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• BRIEF REPORTS •

# Effect of Fuzheng Yiliu decoction combined with chemotherapy on patients with intermediate and late stage gastrointestinal cancer

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## Abstract

**AIM:** To investigate the therapeutic effects of Fuzheng Yiliu (strengthening the body resistance to inhibit tumor) decoction combined with chemotherapy on the patients with intermediate and late stage gastrointestinal cancer.

**METHODS:** Sixty patients were randomly divided into treatment group (chemotherapy combined with Fuzheng Yiliu decoction) and control group (chemotherapy alone). Four indexes, including the tumor recent remission rate (RR), the change of main symptoms, the toxic and side effects caused by chemotherapy and the change of performance status, were observed in the patients. Peripheral blood contents of $CD3^+$, $CD4^+$, $CD8^+$ cells, $CD4^+/CD8^+$ and soluble interleukin-2 receptor (sIL-2R) were tested before and after treatment and the values were compared with those of healthy peoples.

**RESULTS:** The improving rate of main symptoms (69.6%) and performance status (56.7%) were significantly higher in the treatment group than in the control group (34.8%, 26.7%, $P<0.05$). The occurrence rates of grade II toxic and side-effects on both bone marrow (13.3%) and digestive tract (30%) were lower in the treatment group compared to the control group (36.7%, 63.3%, $P<0.05$). Before treatment, the proportion of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ decreased and the proportion of $CD8^+$ and sIL-2R raised markedly both in the control group and treatment group as compared to the healthy people. After treatment, that increased of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ increased (62.25±10.01% *vs* 68.31±9.72%, 36.83±10.44% *vs* 42.6±9.62%, 1.24±0.65 *vs* 1.66±0.85, $P<0.05$) and the values of $CD8^+$ and sIL-2R decreased obviously (33.06±7.69% *vs* 29.24±6.25%, 588.23±216.86 U/mL *vs* 475.87±211.36 U/mL, $P<0.05$) in the treatment group, whereas these values were opposite in the control group (64.22±6.91% *vs*60.63±5.75%, 35.62±7.49% *vs*31.53±5.53%, 32.95±8.28% *vs* 37.14±7.48%, 1.17±0.43 *vs* 0.94±0.43, 573.63±214.32 U/mL *vs* 692.17±221.33 U/mL, $P<0.05$).

**CONCLUSION:** Fuzheng Yiliu decoction can enhance therapeutic effects of chemotherapy on malignant gastrointestinal tumor, and also reduce the toxic and side effects on bone marrow and digestive tract, thereby improving the quality of life and cellular immunity in patients with malignant gastrointestinal tumor.



**Key words:** Gastrointestinal Cancer; Fuzheng Yiliu decoction; Chemotherapy

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## INTRODUCTION

Malignant tumor of digestive tract is one of the most common cancers in the word[1]. Despite many advances in the treatment of this disease in recent decades, its long-term therapeutic outcome remains poor[2]. As an important method to treat cancer, chemotherapy is widely used in clinic. However, the chemotherapy has many toxic and side effects. The life quality of patients who receive chemotherapy treatment is poor because of the side effects of drugs. At the same time, immunosuppression of chemotherapy can accelerate the recrudescence and metastasis of tumors[3]. Improving the curative effect and mitigating the toxic effect of chemotherapy have become the important task of present clinical researches. At the same time, more and more efforts have been made in searching natural materials and foods as a complementary means for the treatment of cancer.

Characterized by effectiveness and low toxicity, traditional Chinese herbs have aroused more interests in the treatment of tumors[4,5]. Fuzheng Yiliu decoction (FZYLD) is made of medicinal Chinese herbs for treating malignant tumors of digestive tract developed by our laboratory based on the basic traditional Chinese medicine (TCM) theories of "nourishing Qi and invigorating spleen, activating blood flow and removing blood stasis, and expelling toxin cooling" as the key principle in combination with our clinical experiments in preventing and treating cancers. Our previous experiment demonstrated that FZYLD could inhibit the growth of gastric cancer cells[6]. In the present study, we observed the clinical effects of FZYLD combined with chemotherapy in treating intermediate and late malignant tumors of digestive tract and the changes of cell immune status in malignant tumor patients after FZYLD treatment.

## MATERIALS AND METHODS

### *Patients*

Sixty patients with gastrointestinal malignant tumors were

enrolled in this study between 2000 and 2002 in the Department of Oncology, First Hospital of Xi'an Jiaotong University and Shaanxi Provincial People's Hospital. There were 51 males and 9 females with an average age of 51±10 years. There were 39 cases of gastric cancer, 8 cases of esophageal cancer and 13 cases of large intestinal cancer. Each case was diagnosed by X-ray barium meal, computed tomographic (CT) scan, gastroscopy, enteroscopy and post-operative definite histopathological examination. Only the patients receiving the first time treatment or the last treatment for more than 1 mo, whose Karnofsky performance status (KPS) was higher than 60 with no taboo of chemotherapy were included in this study. The patients were randomly divided into treatment group (chemotherapy combined with FZYLD, group 1) and control group (chemotherapy alone, group 2). There were no differences in sex, age, site of lesion, pathological type and pathological stage between the two groups. Fifteen healthy controls (mean age 50 years, range 48-53 years), who had no history of tumor, hepatic disease, renal disease and other disease with changed immunological functions, were included in normal control group. All patients were required to sign a written informed consent according to the national and institutional guidelines.

### *Drug application*

The chemotherapy scheme and usage were the same in the two groups. ELF etoposide+calcium leucovorin+5-fluorouracil (ELF), cisplatine+calcium leucovorin+5-fluorouracil (PLF) and calcium leucovorin+5-fluorouracil (LF) were used for gastric cancer, esophageal cancer and large intestinal cancer respectively. One chemotherapeutic cycle included 21 d, 2 cyles for each period of treatment. FZYLD was applied 3 d before chemotherapy and lasted to the end of 2 cycles of chemotherapy. Evaluation of treatment effects was carried out after one period of treatment.

### *Sample collection*

Immediately before and after 1 period of treatment, the levels of T lymphocyte subgroup and soluble interleukin-2 receptors (sIL-2R) were detected. Three milliliters of blood samples was drawn from patients in the morning and transferred into two test tubes. Ethylenediaminetetra-aceticacid (EDTA) was used as anticoagulant. One share was used to detect the expression level of T lymphocyte subgroup. Serum in the other tube was separated by centrifugation at 4 000 r/min for 10 min and stored at -70 ℃ for detection of sIL-2R.

### *Reagents*

Mouse anti-human CD3, CD4 and CD8 monoclonal antibodies and negative control were obtained from Beckman-Coulter Immunotech Company (USA) for the detection of total T lymphocytes, helper T lymphocytes and inhibitor T lymphocytes respectively. sIL-2R detection kit was obtained from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA). EDTA, PBS and red cell fragmentation solution were obtained from Molecular Biology Center of Xi'an Jiaotong University.

### *Evaluation of treatment effects*

For the evaluation of the tumor recent remission rate (RR), endoscope, X-ray barium meal and CT were used before and after treatment in 46 patients with specific focal tumors. A complete response (CR) was defined as the disappearance of all clinical evidence of tumors without new lesions for more than 4 wk. A partial response (PR) required 50% decrement in the maximal perpendicular tumor measurements, with no new lesion for at least 4 wk. No change (NC) was defined as less than 50% reduction and less than 25% increase of a measurable tumor lesion. A progressive disease (PD) was defined as more than 25% increase of measurable tumor lesions or new lesions. Response rate of the patients included CR and PR.

For the evaluation of changes in the main symptoms, 1 to 2 symptoms that were relevant to tumors and reflected the main suffering were used. It was classified into the following results: amelioration (remission of main symptoms and lasted for at least 4 wk), stableness (no changes in the main symptoms and lasted for at least 4 wk) and deterioration (deterioration in the main symptoms).

For the evaluation of toxic and side effects of chemotherapy in the two groups, hematologic test and gastrointestinal response during the treatment period were observed. Toxic and side effects of chemotherapy were classified according to the common criteria. Routine tests of blood, urine, stool, hepatic function, renal function and electrocardiogram were performed before and after each chemotherapeutic cycle and routine test of blood was re-examined on the 3rd, 7th, 10th and 14th chemotherapeutic cycle days, respectively. The most severe side effect was observed as the final outcome to reflect toxic response degree. KPS was estimated prior to treatment and recorded as it was improved, stable, or deteriorated after treatment. The standard was described as follows: improvement that means KPS score was larger than or equal to 10 and lasted for at least 4 wk, stableness that means no changes in KPS score and lasted for at least 4 wk, deterioration that means KPS score was less than 10.

### *Assay of CD3, CD4, CD8 and sIL-2R*

Direct immunofluorescence labeling with flow cytometer was used to detect the subtype of T lymphocytes in peripheral blood following the instructions of the kits. An enzyme-linked immunosorbent assay was used to determine sIL-2R according to the protocols of kits. Plates were coated with sheep anti-human sIL-2R antibody. Each serum was tested at a dilution of 1:1 000. At the same time, one positive control, two negative controls and one blank were included.

### *Statistical analysis*

Data were expressed as mean±SD. Comparison of data between two groups was made by chi-square test. Comparison of the measurement data between experiment groups was made by the paired and unpaired Student's *t* test. $P<0.05$ was considered statistically significant.

## RESULTS

### *Clinical benefit of FZYLD combined with chemotherapy*

Effective rate (CR+PR) in the treatment group (8/23) was higher than that in the control group (5/23), but there was no difference in statistics. PD in the treatment group (2/23) was significantly lower than that in the control group (8/23) ($P<0.05$). The improvement rate of main symptoms in the treatment group (16/23) was significantly higher than that in the control group (8/23) ($P<0.05$). The deterioration rate of main symptoms in the treatment group (1/23) was markedly lower than that in the control group (6/23) ($P<0.05$). In FZYLD treatment group, KPS improved in 56.7% (17/30) cases, which was higher than that in the control group (26.7%, 8/30) ($P<0.05$), whereas KPS decreased in 6.61% (2/30) cases, which was markedly lower than that in the control group (26.7%, 8/30) ($P<0.05$).

There was no difference in bone marrow depression between the treatment group (16/30) and control group (21/30). The incidence of grade II bone marrow depression in the treatment group (4/30) was markedly lower than that in the control group (11/30) ($P<0.05$). The incidence of grade II nausea

**Table 1** Changes of immunological function in two groups of patients (mean±SD)

| Group | Case | $CD3^+$ (%) | $CD4^+$ (%) | $CD8^+$ (%) | $CD4^+/CD8^+$ | $_S$IL-2R (U/mL) |
|---|---|---|---|---|---|---|
| Treatment group | 30 | | | | | |
| Pre- | | 62.25±10.01[a] | 36.83±10.44[b] | 33.06±7.69[b] | 1.24±0.65[a] | 588.23±216.86[b] |
| Post- | | 68.31±9.72[c] | 42.6±9.62[c] | 29.24±6.25 | 1.66±0.85[c] | 475.87±211.36[c] |
| Control group | 30 | | | | | |
| Pre- | | 64.22±6.91[a] | 35.62±7.49[a] | 32.95±8.28[a] | 1.17±0.43[b] | 573.63±214.32[b] |
| Post- | | 60.63±5.75[c] | 31.53±5.53[c] | 37.14±7.48[c] | 0.94±0.43[c] | 692.17±221.33[c] |
| Normal | 15 | 68.72±5.66 | 47.22±8.39 | 26.18±5.64 | 1.83±0.22 | 143.58±23.05 |

[a]$P<0.05$, [b]$P<0.01$ *vs* normal control group; [c]$P<0.05$ *vs* pre-treatment.

and vomiting in the treatment group (9/30) was significantly lower than that in the control group (19/30) ($P<0.05$). No patient had diarrhea greater than grade II in the treatment group and one patient in the control group suffered from grade III diarrhea. The incidence of diarrhea in the treatment group (4/30) was lower than that in the control group (11/30) ($P<0.05$).

### *Changes of immunological function in two groups of patients*

As shown in Table 1, the proportion of $CD3^+$ and $CD4^+$ cells was lower, and that of $CD8^+$ cells was higher than that in the normal control group before treatment ($P<0.05$). The ratio of $CD4^+/CD8^+$ decreased in cancer patients. The content of sIL-2R increased obviously. After chemotherapy, the proportion of $CD3^+$ and $CD4^+$ cells and the ratio of $CD4^+/CD8^+$ further decreased, and the content of sIL-2R increased. In the FZYLD treatment group, the ratio of $CD4^+/CD8^+$ increased and the concentration of sIL-2R decreased.

## DISCUSSION

FZYLD is mainly composed of Huangqi (*radix astragali*), Baizhu (largehead atractylodes rhizome), Ezhu (*radix notogenseng*), Baihuasheshecao (*herba hedyotis diffusae*) and Shishangbo (*selaginellae doederleinii herba*). In this experiment, FZYLD combined with chemotherapy could improve the tumor recent remission rate and decrease the deterioration of cancer patients. Previous researches have proved that some herbs in FZYLD could kill tumor cells directly[7]. Other than that in its direct anti-tumor effects, *radix astragali, largehead atractylodes rhizome* and *radix notogenseng* could enhance the action of immunity[8]. We suppose that FZYLD might possess anti-inflammatory effects, which could promote gastrointestinal vermiculation and improve immune functions and adrenal cortex to mitigate clinical symptoms of tumors.

In theory of TCM, toxic effects on digestive tract and bone marrow depression induced by chemotherapy are due to the fact that drugs could impair appetite, and cause Qi and blood deficiency. In our experiment, FZYLD could relieve the toxic effect on digestive tract and bone marrow depression induced by chemotherapy obviously. We suggest that FZYLD takes effects of "nourishing Qi and invigorating spleen, expelling toxin cooling". At the same time, it was reported that some components in FZYLD could protect and promote the hemopoietic function of human beings[9].

At present, there is no generally accepted definition about the quality of life. Generally, qualities of life mainly include somatic function, emotion, psychological function and social role. At the same time, syndromes and physical signs caused by diseases and treatment are also important components in the life qualities of cancer patients[10]. Methods for physical strength score evaluation, such as KPS, have been widely used to evaluate the life qualities of cancer patients[11,12]. Our study demonstrated that FZYLD could improve the performance status of patients by increasing the therapeutic effects and reducing the side effects of chemotherapy. As a result, the confidence of cancer patients improved, thus having optimistic emotions, and improving their qualities of life.

T lymphocytes are important immunoloregulation and effector cells. It is believed that detection of subtype of T lymphocytes in peripheral blood is important for evaluating the immunological status, effect of treatment and prognosis of cancer patients[13,14]. There are binding sites of IL-2 in sIL-2R, which can competitively bind IL-2 when its concentration increases. As a result, IL-2 dependent lymphocyte proliferating effects are inhibited. It was reported that concentrations of sIL-2R in peripheral blood increased obviously in patients suffering from various cancers, and increased progressively accompanied by disease progress and transfer of tumors[15,16]. In this experiment, we found that there were disorders in the ratio of T lymphocyte subtypes and a high concentration of sIL-2R in all the patients compared with healthy people, and FZYLD could reverse this tendency, suggesting that FZYLD can reduce the immunosuppression induced by chemotherapy.

Previous studies reported that some herbs in FZYLD could improve immunity of patients[17]. Especially, *membranous milkvetch root* used in FZYLD was 60 g, which was larger than that in the other TCM prescriptions. *Membranous milkvetch root* could improve the function of T-cells not only in normal healthy persons but also in patients with immunosuppression[4]. It could also improve the activity of IL-2 in the model mice with spleen deficiency induced by *rhubarb*[18]. In malignant tumor patients, it could improve the cell number of $CD4^+$ and down-regulate the cell number of $CD8^+$[4]. All these researches show that *membranous milkvetch root* possesses versatile positive regulatory effects on immunological functions. Furthermore, saponin in the *root of pseudo-genseng* and *large-head atractylodes rhizome* could improve phagocytic functions of the reticuloendothelial system, transformation efficiency of lymphocytes and rate of E-rosette formation[9,19].

Based on the results from our experiment, it is concluded that FZYLD can enhance the therapeutic effects of chemotherapy on malignant tumors of the digestive tract, and reduce the toxic and side effects of chemotherapy on bone marrow and digestive tract. It also can improve the life quality and cellular immunity of patients with malignant tumors.

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