverse reactions including leukopenia, thrombocytopenia, anemia, nausea and vomiting, and liver and kidney dysfunction between two groups ($P > 0.05$). See Table 4.

Table 4 Comparison of the incidence of adverse reactions between groups [n (%)]

Groups	Cases	Hypoleucocytosis	Thrombopenia	Anemia	Nausea and vomiting	Abnormal liver and kidney
Control group	30	3 (10.00)	4 (13.33)	5 (16.67)	9 (30.00)	10 (33.33)
Observation group	31	5 (16.13)	6 (19.35)	8 (25.81)	10 (32.26)	12 (38.71)
χ^2		0.503	0.403	0.759	0.036	0.191
<i>P</i>		0.707	0.731	0.384	0.849	0.662

3. Discussion

The prognosis of advanced esophageal cancer is poor, and the patients mainly present as dysphagia, feeling of choking when swallowing food, feeling of burned and pain behind sternum after eating, hard to swallow dry food, hard to swallow semi-liquid diets in the middle stage of the disease, and hard to drink water for patients at the advanced stage of the disease [20, 21]. The pathogenesis of esophageal cancer is currently considered to be correlated with malignant lesions from dysplasia of esophageal glandular epithelium and squamous epithelium. Early discovery and early treatment could cure the cancer [22, 23]. However, since the symptoms of this disease are atypical, this disease often has progressed to the middle or advanced stage when patients go to see the doctor. Chinese traditional medicine classifies the esophageal cancer to the category of “dysphagia”, which presents mainly as stasis of sputum, qi stagnation and blood stasis with root cause of weakened body resistance. The pathogenesis of this disease is the pathological change presented as stasis of sputum, qi stagnation and blood stasis resulting from long-term invasion of exogenous pathogens into the body, loss of healthy qi and disorder of qi-blood-body fluid as well as obstruction of esophagus by sputum silt resulting in difficulty of eating and drinking [24, 25].

Zhongjiefeng is the complete stool of *sarcandra glabra* belonging to Chloranthaceae and has effects with respect to antiseptis and anti-inflammation, expelling wind and dredging collat, promoting blood flow and resolving masses as well as anti-tumor. The Zhongjiefeng Injection is extracted and refined from the herbal of Zhongjiefeng, and current pharmacological studies showed that the main ingredients of Zhongjiefeng Injection were fumaric acid, flavonoid glycoside, ficusin and coumarin, etc., which played roles in anti-tumor, anti-bacteria and immune

regulations^[30]. Zhongjiefeng Injection can directly kill cancer cells and inhibit the division and proliferation of cells. The results of this study showed that the improvement of clinical symptoms and quality of life of patients in the observation group were significantly better than those in the control group, and the overall response rate and disease control rate in the observation group were significantly higher than those in the control group, indicating that the Zhongjiefeng Injection combined with chemotherapy following TP have better clinical efficacies in symptom control, improvement of quality of life of patients, etc.. Such efficacies may be related to the effects of Zhongjiefeng Injection in regulating immune functions of patients and its significant effect in anti-tumor and anti-bacteria activities.

Angiogenesis is the basis of the growth, infiltration and metastasis of tumors, while new vessels mainly provide nutrients for tumors and paths for the spreading of cancer cells. VEGF is the most potent vascular endothelial growth factor which plays an important role in the process of angiogenesis of tumors. VEGF can weaken the vascular barrier, induce the formation of a lumen of blood capillary, increase the vascular permeability and allow a great amount of cancer cells permeate into the blood circulation so as to promote the angiogenesis, infiltration and metastasis of tumors^[26, 27]. S100A4 is closely related to multiple malignant tumors, which can regulate proliferation and inhibit apoptosis of cells, enhance the motility of cells, reduce their adhesion and accelerate angiogenesis, and high expression levels of S100A4 is closely related to high level of infiltration and metastasis as well as poor prognosis of tumors^[28, 29]. The results of this study showed that the serum VEGF and S100A4 levels of patients significantly decreased in the observation group after treatment, and they were lower than those in the control group, suggesting that the mechanism of improving efficacy by Zhongjiefeng Injection combined with chemotherapy following TP may be related to the significantly decreased serum VEGF and S100A4 levels of patients. With respect to adverse reactions, the therapy in combination with Zhongjiefeng Injection did not increase the incidence of adverse reactions in patients and had a high level of safety.

In conclusion, Zhongjiefeng Injection combined with chemotherapy can significantly improve the clinical efficacy and the quality of life of patients suffering from advanced esophageal carcinoma, which may be related to its effective reduction of serum VEGF and S100A4 levels.

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