Journal of Hainan Medical University

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Effect of S−1 combined with oxaliplatin on serum tumor markers, matrix metalloproteinase and immune function in elderly patients with gastric cancer

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ARTICLE INFO

Article history:
Received 27 Sep 2017
Received in revised form 30 Sep 2017
Accepted 3 Oct 2017
Available online 14 Oct 2017

Keywords:
S-1
Oxaliplatin
Gastric cancer
Tumor marker
Matrix metalloproteinase
Immune function

ABSTRACT

Objective: To investigate the effect of Compound Tegafur and Oteracil Potassium Sustained Capsules (S-1) combined with oxaliplatin chemotherapy on serum tumor marker matrix metalloproteinase and immune function in elderly patients with gastric cancer. **Methods:** According to the random data table, 80 cases of elderly patients with gastric cancer were divided into control group and observation group (n=40), patients in the control group were treated with oxaliplatin combined with Capecitabine Tablets, and the observation group patients were treated with S-1 combined with oxaliplatin, all treated for 6 cycles, before and after treatment, levels of serum tumor markers, matrix metalloproteinase and immune function were compared between the two groups. **Results:** Before treatment, there was no significant difference in the levels of CEA, CA125, CA19-9, MMP-2, MMP-9, $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ between the two groups; After treatment, the levels of CEA, CA125, CA19-9, MMP-2, MMP-9 and $CD8^+$ in the two groups were significantly lower than those in the same group before treatment, and the levels of the observation group[(7.79±2.78) ng/mL, (22.56±7.31) U/mL, (13.48±3.05) U/mL, (57.84±8.93) ng/mL, (199.14±67.39) ng/mL and (26.21±4.18)%] were significantly lower than those in the control group; Compared with the group before treatment, the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in the two groups were significantly increased, and the observation group [(66.89±5.84)%, (41.63±5.24)% and (1.37±0.29)] was significantly higher than the control group. **Conclusion:** S-1 combined with oxaliplatin chemotherapy can effectively reduce serum tumor markers and matrix metalloproteinase levels, improve immune function, has an important clinical value.

1. Introduction

Gastric cancer is a common malignant tumor of digestive tract. Its incidence and fatality rate are very high and the risk of gastric cancer is increasing year by year[1]. Combined therapy with surgery and chemotherapy is the standard therapy for gastric cancer, but because after early gastric cancer without typical symptoms, most patients with advanced stage at diagnosis, after treatment, the recurrence rate and metastasis risk are higher after operation, so chemotherapy is the key to comprehensive treatment of gastric cancer[2]. Fluorouracil is the main treatment for gastric cancer , for the new type of fluorouracil chemotherapy drugs in the treatment of gastric cancer has achieved good results[3,4]. In this study, serum tumor markers, matrix metalloproteinases and immune function of three aspects, in order to clear the combination of tiaglio and oxaliplatin chemotherapy in elderly patients with gastric cancer.

2. Materials and methods

2.1. Clinical data

A total of 80 elderly patients with gastric cancer admitted to Wuxi Fifth People's Hospital from March 2015 to March 2017 were enrolled in this study. According to the random data table, they were divided into the control group and the observation group, each with 40 cases. The study conforms to the hospital ethics committee criteria and is granted after approval. In the control group, there

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Fund Project: Jiangsu Provincial Health Department of Key Disciplines in the Province Open Subject; (No.: KF201512).

were 24 male patients and 16 female patients. The age was 61-79 years. Pathological stage: stage II A 12 cases, stage II B 7 cases, stage III A 10 cases, stage III B 8 cases, stage III C 3 cases. The observation group consisted of 25 males and 15 females, aged 60-78 years. Pathological stage: stage II A stage 13, stage II B 7, stage III A 11, stage III B 7, stage III C 2. There was no significant difference between the two groups in general data (P>0.05).

2.2. Screening criteria

In the standard: (1) all patients diagnosed by endoscopy, CT, MRI and pathological examination, in line with the diagnosis of gastric cancer-related criteria[5]; (2) age≥60 years; (3) liver and kidney function and ECG and other laboratory tests were no significant abnormalities; (4) All patients with clinical data is complete, patients and their families are informed consent.

Exclusion criteria: (1) accompanied by severe acute and chronic infectious diseases, mental illness; (2) allergic patients, the presence of contraindications to chemotherapy drugs; (3) poor compliance with treatment, failed to complete the treatment by treatment, half-way off their own cases; (4) Liver, heart and other important organ dysfunction patients; (5) recent use of immunomodulators and other indicators of the impact of drugs; (6) clinical data incomplete.

2.3 Treatment

The control group were treated with Capecitabine Tablets (Shiroda, Shanghai Roche Pharmaceutical Ltd, Zhunzi H20073024, size 0.5 g 12 s) oral treatment, 2 500 mg/m^2 daily, and the two taking half an hour after a meal, taking consecutive 14 D, rest a week, at the same time in the first 1 d intravenous administration of oxaliplatin mannitol injection (Sichuan Oxaliplatin and Mannitol Injection Meida Kang Jiale Pharmaceutical Co. Ltd., Zhunzi H20050141, 100 mL), according to the specifications of a surface area of 130 mg/m^2 administration, 250-500 mL agent dissolved in 5% glucose solution, intravenous infusion of 2-6 h, 21 d as a cycle, 6 cycles of treatment. The patients in the observation group were treated with ticillin and oxaliplatin, in the first 1 d intravenous infusion of oxaliplatin, the same method with the control group, while oral tiggio capsules (Heng Rui, Jiangsu Heng Rui pharmaceutical Limited by Share Ltd, Zhunzi H20100135, size 20 mg 12 s) treatment, 40-60 mg/times, 2 times a day, morning and evening after meals, continuous medication 14 d, rest for a week, with 21 d for a cycle, the treatment time with the control group.

2.4 Index detection

Two groups of patients received early morning fasting peripheral venous blood before and after treatment, centrifuged to take serum, and tumor markers and matrix metalloproteinase (MMPs) levels were measured. Tumor markers including carcinoembryonic antigen index (CEA), carbohydrate antigen 125 (CA125) and carbohydrate antigen 19-9 (CA19-9), matrix metalloproteinase [including matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9)], in which CEA was detected by electrochemical luminescence method, electrochemical detection instrument for light emitting apparatus. MMP-2, MMP-9, CA125 and CA19-9 was detected by ELISA (enzyme linked Shanghai Biological Technology Co. Ltd.); Meanwhile, Backman Kurt automatic biochemical analyzer was used to detect the immune function of patients ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$), and all operations were strictly conducted according to the instructions.

2.5 Statistical processing

The research data by SPSS 17.0 statistical software for processing, serum tumor markers, matrix metalloproteinases and immune function indexes accord with the normal distribution, mean standard deviation (Mean ± SD) said, in and between groups of each index level were compared by t test, P<0.05 said the difference was significant.

3. Result

3.1 Comparison of serum tumor markers

The serum tumor markers CEA, CA125 and CA19-9 before and after treatment were shown in Table 1. The levels of CEA, CA125 and CA19-9 were similar before treatment, the difference was not statistically significant (P>0.05). After treatment, the levels of CEA, CA125 and CA19-9 in the two groups were significantly lower than those before treatment (P<0.05). The levels of CEA, CA125 and CA19-9 in the observation group were (7.79±2.78) ng/mL, (22.56±7.31) U/mL and (13.48±3.05) U/mL, significantly lower than those after treatment in the control group (P<0.05).

Table 1.
Comparison of serum tumor markers level.

Group	n	Treatment time	CEA (ng/mL)	CA125 (U/mL)	CA19-9 (U/mL)
Control group	40	Before treatment	44.35±9.84	74.91±13.32	77.98±17.35
		After treatment	17.95±4.48*	40.89±8.65*	28.91±3.16*
Observation group	40	Before treatment	45.52±10.48	75.41±13.87	78.13±17.91
		After treatment	7.79±2.78$^{*\#}$	22.56±7.31$^{*\#}$	13.48±3.05$^{*\#}$

Note: Compared with before treatment, $^*P$<0.05; compared with after treatment, $^\#P$<0.05.

Table 2.
Comparison of matrix metalloproteinase levels.

Group	n	Treatment time	MMP-2 (ng/mL)	MMP-9 (ng/mL)
Control group	40	Before treatment	117.09±12.21	407.33±108.95
		After treatment	81.68±10.49*	292.17±94.38*
Observation group	40	Before treatment	115.32±13.77	409.96±119.23
		After treatment	57.84±8.93*#	199.14±67.39*#

Note: Compared with before treatment, *P<0.05; compared with after treatment, #P<0.05.

Table 3.
Comparison of immune function between the two groups.

Group	n	Treatment time	CD3+ (%)	CD4+ (%)	CD8+ (%)	CD4+/CD8+
Control group	40	Before treatment	53.36±5.26	29.07±4.42	36.83±6.29	1.03±0.31
		After treatment	59.27±5.64*	34.07±5.29*	32.78±3.74*	1.23±0.44*
Observation group	40	Before treatment	53.17±5.02	28.98±4.34	36.57±6.09	1.02±0.37
		After treatment	66.89±5.84*#	41.63±5.24*#	26.21±4.18*#	1.37±0.29*#

Note: Compared with before treatment, *P<0.05; compared with after treatment, #P<0.05.

3.2 Comparison of matrix metalloproteinase levels

The results of two groups of matrix metalloproteinase levels are shown in Table 2. There was no significant difference in MMP-2 and MMP-9 levels between the two groups before treatment (P>0.05). After treatment, the levels of MMP-2 and MMP-9 in the two groups were significantly lower than those before treatment (P<0.05), and the level of MMP-2 and MMP-9 in the observation group after treatment was significantly lower than that in the control group after treatment (81.68±10.49) ng/mL, (199.14±98.39) ng/mL, (292.17±94.38) ng/mL, the difference was statistically significant (P<0.05).

3.3 Comparison of two groups of immune function

The levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ before and after treatment were shown in Table 2 (P>0.05). Before treatment, there was no significant difference in the levels of $CD3^+$, $CD4^+$, $CD8^+$ and CD4+/CD8+ between groups (P>0.05), after treatment, the two groups were significantly higher than the group before treatment, and the level of the observation group was significantly higher than that of the control group (P<0.05); The levels of $CD8^+$ in the observation group and the control group were (26.21±4.18)% and (32.78±3.74)%, respectively, significantly lower than in group before treatment, and the level of the observation group was significantly lower than that of the control group (P<0.05).

4. Discussion

Epidemiological studies of gastric cancer pointed out that the new incidence and mortality rates of global gastric cancer in 2012 were ranked fifth and third in malignant tumors, of which 70% of new patients from developing countries, mostly in China[6]. In China, the incidence of gastric cancer and mortality in 2015 were 15.8% and 17.6%, ranking second in malignant tumors[7]. The incidence and mortality of gastric cancer increased with age, and men were higher than women, the incidence of significant regional differences, environmental factors in which plays an important dominant position[8]. Studies have shown that the occurrence of gastric cancer is closely related to helicobacter pylori infection, diet, smoking, and host genetic susceptibility[9]. In recent years, with the aging of the population and lifestyle changes, the incidence of gastric cancer showed an upward trend, a serious threat to human health. How to extend the survival of patients, improve the quality of life, is the focus of the current study. Related research shows that effective chemotherapy can improve patient survival and quality of life, is the main means of treatment of gastric cancer[10].

At present, the commonly used chemotherapy drugs of gastric cancer mainly include fluorouracil, platinum and taxane, and more commonly used chemotherapy regimen. It is pointed out that the combined chemotherapy regimen with fluorouracil and platinum chemotherapeutic drugs can effectively improve the therapeutic effect of gastric cancer, prolong the survival of patients, but the occurrence of adverse drug reactions tend to reduce the life quality of patients[11,12]. Oxaliplatin is a broad spectrum of anti-cancer activity of the drug, can quickly combine with DNA, and the adverse drug reactions is smaller. Capecitabine is a fluorouracil deoxynucleoside carbamate antimetabolite, which has a strong inhibitory effect on cell division, RNA and protein synthesis. Compared with other fluorouracil drugs, the effect on the normal tissue cells is smaller[13]. The study found that capecitabine and oxaliplatin combined with chemotherapy in the treatment of advanced gastric cancer significantly, can effectively reduce the level of serum tumor markers in patients[14,15]. Tiggio is a complex preparation composed of fluorouracil precursor for fluoride, gemcopyrimidine and otializine potassium. It has the advantages of good bioavailability, long duration of action, good patient tolerance and high safety[16]. This study was designed to investigate the efficacy of tiggio combined with oxaliplatin in elderly patients with gastric cancer.

CEA, CA125 and CA19-9 are important indexes in the diagnosis, curative effect and prognosis of gastric cancer. CEA is expressed in a variety of malignancies, especially in patients with gastrointestinal cancer. The level of CEA is often accompanied by local progression or distant metastasis rise. CA125 is also a multi-cancer tumor markers, the most widely used in ovarian epithelial tumors, recent years research found that whch in patients with gastric cancer serum levels have increased[17]. CA19-9 is a highly specific digestive tumor antigen, with the tumor development and high expression, can be used as an independent indicator of gastric cancer indicators[18]. This study found that both chemotherapy regimens were able to effectively reduce the level of serum tumor markers in patients, and tiggio combined with oxaliplatin group is more significant,

indicating that the two programs are effective treatment of elderly patients with gastric cancer, and relative to capecitabine, the efficacy of tiggio may be better, which may be related to the composition of the superimposed antitumor effect, the specific reason remains to be further explored.

Studies have shown that matrix metalloproteinases can degrade proteins in the extracellular matrix and play an important role in tumor metastasis and infiltration, with a significant positive correlation with tumor malignancy and invasive ability[19]. MMP-2 and MMP-9 are two important factors in the matrix metalloproteinase family and have become potential markers for assessing tumor malignancy and invasive ability[20]. The results of this study suggest that tiggio combined with oxaliplatin regimen can further reduce the levels of MMP-2 and MMP-9 in patients with gastric cancer, indicating that combined chemotherapy regimens can reduce the degradation of tumor cells around the outer matrix and basement membrane, and thus inhibit the malignant tumor transfer and invasion.

In the process of tumorigenesis and development, the immune function plays an important role in which T lymphocyte-mediated cellular immunity is particularly important[21]. Studies have shown that the immune function of tumor patients is inhibited. compared with normal healthy subjects, $CD3^+$ and $CD4^+$T cells decrease, $CD8^+$T cells increase and $CD4^+/CD8^+$ levels decrease significantly[22,23]. This study found that tiggio combined with oxaliplatin regimen to further improve cellular immune function, significantly better than capecitabine and oxaliplatin combination program, may be associated with a large number of tumor cells after chemotherapy to reduce the immune system to reduce the immune, it is of important value i on the immune system reconstruction, tumor immune surveillance recovery and improvement etc[24].

In summary, tiggio combined with oxaliplatin chemotherapy in the treatment of elderly patients with gastric cancer can effectively reduce the serum tumor markers and matrix metalloproteinase levels in patients with improved immune function, has important clinical value.

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