

Original Article

Evaluation of the efficacy of Shenqi Fuzheng injection as adjuvant therapy for the treatment of gastrointestinal malignant tumor

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Received January 16, 2018; Accepted February 21, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Objective: To investigate the clinical efficacy of the treatment of combined Shenqi Fuzheng (SF) injection with 5-fluorouracil and oxaliplatin on gastrointestinal cancer after surgery. Methods: Fifty-six patients with middle and end stages gastrointestinal cancer treated at our hospital from January 2015 to June 2017 were enrolled in this study. The patients were randomly divided into SF plus chemotherapy group and control group (28 cases in each group). After the resection of lesions for all patients, 5-fluorouracil and oxaliplatin were used after the operation in the control group. The combination of SF injection with 5-fluorouracil and oxaliplatin were performed in the SF plus chemotherapy group after the resection of lesions. The age, gender, degree of tumor differentiation and stage were recorded. The concentration of immunoglobulin in patient was also measured before chemotherapy. The recovery time of gastrointestinal motility (aerofluxus time) and feed time (no gastrointestinal symptoms after eating semi-fluid) were determined. Moreover, the changes of T cell subsets and phagocytosis function of mononuclear macrophages were analyzed before and after chemotherapy. Results: There were no differences in average age, gender, degree of tumor differentiation and stage between SF plus chemotherapy group and control group (all $P > 0.05$). The concentrations of albumin and the primary diseases of patients in SF plus chemotherapy group also showed no significant difference when compared with that in control group (both $P > 0.05$). The lengths of aerofluxus time, defecations time, and feeding time in SF plus chemotherapy group were significantly shorter than that in control group (all $P < 0.05$). The phagocytosis ratio of mononuclear macrophages in SF plus chemotherapy group was significantly higher than that in control group from 3 to 7 days after chemotherapy (all $P < 0.05$). The CD4+/CD8+ T cell ratios in SF plus chemotherapy group were escalated from the third day after chemotherapy. Moreover, there were significantly higher CD4+/CD8+ T cell ratios in SF plus chemotherapy group than that in control group (all $P < 0.05$) in each day. For the comparison within the SF plus chemotherapy group, the CD4+/CD8+ T cell ratios in patients from the third day after chemotherapy were significantly higher than that before the chemotherapy in each day (all $P < 0.05$). Conclusion: For the treatment of gastrointestinal malignant tumor after surgery, the combination of SF and chemotherapy could improve the CD4+/CD8+ T cell ratio, enhance the functions of phagocytosis by mononuclear macrophages and cellular immune, then promote the recovery of gastrointestinal function in patient.

Keywords: Integrative Chinese and western medicine, Shenqi Fuzheng injection, gastrointestinal malignant tumor, cellular immunity

Introduction

The incidence of gastrointestinal malignancy was increased significantly in China in the last 20 years. The incidence rate of this cancer is as high as 3.4% now, which has become one of the important causes for cancer death in China [1, 2]. The main medication for the patients with middle or end stages of gastrointestinal malignant tumor was removing the lesions and

surrounding lymph nodes with surgery, then treated with adjuvant chemotherapy after the operation. This treatment could improve the survival time of the patient [3, 4]. However, the adverse reaction of chemotherapy was relatively high. The vomiting, low immune function, hair loss, and other side effects were observed in many patients, and induced daunting for the patients [5]. Therefore, novel treatment approaches are urgent for the patients, which can

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alleviate the adverse reaction in patient, improve the efficacy of chemotherapy, prolong the survival time, and promote the quality of life.

Shenqi Fuzheng (SF) injection, which benefited Qi and strengthened immunity, was employed in adjuvant treatment for the lung and gastric cancer with syndrome of deficiency of Qi. As an injection in Chinese medicine, the main ingredients of SF were astragalus and codonopsis. The combination of SF injection and chemotherapy could improve the efficacy, maintain the routine index of blood, enhance the immune function in patients with deficiency of Qi, promote the syndrome of deficiency of Qi and the quality of life [6, 7]. The SF injection was widely used in treatment for patients with gastric cancer as adjuvant drug for chemotherapy. However, the specific mechanism of SF injection is still not clear until now.

In this study, the efficacy and mechanism of SF injection were evaluated for the treatment of patients with gastrointestinal malignant tumor in chemotherapy after the surgery.

Materials and methods

Patient information

This study has got approval from local ethical committee. Fifty-six patients with middle and end stages gastrointestinal cancer treated at our hospital from January 2015 to June 2017 were enrolled in this study. There were 7 cases of cardiac carcinoma, 28 cases of gastric carcinoma, 2 cases of small intestine cancer, 13 cases of colorectal carcinoma, 6 cases of rectal carcinoma. The patients were randomly divided into SF plus chemotherapy group and control group (28 cases in each group). After the resection of lesions for all patients, 5-fluorouracil and oxaliplatin were used after the operation in the control group. The combination of SF injection with 5-fluorouracil and oxaliplatin were performed in the SF plus chemotherapy group after the resection of lesions. In control group, there were 19 males and 9 females, whereas there were 20 males and 8 females in SF plus chemotherapy group. The average age of control group and SF plus chemotherapy group were 56.7 ± 12.4 and 60.3 ± 8.9 yearsold, respectively. The patients and family members understood and signed the informed consent.

The inclusion criteria were consisted of (A) meeting the pathology diagnostic criteria for middle or end stage highly differentiated tumor, (B) the first time for chemotherapy and could tolerate one chemotherapy cycle, (C) no hormone therapy used recently, (D) expecting to survive more than three months. The exclusion criteria consisted of (A) severe cardiac, liver, brain, pulmonary, renal, and other substantive damage, (B) serious circulation system, immune system, blood system and other damages, (C) patients with mental diseases, (D) pregnant women, (E) patients who give up during the treatment.

Treatment program

One week after the surgery, 130 mg/m^2 oxaliplatin was titrated continuously between 2-6 h on the first day of the chemotherapy in control group. Then 5-fluorouracil (0.5 g/m^2) was titrated once per a day subsequently, and lasted 4 days as one cycle of chemotherapy. Three cycles indicated one course of treatment. In the SF plus chemotherapy group, 250 mL of SF solution (Livzon, China) was titrated once per a day after the operation until the day of chemotherapy. During the chemotherapy, 0.4 mg/mL oxaliplatin was titrated continuously between 2-6 h. Then 5-fluorouracil (0.5 g/m^2) was titrated once per a day subsequently, and lasted 4 days as one cycle of chemotherapy. Three cycles indicated one course of treatment.

Outcome measures

Determination of lymphocyte subset: The fasted peripheral blood of patients was collected. The EDTA was added in the blood as anticoagulant. The detection was measured through flow cytometry. To determine the subsets of T cells, specific fluorescence labeled monoclonal antibodies were added in the tubes, respectively. After shaking well slightly, the tubes were incubated at room temperature for 15 min away from light. Then the red blood cells lysis buffer (1 mL) was added and incubated for 10 min away from light. After the complete lysis of red blood cells, the tubes were centrifuged to remove supernatants. Then 1 mL PBS buffer was added in the tube. Finally, the samples were determined by flow cytometry (Accuri C6, BD, US). The changes of CD4+ T cell and CD4+/CD8+ ratio were analyzed by instrumentation supporting software.

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Table 1. Comparison of patient information between two groups

Item	Control group (n=28)	SF plus chemotherapy group (n=28)	t/X ²	P
Age	56.7 ± 12.4	60.3 ± 8.9	-0.409	0.704
Gender			0.085	1.000
Male	19	20		
Female	9	8		
Differentiation of tumor (high)	28	28	1.000	1.000
Stages of tumor			1.385	0.244
Middle stage	6	10		
End stage	22	18		
Albumin concentration before chemotherapy (g/L)	38.64 ± 4.01	40.25 ± 4.58	-0.458	0.671
Immunoglobulin concentration before chemotherapy (g/L)	14.49 ± 1.48	16.47 ± 5.13	-0.642	0.556
Albumin/Immunoglobulin ratio before chemotherapy	2.67 ± 0.45	2.44 ± 0.53	0.573	0.597
Primary disease			0.951	0.346
Cardiac carcinoma	3	4		
Gastric carcinoma	13	15		
Small intestine cancer	2	0		
Colorectal carcinoma	5	8		
Rectal carcinoma	5	1		

Note: SF: Shenqi Fuzheng.

Determination of phagocytosis on mononuclear macrophage: The mononuclear macrophages were separated as follows. Peripheral venous blood was collected in heparin anticoagulant tube. Then the samples were centrifuged at 1,500 rpm for 15 min under 4°C. After collecting the supernatant, the blood cells were transferred in equal volume of lymphocyte separation medium (Ficoll solution, GE, US). Then the solutions were centrifuged at 400 rpm for 15 min under 4°C. The monocytes which located in the middle layer was collected, and washed three times by PBS buffer. Then the amount of monocytes was measured.

The chicken red blood cells were prepared as follows. The chicken blood (1-2) mL was collected, then the Alsever's solution was added in the blood as anticoagulant. The samples were washed three times through sterile saline, and diluted to 5% chicken red blood cell solution (5×10^6 - 6×10^6 /mL) in 0.9% sodium chloride injection of 95% volume for the phagocytosis study.

Then the monocytes and chicken red blood cell solutions were mixed together. The mixture was incubated at 37°C in water bath for 30 min, and shaken slightly at every 10 min. After cen-

trifuging at 1,000 rpm for 5 min, the supernatant was removed. Then the little remaining fluids were mixed with the cells. After smearing the slide, the samples were fixed by methanol, and stained by Giemsa approach. Then the samples were determined by oil microscopy. Two hundred mononuclear macrophages were counted and analyzed for the phagocytosis function. The percentage and index of phagocytosis were measured as follows. The phagocytosis ratio = (mononuclear macrophages with phagocytosis for chicken red cells/200) *100%.

Recovery of gastrointestinal function, the first feeding time, and incidence of obstructive vomiting: The gastrointestinal function recovery time, and first feeding time were recorded before the surgery and chemotherapy, also for the times after the chemotherapy respectively. The incidence of obstructive vomiting was measured for both groups.

The recovery of gastrointestinal function was measured as follows.

The auscultation of abdominal bowel sound was recorded. Normally, the intestine sounds were 4-5 times per minute, and the frequency,

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Table 2. Comparison of recovery of gastrointestinal function and obstructive vomiting in patients between two groups

Item	Control group (n=28)	SF plus hemotherapy group (n=28)	t/X ²	P
Aerofluxus time (d)	5.64 ± 0.83	2.29 ± 0.62	3.450	0.026
Defecations time (d)	6.72 ± 0.87	4.25 ± 0.92	3.379	0.028
Feeding time (d)	11.37 ± 1.30	6.21 ± 1.39	2.831	0.047
Obstructive vomiting (n)	9 (32.14%)	2 (7.14%)	5.543	0.019

Note: SF: Shenqi Fuzheng.

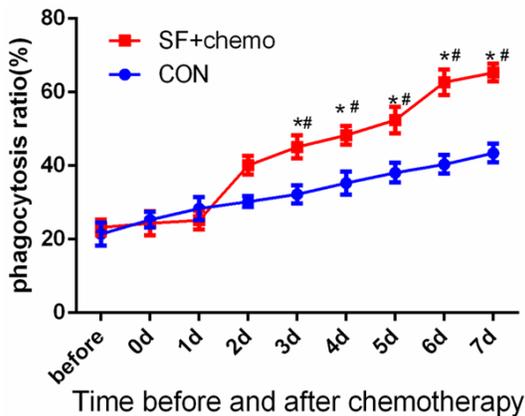


Figure 1. Changes of phagocytosis ratios on mononuclear macrophages in patients after chemotherapy. There were higher phagocytosis ratios on mononuclear within the SF plus chemotherapy group and control group respectively, from 3 to 7 days after chemotherapy than that before chemotherapy (*P<0.05). The phagocytosis ratio on mononuclear macrophages in SF plus chemotherapy group was significantly higher than that in control group from 3 to 7 days after chemotherapy (*P<0.05). SF + Chemo: SF plus chemotherapy group. CON: control group. Before: one day before chemotherapy. 0 d: the day of chemotherapy. 1 d: one day after chemotherapy. 2 d: two days after chemotherapy. 3 d: three days after chemotherapy. 4 d: four days after chemotherapy. 5 d: five days after chemotherapy. 6 d: six days after chemotherapy. 7 d: seven days after chemotherapy.

sound and tone showed large variation. After improving the intestine peristalsis, the borborygmus could reach more than 10 times per minute, but the tone of this sound was not particularly high. This phenomenon was called active borborygmus. If there were many times bright, high-tonal (even jingle or metallic notes) borborygmus, this phenomenon was called hyperfunction borborygmus. Moreover, if there was no borborygmus during auscultation (3-5 min), it was defined as disappeared borborygmus.

Statistical analysis

SPSS 17.0 and GraphPad Prism 6.0 were used for data analysis. The data were expressed by mean ± standard deviation ($\bar{x} \pm sd$). The comparison between groups was conducted with independent sample t test. The counting data was tested by X². P<0.05 indicated statistically significant difference (significant level=0.05).

Results

Patient information

There was no significant difference for average age, gender, differentiation and stage of tumor between SF plus chemotherapy group and control group (P=0.704, P=1.000, P=1.000 and P=0.244, respectively). There was also no significant difference for preoperative albumin and immunoglobulin concentrations and ratio between two groups (P=0.671, P=0.556, P=0.597, respectively). For the primary diseases of patients, no significant difference was observed between two groups (P=0.346, **Table 1**).

Effect of SF injection on gastrointestinal function recovery time and obstructive vomiting

After combination of SF injection and chemotherapy, the aerofluxus time, defecations time, and feeding time in SF plus chemotherapy group were significantly earlier than that in control group (P=0.026, P=0.028, P=0.047, respectively). Moreover, there was significant lower incidence of obstructive vomiting in SF plus chemotherapy group than that in control group (P=0.019, **Table 2**).

Effect of phagocytosis on mononuclear macrophages in patients after chemotherapy

There were no significant differences in phagocytosis ratios on mononuclear macrophages before surgery and the day of chemotherapy in both groups (P=0.072 and P=0.055). The phagocytosis ratios on mononuclear macrophages were escalated in both groups 3 days after chemotherapy. Moreover, the phagocytosis ratio on mononuclear macrophages in SF plus chemotherapy group was significantly higher

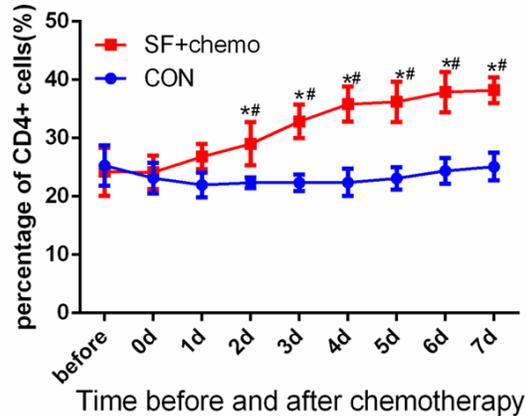


Figure 2. Changes of the percentage of CD4+ T cells in both groups before and one week after chemotherapy. There was significantly higher percentage of CD4+ T cell within the SF plus chemotherapy group from 2 days to 7 days after chemotherapy than that before chemotherapy (* $P < 0.05$). Comparison of percentage of CD4+ T cell within the control group, there was no significant difference before and after chemotherapy. There were significantly higher percentages of CD4+ T cell in SF plus chemotherapy group than that in control group from 2 days to 7 days after chemotherapy (* $P < 0.05$). SF + Chemo: SF plus chemotherapy group. CON: control group. Before: one day before chemotherapy. 0 d: the day of chemotherapy. 1 d: one day after chemotherapy. 2 d: two days after chemotherapy. 3 d: three days after chemotherapy. 4 d: four days after chemotherapy. 5 d: five days after chemotherapy. 6 d: six days after chemotherapy. 7 d: seven days after chemotherapy.

her than that in control group from 3 days to 7 days after chemotherapy ($P = 0.040$, $P = 0.038$, $P = 0.037$, $P = 0.030$ and $P = 0.030$, respectively, **Figure 1**).

Comparison of phagocytosis ratio on mononuclear within the control group, there was no significant difference before and after chemotherapy ($P > 0.05$). There was significantly higher phagocytosis ratio in SF plus chemotherapy group from 3 days to 7 days after chemotherapy than that before chemotherapy ($P = 0.044$, $P = 0.040$, $P = 0.040$, $P = 0.035$ and $P = 0.032$, respectively, **Figure 1**).

Effect of SF injection on changes of the percentage of T cells after chemotherapy

Effect of SF injection on changes of the percentage of CD4+ T cells after chemotherapy: There were no significant differences in percentages of CD4+ T cell between two groups before surgery and the day of chemotherapy

($P = 0.872$ and $P = 0.065$, respectively). Moreover, the percentages of CD4+ T cell were lower than the reference range (around 60% in lymphocytes in peripheral blood). From 2 days after the chemotherapy, the percentages of CD4+ T cell were escalated in SF plus chemotherapy group. There were no significant differences in percentages of CD4+ T cell among observation days in control group from 2 days after the chemotherapy. There were significantly higher percentages of CD4+ T cell in SF plus chemotherapy group than that in control group from 2 days to 7 days after chemotherapy ($P = 0.045$, $P = 0.040$, $P = 0.038$, $P = 0.034$, $P = 0.030$ and $P = 0.024$, respectively, **Figure 2**).

Comparison of percentage of CD4+ T cell within the control group, there was no significant difference before and after chemotherapy ($P > 0.05$). There was significantly higher percentage of CD4+ T cell within the SF plus chemotherapy group from 2 days to 7 days after chemotherapy than that before chemotherapy ($P = 0.048$, $P = 0.044$, $P = 0.040$, $P = 0.038$, $P = 0.035$ and $P = 0.030$, respectively, **Figure 2**).

Effect of SF injection on changes of the percentage of CD8+ T cells after treatment: There were no significant differences in percentages of CD8+ T cell in two groups before surgery and the day of chemotherapy (both $P > 0.05$, **Figure 3**). Moreover, the percentages of CD8+ T cell were lower than the reference range (around 35% in lymphocytes in peripheral blood). Comparison of percentage of CD8+ T cell within the control group or SF plus chemotherapy group respectively, there were no significant difference before and after chemotherapy (both $P > 0.05$, **Figure 3**).

Changes of CD4+/CD8+ T cell ratio before and after chemotherapy: There were no significant differences in CD4+/CD8+ T cell ratios in both groups ($P = 0.832$, $P = 0.760$, $P = 0.651$ and $P = 0.074$, for the day before chemotherapy, 0 day, 1 day and 2 days after chemotherapy respectively, **Figure 4**). Moreover, the CD4+/CD8+ T cell ratios were lower than the reference range. From 3 days after the chemotherapy, the CD4+/CD8+ T cell ratios were escalated in SF plus chemotherapy group. Whereas there were no significant differences in CD4+/CD8+ T cell ratios among observation days in control group from 3 days after the chemotherapy. There were significantly higher CD4+/CD8+

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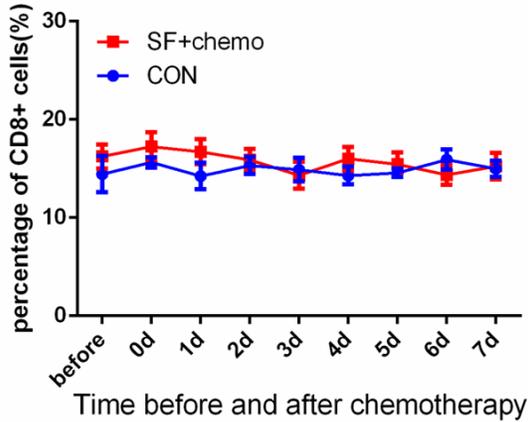


Figure 3. Changes of the percentage of CD8+ T cells in both groups before and one week after chemotherapy. There were no significant differences in percentages of CD8+ T cell in two groups before surgery and the day of chemotherapy. Comparison of percentage of CD8+ T cell within the control group or SF plus chemotherapy group respectively, there were no significant difference before and after chemotherapy. SF + Chemo: SF plus chemotherapy group. CON: control group. Before: one day before chemotherapy. 0 d: the day of chemotherapy. 1 d: one day after chemotherapy. 2 d: two days after chemotherapy. 3 d: three days after chemotherapy. 4 d: four days after chemotherapy. 5 d: five days after chemotherapy. 6 d: six days after chemotherapy. 7 d: seven days after chemotherapy.

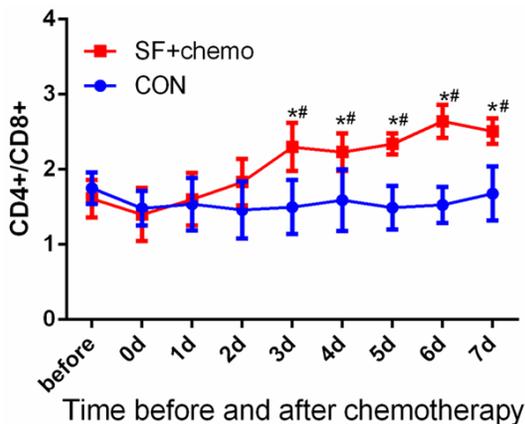


Figure 4. Changes of the CD4+/CD8+ T cell ratio in both groups before and one week after chemotherapy. There was significantly higher percentage of CD4+ T cell within the SF plus chemotherapy group from 3 days to 7 days after chemotherapy than that before chemotherapy (* $P < 0.05$). Comparison of CD4+/CD8+ T cell ratios within the control group, there was no significant difference before and after chemotherapy. There were significantly higher CD4+/CD8+ T cell ratio in SF plus chemotherapy group than that in control group from 3 days to 7 days after chemotherapy (* $P < 0.05$). SF + Chemo: SF

plus chemotherapy group. CON: control group. Before: one day before chemotherapy. 0 d: the day of chemotherapy. 1 d: one day after chemotherapy. 2 d: two days after chemotherapy. 3 d: three days after chemotherapy. 4 d: four days after chemotherapy. 5 d: five days after chemotherapy. 6 d: six days after chemotherapy. 7 d: seven days after chemotherapy.

T cell ratios in SF plus chemotherapy group than that in control group from 3 to 7 days after chemotherapy ($P = 0.042$, $P = 0.036$, $P = 0.030$, $P = 0.025$ and $P = 0.028$, respectively, **Figure 4**).

Comparison of CD4+/CD8+ T cell ratios within the control group, there was no significant difference before and after chemotherapy ($P > 0.05$). There was significantly higher percentage of CD4+ T cell within the SF plus chemotherapy group from 3 days to 7 days after chemotherapy than that before chemotherapy ($P = 0.046$, $P = 0.040$, $P = 0.034$, $P = 0.030$ and $P = 0.028$, respectively, **Figure 4**).

Discussion

After the abdominal surgery, the most common complication is gastrointestinal dysfunction. The reasons were the inhibition of nerve and muscle movement function, and adynamic enteroplegia which was induced by sympathetic nervous excitement in surgery [8, 9]. Therefore, the intestinal motility, secretion and absorption functions were inhibited significantly. Then the complications of biliary dyskinesia (such as prolonged gastric emptying and aerofluxus times, and difficulty in defecation) were emerged. In this study, the aerofluxus time and defecation time were 5.64 ± 0.83 days and 6.72 ± 0.87 days in control group, respectively. In SF plus chemotherapy group which using SF after chemotherapy, the aerofluxus time and defecation time were significantly shorter than that in control group. Those results indicated that SF could improve intestinal function recovery, and promote intestinal movement. Liu et al. and Gu et al. reported that SF could adjust gastrointestinal function, improve choleresis increasing, and coordinate gastrointestinal motility [10, 11]. Those results were conformed to the data in our study.

As one of the important component of cellular system in immune system, mononuclear macrophages play an important role in specific and

nonspecific immunities. For the nonspecific immunity, mononuclear macrophages can engulf the invading pathogens, foreign bodies, and senescent, apoptosis and necrotic cells. For the specific immunity, mononuclear macrophages have immune recognition function, and participated in the identification, processing and transmission of antigens [12, 13]. In this research, the results showed that combination of chemotherapy and SF injection induced significantly higher phagocytosis ratio on mononuclear macrophages in SF plus chemotherapy group than that in control group from the third day after chemotherapy. Those results indicated that SF injection could improve the function of phagocytosis on mononuclear macrophages. Those results could partially explain the increasing of immunity for invading pathogens, and direct adhesion then phagocytosis of the clearance of aging cells and tumor cells in patients, who suffered chemotherapy after surgery of gastrointestinal tumors.

Cellular immunity plays an important role in tumor immunological effect. Cellular immune response is mainly induced by T cell-mediated specific cellular immunoreaction. In the human body, T cell (such as CD4+ and CD8+ T cells) plays an important role in regulating anti-tumor response [14, 15]. For the CD4+ T cells, they destroy the tumor cells through identification of MHC/peptide complex, then play an important role in anti-tumor immune response [16, 17]. Whereas the CD8+ T cells normally kill the tumor cell directly to achieve the anti-tumor effect [18, 19]. From Liu et al.'s report, the SF could protect the hemogram, and improve the immunity in patients with Qi deficiency. However, the specific mechanism was not studied yet [20]. In this study, the escalation of CD4+/CD8+ ratios were observed in SF plus chemotherapy group 3 days after chemotherapy. Compared the CD4+/CD8+ ratios before or after chemotherapy, there was no significant difference within the control group. However, there was significantly higher CD4+/CD8+ ratios after the chemotherapy than that before the chemotherapy in SF plus chemotherapy group from the third day after chemotherapy. The possible reason was the improvement of ant-tumor response on CD4+ T cell by SF injection. Then this treatment could promote the immunity in patients.

In this study, the clinical efficacy and mechanism of SF injection were explored and explained. Until now, the specific mechanism of SF injection was still not clear. But the less patients limited the assessment of results in this research. More cases will be studied to explore the mechanism of SF injection for the prognosis improvement in cellular immunity regulation in patients with gastrointestinal malignancy.

In conclusion, SF injection could improve the CD4+/CD8+ T cell ratio, and phagocytosis on mononuclear macrophages, then enhance the cellular immunity, promote the recovery of gastrointestinal function after chemotherapy.

Disclosure of conflict of interest

None.

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