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Original Article

Effects of Tegafur, Gimeracil and Oteracil Potassium Capsules combined with Calf Spleen Extractive Injection on serum VEGF and MMP-9 in patients with advanced gastric cancer

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Abstract: Objective: To explore the effects of Tegafur, Gimeracil and Oteracil Potassium Capsules (TGOPC) combined with Calf Spleen Extractive Injection (CSEI) on vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) in patients with advanced gastric cancer. Methods: A retrospective analysis was conducted on data of 118 patients with advanced gastric cancer treated in Anyang Tumor Hospital from January 2016 to September 2018. The patients were divided into two groups according to treatment modalities, with control group receiving Oxaliplatin and TGOPC and observation group receiving Oxaliplatin, TGOPC and CSEI. Clinical efficacy, changes of serum VEGF and MMP-9 before and after chemotherapy, survival rate and incidence of adverse reactions were compared between the two groups. Results: The number of responded patients was 36 (61.02%) in the observation group and was 18 (30.51%) in the control group ($P<0.05$). The levels of serum VEGF and MMP-9, and incidence of nausea and vomiting in the observation group were lower than those in the control group ($P<0.05$). The 1-year and 2-year survival rates in the observation group were higher than those in the control group ($P<0.05$). Conclusion: The use of CSEI on the basis of Oxaliplatin combined with TGOPC chemotherapy for the treatment of advanced gastric cancer could further improve the clinical efficacy and survival rate, and reduce the incidence of adverse reactions.

Keywords: Advanced gastric cancer, Oxaliplatin, Tegafur, Gimeracil and Oteracil Potassium Capsules, Calf Spleen Extractive Injection, vascular endothelial growth factor, matrix metalloproteinase-9

Introduction

Clinically, gastric cancer is a malignant tumor of the digestive system with high incidence, and if the cancerous tissue has invaded the serosal and the muscle layers, it is defined to be at an advanced stage regardless of the size and metastasis of the lesion [1, 2]. Although surgery is the main clinical treatment for gastric cancer, the rate of distant metastasis and local recurrence remains high after aggressive surgical treatment [3, 4].

Clinical studies have shown that preoperative neoadjuvant chemotherapy can improve the survival rate of patients with advanced gastric cancer, among which Oxaliplatin combined with Tegafur, Gimeracil and Oteracil Potassium Capsules (TGOPC) is a common chemotherapy method [5, 6]. Calf Spleen Extractive Injection (CSEI) is an extract from the spleen of healthy cows (within 24 h of birth), with ribose and active peptides as its main components, can promote the body's immunity, inhibit tumor growth and promote the survival of patients [7, 8]. Serum matrix metalloproteinase-9 (MMP-9) is closely related to tumor metastasis and invasion, while vascular endothelial growth factor (VEGF) can induce endothelial cell proliferation and promote tumor angiogenesis. MMP-9 and VEGF have a certain correlation in the development of tumorigenesis [9, 10]. To further im-

prove the prognosis and increase the survival rate of patients with advanced gastric cancer, this study used CSEI combined with Oxaliplatin + TGOPC chemotherapy to treat patients.

This study specifically analyzed the effects of CSEI combined with Oxaliplatin + TGOPC chemotherapy on serum VEGF and MMP-9 levels, thereby providing more evidence for effective and safe treatments for advanced gastric cancer.

Materials and methods

Baseline data

A retrospective analysis was performed on data of 118 patients with advanced gastric cancer treated in Anyang Tumor Hospital from January 2016 to September 2018, and they were divided into two groups based on treatment modalities. Control group included 59 patients treated with Oxaliplatin + TGOPC chemotherapy, with 39 males and 20 females aged 35-75 years old. Observation group included 59 patients treated with additional CSEI on the basis of the regimen in the control group, with 37 males and 22 females aged 36-74 years old. Inclusion criteria: patients with stage III and IV gastric cancer confirmed by gastroscopic examination; patients with no contraindication to chemotherapy and surgery. Exclusion criteria: patients in lactating or pregnant; patients with myeloproliferative disorder; patients with abnormal liver or renal function. The approval of this study was obtained from the medical ethics committee of Anyang Tumor Hospital (No. NCT01536842).

Methods

The control group was treated with Oxaliplatin combined with TGOPC chemotherapy. Patients were given 40 mg/m^2 TGOPC capsules (H20-080803, Shandong New Age Pharmaceutical Co., specification: 25 mg × 6 capsules × 2 packs) orally, once in the morning and once in the evening for 14 d. In addition, 130 mg/m^2 Oxaliplatin (H20064296, Jiangsu Oxycon Pharmaceutical Co., specification: 50 mg/dose) dissolved in 500 mL of 5% glucose solution (H21023924, Shenyang Zhiying Pharmaceutical Co., Ltd., specification: 500 mL:25 g) was infused intravenously within 2 h on day 1 of each cycle. With 21 d as a cycle, 2 cycles of treatment were performed in total.

In the observation group, additional CSEI was given on the basis of the treatment in the control group. Patients were given intravenous infusion of CSEI (H22026121, Jilin Aodong Taonan Pharmaceutical Co., Ltd., specification: 2 mL × 2 doses), 8 mL/d, for consecutive 10 d. With 21 d as a cycle, 2 cycles of treatment were performed.

Outcome measurement

The primary indicators included efficacy, survival rate, serum VEGF and MMP-9 levels, and the secondary indicators included the incidence of adverse reactions and quality of life.

(1) Efficacy. Based on the efficacy criteria of World Health Organization (WHO) for solid tumors [11, 12], the clinical efficacy can be determined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Overall response (OR) = CR + PR.

(2) Serum VEGF and MMP-9 levels. Before and after treatment, 2 mL of fasting elbow venous blood was collected in the morning and placed in non-anticoagulant tubes at room temperature for 30-60 min, and then centrifuged for 10 min at 3500 r/min. Serum VEGF and MMP-9 levels were measured by enzyme linked immunosorbent assay in accordance with the kit instruction. The kit was supplied by Shanghai Enzyme-linked Biotechnology Co., Ltd., batch number: 2012-03-12.

(3) Survival rate: The 1-year and 2-year survival rates of the two groups were analyzed.

(4) Incidence of adverse reactions: The occurrence of adverse reactions was determined strictly according to the WHO criteria for adverse reactions [13, 14], where degree 0-II was considered as mild adverse reactions and degree III-IV as severe adverse reactions.

(5) Quality of life: Before and after treatment, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) was used to evaluate the quality of life in both groups, including five functional scales: social (2 items),

Table 1. Comparison of baseline data [n (%)]/($\bar{x}$ ± s)

Data		Observation group (n = 59)	Control group (n = 59)	t/χ^2	*P*
Sex (cases)	Male	37 (62.71)	39 (66.10)	0.148	0.701
	Female	22 (37.29)	20 (33.90)		
Age (years)		59.96±5.18	59.62±5.15	0.358	0.721
TNM Staging					
IIIA		28 (47.46)	30 (50.85)	0.142	0.931
IIIB		20 (33.90)	19 (32.20)		
IV		11 (18.64)	10 (16.95)		
Degree of pathological differentiation					
Moderately differentiated		26 (44.07)	27 (45.76)	0.317	0.957
Lowly differentiated		24 (40.68)	23 (38.98)		
Mucinous adenocarcinoma		7 (11.86)	6 (10.17)		
Indolent cell carcinoma		2 (3.39)	3 (5.08)		

Table 2. Comparison of clinical efficacy [n (%)]

Group	Number of cases	CR	PR	SD	PD	OR
Control group	59	0 (0.00)	18 (30.51)	21 (35.59)	20 (33.90)	18 (30.51)
Observation group	59	2 (3.39)	34 (57.63)	13 (22.03)	10 (16.95)	36 (61.02)
χ^2						11.063
P						0.001

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; OR: Overall Response.

emotional (4 items), cognitive (2 items), role (2 items) and physical (5 items), each of which was evaluated on a 4-point Likert scale, with total scores ranging from 15 to 60 points. The quality of life was proportional to the scores.

Statistical methods

Statistical Package for Social Science (SPSS) 22.0 was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (SD), and for data conforming to a normal distribution, independent sample *t* test was performed for inter-group comparison, and paired *t* test for intra-group comparison before and after treatment. Counting data [n (%)] were compared by χ^2 test. $P<0.05$ indicated statistical significance.

Results

Comparison of baseline data

There was no significant difference in baseline data such as sex, mean age, TNM stage, and degree of pathological differentiation between the two groups ($P>0.05$) (**Table 1**).

Comparison of clinical efficacy

The number of responded patients was 36 (61.02%) in the observation group and was 18 (30.51%) in the control group, showing statistically significant difference in the total treatment efficacy between the two groups ($P<0.05$) (**Table 2**).

Comparison of serum VEGF and MMP-9 levels

No significantly difference was observed in serum VEGF and MMP-9 levels between the two groups before chemotherapy ($P>0.05$). Compared with the before treatment, serum VEGF and MMP-9 levels were significantly reduced in both groups after treatment ($P<0.05$). Moreover, the post-treatment serum VEGF and MMP-9 levels in the observation group were significantly lower than those in the control group ($P<0.05$) (**Figure 1**).

Comparison of survival rate and incidence of adverse reactions

The 1-year survival rate of patients in the observation was 88.14% (52/59), higher than 64.40% (38/59) in the control group, and the

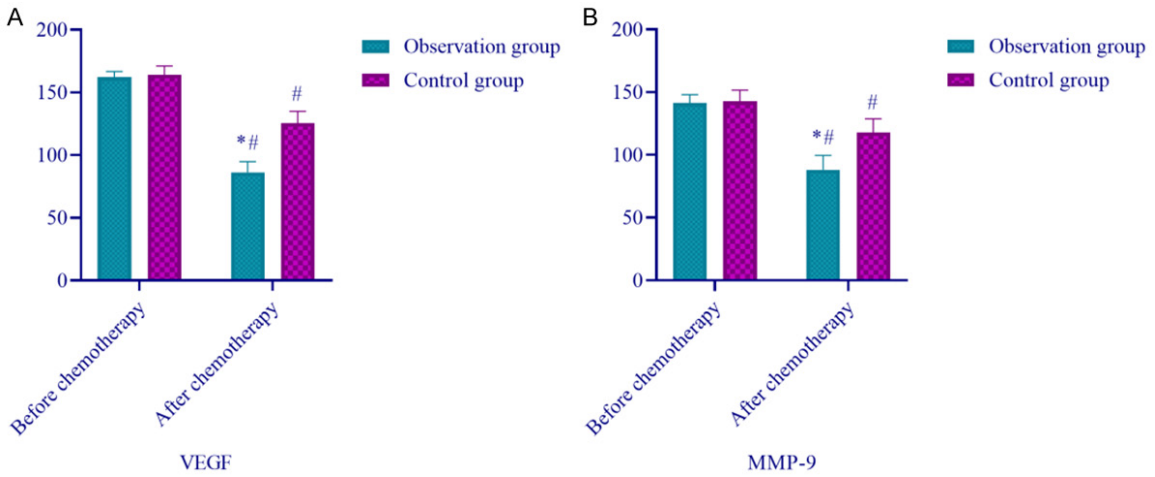

Figure 1. Comparison of serum VEGF and MMP-9 levels between the two groups. A: VEGF, Vascular Endothelial Growth Factor; B: MMP-9, Matrix Metalloproteinase-9. Compared with the control group, *P<0.05; compared with before chemotherapy, #P<0.05.

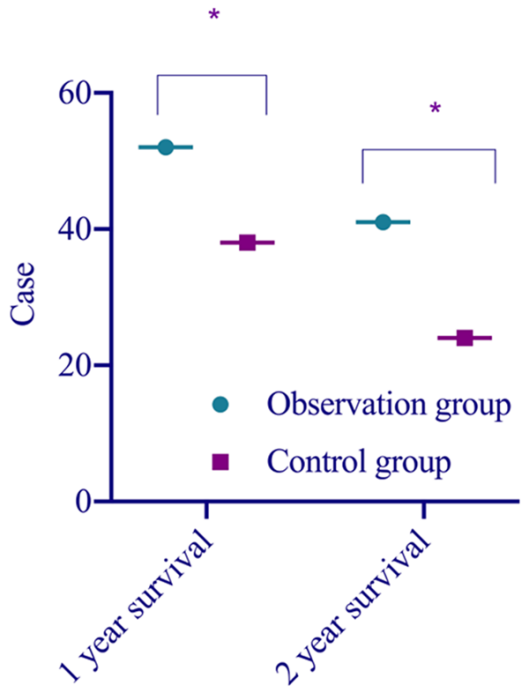

Figure 2. Survival rates of patients in the two groups. Compared with the control group, *P<0.05.

2-year survival rate in the observation group was 69.49% (41/59), higher than 40.68% (24/59) in the control group (χ^2 = 6.141, 6.661, P<0.05) (**Figure 2**). No significant difference was found in the incidence of abnormal liver function, decreased red blood cells, reduced platelets and diarrhea between the two groups (P>0.05), and the incidence of nausea and vomiting in the observation group was lower than that in the control group (P<0.05) (**Table 3**).

Comparison of quality of life

No significantly difference was observed in quality of life scores (social, emotional, cognitive, role and physical functional scales) between the two groups before chemotherapy (P>0.05). After treatment, the scores of the five functional scales were significantly increased in both groups (P<0.05), and in increases in the observation group were more significant than those in the control group (P<0.05) (**Figure 3**).

Discussion

Clinically, advanced gastric cancer refers to the tumor breaking through the submucosa layer and invading the serosal layer and the muscular layer of the stomach wall, with or without metastasis [15, 16]. Chemotherapy is a common clinical treatment for advanced gastric cancer. Although this treatment can kill tumor cells, it also damages normal tissues to a certain extent and reduce the body's immunity [17-19].

Studies have shown that the immune enhancers combined with chemotherapy can not only effectively kill tumor cells, but also enhance the immunity, thus effectively guaranteeing the quality of life of patients [20, 21]. TGOPC is a 5-fluorouracil anticancer drug composed of

Table 3. Comparison of the incidence of adverse reactions [n (%)]

Group	Number of cases	Grade	Abnormal liver function	Red Blood Cell Decline	Decreased platelets	Diarrhea	Nausea and vomiting
Observation group	59	Class I-II	7 (11.86)	13 (22.03)	16 (27.12)	3 (5.08)	17 (28.81)
		Class III-IV	0 (0.00)	1 (1.69)	0 (0.00)	0 (0.00)	4 (6.78)
Control group	59	Class I-II	6 (10.17)	19 (32.20)	8 (13.56)	9 (15.25)	31 (52.54)
		Class III-IV	0 (0.00)	3 (5.08)	0 (0.00)	0 (0.00)	19 (32.20)
		$\chi^2/P_{\text{Class I-II}}$	0.086/0.768	1.544/0.214	3.348/0.067	3.340/0.067	6.883/0.009
		$\chi^2/P_{\text{Class III-IV}}$	-	1.035/0.309	-	-	12.151/0.004

Note: "-" means none.

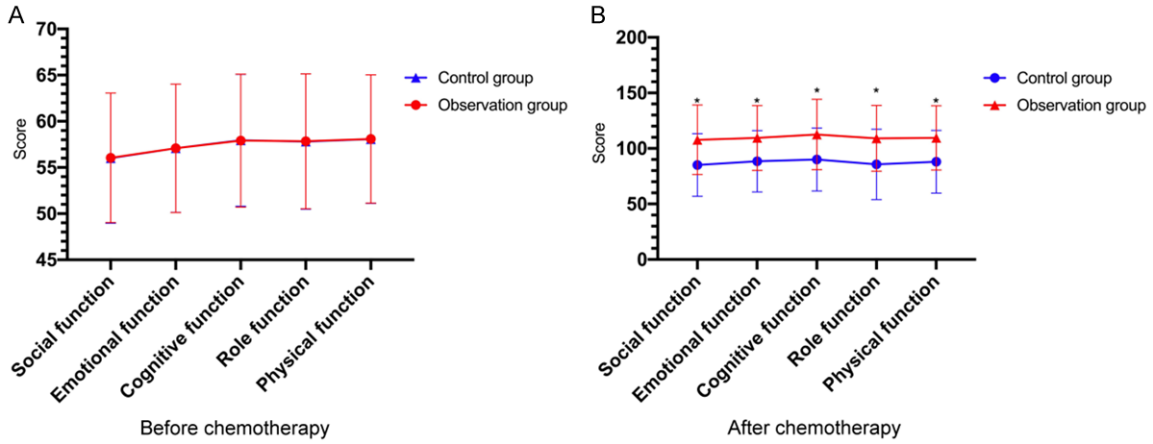

Figure 3. Comparison of quality of life between the two groups. A: Quality of life before chemotherapy; B: Quality of life after chemotherapy. Compared with the control group, *P<0.05.

Oteracil Potassium, Gimeracil and Tegafur, of which Gimeracil inhibits the catabolism of 5-fluorouracil, thus ensuring consistent blood levels with continuous intravenous dosing after oral administration [22, 23]. Oteracil Potassium inhibits orotate phosphoribosyltransferase in intestinal mucosal cells, blocks 5-fluorouracil phosphorylation and reduces its gastrointestinal toxicity [24].

In this study, the OR rate in the observation group was 61.02%, higher than 30.51% in the control group (P<0.05). The 1-year and 2-year survival rates of patients in the observation group were 88.14% and 69.49%, respectively, which were higher than those of the control group (P<0.05). This suggested that CSEI combined with Oxaliplatin and TGOPC could further improve the clinical efficacy and prolong the survival of patients. Zhang et al. [25] also found that the OR rate of patients with combined treatment of TGOPC and CSEI was 62.5%, significantly higher than that in patients received TGOPC alone (32.5%), which is highly consistent with the results of this study. CSEI is an extract from the fetal bovine spleen, with small molecule peptides as the main active ingredient, which inhibits the glycolysis of tumor cells, induces an impairment of energy metabolism, and blocks the cells in the G0/G1 phase, thus effectively playing an anti-tumor role [7]. Moreover, CSEI can also activate the non-specific immune function, enhance the activity of T-lymphocyte and improve the immunity of the body. It can also promote the proliferation of bone marrow stem cells, enhance hematopoietic function, increase the number of peripheral blood cells and reduce adverse reactions of chemotherapy drugs such as blood cytopenia and impaired immune function. In this study, the incidence of nausea and vomiting was lower in the observation group than that in the control group (P<0.05), which may be attributed to the pharmacological effect of CSEI.

VEGF and MMP-9 both play a crucial role in tumor angiogenesis. MMP-9 is mainly secreted and synthesized by tumor cells, macrophages,

connective tissue cells and endothelial cells, and it plays an important role in extracellular matrix (ECM) metabolism, promoting the degradation of type IV collagen [26, 27]. MMP-9 usually exists in the form of proenzyme and is inactive. Under some pathological conditions, MMP-9 can be activated, together with other members of matrix metalloproteinase family, to regulate the metabolism of the ECM. MMP-9 promotes the degradation of elastin, as well as type V and type IV collagen, thus triggering the breakthrough of the basement membrane of tumor cells to invade into lymphatics and blood vessels, and eventually resulting in metastasis. VEGF induces tumor angiogenesis and is highly expressed in a variety of paraneoplastic tissues and cancers. In this study, compared with those in the control group, the levels of serum VEGF and MMP-9 were lower in the observation group after chemotherapy ($P<0.05$), suggesting that the anti-tumor effect of CSEI is satisfactory. CSEI may exert anti-tumor effects through blocking the formation of vascular tumors and ECM degradation.

However, because of the small number of subjects included in this study, the results obtained cannot provide a large-scale representativeness, so more comprehensive studies need to be conducted in the future. Meanwhile, the effectiveness of TGOPC and CSEI in the treatment of advanced gastric cancer needs to be verified from more aspects, and its specific mechanism of action also needs to be further explored.

In conclusion, CSEI combined with Oxaliplatin and TGOPC could further improve the clinical efficacy and survival of patients, reduce the incidence of adverse reactions, and exerts significant anti-tumor effects, so this combined treatment is worthy of promotion.

Disclosure of conflict of interest

None.

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