Journal of Hainan Medical University

http://www.hnykdxxb.com

Effect of S−1 chemotherapy and FP chemotherapy on prognosis, imaging characteristics and serum marker levels after operation for gastric carcinoma

Qing−Hao Gong, Yi−Ting Cai, Hai−Qun Chen, Chao−Feng Zhang, Gang Dai, Song−Ming Zhu✉

Department of General Surgery, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine Chongming Branch, Shanghai, 202150, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Gastric carcinoma
S-1 chemotherapy
FP chemotherapy
Imaging characteristics

ABSTRACT

Objective: To analyze the effect of S-1 chemotherapy and FP chemotherapy on prognosis, imaging characteristics and serum marker levels after operation for gastric carcinoma. **Methods:** A total of 68 patients with gastric cancer who underwent radical surgery were included in the study and divided into observation group and control group patients (n=34) according to random number table. Control group received FP chemotherapy, observation group received S-1 chemotherapy, and then differences in serum tumor markers, illness-related factors, nutrition indexes and T cell immune function values were compared between two groups. **Results:** After observation group received systematic chemotherapy, serum tumor markers such as MMP-9, MMP-2, MG7-Ag, TSGF, CA72-4, CA19-9, TP and DpD as well as illness-related factors such as DKK1, MK, Leptin, Exosome and OPN were all lower than those of control group (P<0.05); nutrition and cellular immune function indexes such as TP, ALB, PA, $CD4^+$ T and $CD4^+$ T/ $CD8^+$ T values were higher than those of control group and $CD8^+$ T value was lower than that of control group (P<0.05). **Conclusions:** S-1 chemotherapy after operation for gastric carcinoma can inhibit the tumor activity and optimize patients' overall condition, and it has positive clinical significance.

1. Introduction

Appropriate choice of chemotherapy after radical operation for gastric carcinoma is directly correlated with patients′ prognosis, FP chemotherapy is a typical postoperative chemotherapy regimen, but because the dose of 5-fluorouracil (5-FU) is small and the inhibiting effect on tumor is limited, long-term recurrence rate is high[1]. S-1 is a new type of chemotherapy drug for advanced gastric cancer, is a kind of oral fluorouracil derivative anticancer agent, is the combined preparation of Futraful (FT), gimeracil (CDHP) and Oteracil (Oxo), and has positive effect on promoting chemotherapy drug concentration, reducing the side effects of chemotherapy, *etc*[2,3]. In the study, the effect of S-1 chemotherapy and FP chemotherapy on prognosis, imaging characteristics and serum marker levels after operation for gastric carcinoma was mainly analyzed, hereby reported as follows.

2. Materials and methods

2.1. General information

A total of 68 patients with gastric cancer who underwent radical surgery in our hospital from September 2012 to March 2015 were selected as research subjects, inclusion criteria were as follows: (1) histopathologically diagnosed with II (excluding T1), IIIA or IIIB-stage gastric cancer, R0 resection (resection margin tumor cells were negative) after D2 or extended radical operation; (2) without previous history of treatment (with the exception of early primary gastric cancer lesion resection); (3) without the evidence of liver, peritoneum or distant metastasis, no tumor cells in the ascites by cytological analysis testing; (4) the ECOG score 2, and the expected lifetime more than 3 months; (5) signed informed consent,

✉Corresponding author: Song-Ming Zhu, No. 25, Nanmengang Street, Chengqiao Town, Chongming County, Shanghai, 202150, China.
Tel: 021-69691593
Fund project: Foundation for Development of Science and Technology of Chongming County Shanghai No: CKY2013-06.

and willing to accept the clinical trials. Exclusion criteria were as follows: (1) HER-2 positive; (2) having received fluoropyrimidine-type drug treatment within 6 months; (3) having received platinum drug treatment within 12 months; (4) with total previous dose of more than 120mg/m cisplatin; (5)with the history of severe allergic reactions to fluoropyrimidine-type and platinum drugs; (6) with obvious infection or inflammation (body temperature of fever more than 38℃); (7) with more than one kind of tumor at the same time, but with the exception of cured carcinoma in situ or skin cancer; (8) receiving or needing to receive flucytosine, phenytoin or warfarin treatment; (9) couldn't take oral drugs; (10) with mental disorder requiring drug treatment.

Patients were divided into observation group and control group patients (n=34) according to random number table. Control group included 18 male cases and 16 female cases, they were 43-69 years old and the average was (61.83±7.92) years; observation group included 19 male cases and 15 female cases, they were 45-71 years old, the average was (60.73±8.42) years. The two groups showed no significant difference in baseline information (P<0.05), and they were comparable.

2.2. Postoperative chemotherapy

Observation group received postoperative S-1 chemotherapy, specifically as follows: oral administration of S-1 60 mg, 2 times/d, the 1-28 d, 6 weeks as a cycle, a total of four cycles of treamtent. Control group received postoperative FP chemotherapy, specifically as follows: 5-FU 250 mg/m^2, the 1-14 d, continuous intravenous administration by infusion pump; intravenous drip of DDP 8 mg/m^2, the 1-5 d, 21 d as a cycle, a total of four cycles of chemotherapy.

2.3. CT examination

All patients were fasting for 4-6 h before examination, orally took 1 000 mL warm water 10 min before examination, and took supine position during scan. GE lightspeed-16 multi-slice spiral CT machine was used, pipe voltage was set to 120 KV, pipe current was 120 mA, scanning range was plain scan, arteriovenous and venous-phase scanning range included the whole stomach, balanced-phase scanning range was from the dome of diaphragm to the pelvic cavity, scanning slice thickness was 5 mm, and the interval was 5 mm.

2.4. Observation indexes

2.4.1. Tumor markers

A total of 5 mL of fasting venous blood was extracted from patients in the morning after treatment to determine the levels of tumor markers in it, including matrix metalloproteinase-9 (MMP-9), matrix metalloproteinase-2 (MMP-2), MG7-Ag, malignant tumor-specific growth factor (TSGF), carbohydrate antigen 72-4 (CA72-4), carbohydrate antigen 19-9 (CA19-9) and thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DpD).

2.4.2. Serum illness-related factors

RIA method was used to determine serum levels of illness-related factors, including Dickkopf-1 (DKK1), midkine (MK), leptin, exosome and osteopontin (OPN).

2.4.3. Serum nutrition indexes and T cell immune function

Automatic biochemical analyzer was used to determine serum levels of nutrition indicators, including total protein (TP), albumin (ALB) and prealbumin (PA). Enzyme-linked immunosorbent assay was used to determine serum levels of T cell subsets, including $CD4^+$ T and $CD8^+$ T, and their ratio was calculated.

2.5. Statistical methods

SPSS23.0 software was used to input and analyze data, measurement data was by t test, count data was by chi-square test and P<0.05 indicated statistical significant differences.

3. Results

3.1. Tumor markers

It was found out that after observation group received systematic

Table 1
Comparison of serum levels of tumor markers between two groups after treatment (U/mL).

Groups	MMP-9	MMP-2	MG7-Ag	TSGF	CA72-4	CA19-9	TP	DpD
Observation group	12.74±1.69	21.73±3.02	4.73±0.58	83.72±9.12	2.93±0.32	78.14±8.29	9.39±1.15	32.23±5.58
Control group	16.32±1.54	26.88±3.14	8.16±0.92	178.91±20.45	4.13±0.52	163.55±21.49	14.84±2.42	55.27±7.81
t	5.832	6.192	6.783	9.283	6.172	12.384	6.952	8.174
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Table 2
Comparison of serum levels of markers between two groups after treatment.

Groups	DKK1 (pg/mL)	MK (pg/mL)	Leptin (ng/mL)	Exosome (pg/mL)	OPN (μg/L)
Observation group	32.84±4.01	244.73±35.19	3.27±0.41	321.64±45.76	23.74±3.89
Control group	76.23±8.29	462.84±59.63	5.18±0.69	622.18±79.64	58.66±7.12
t	8.394	10.274	5.783	9.384	6.283
P	<0.05	<0.05	<0.05	<0.05	<0.05

chemotherapy, the values of serum tumor markers such as MMP-9, MMP-2, MG7-Ag, TSGF, CA72-4, CA19-9, TP and DpD were all lower than those of control group (P<0.05), shown in Table 1.

3.2. Serum illness-related factors

In the study, serum DKK1, MK, Leptin, Exosome and OPN values of observation group after treatment were lower than those of control group (P<0.05), shown in Table 2.

3.3. Serum nutrition indexes and T cell immune function

It showed that TP, ALB, PA, $CD4^+$ T and $CD4^+$ T/ $CD8^+$ T values of observation group after treatment were higher than those of control group, and $CD8^+$ T value was lower than that of control group (P<0.05), shown in Table 3.

4. Discussion

Radical surgery is the best way in the clinical treatment of gastric cancer, but there may be peritoneal metastasis during surgery and there may be incomplete resection of micrometastases in tumor, so postoperative chemotherapy is an effective method of consolidating treatment achievements. FP chemotherapy regimens (5-FU and cisplatin DDP) is the chemotherapy scheme with more application after operation for gastric carcinoma, and the combined use of DDP and 5-FU has mutual biochemical modification effect, and achieves the purpose of inhibiting DNA synthesis[4,5]. But the 5-FU and DDP dose is small in FP regimens, it can reduce the incidence of adverse reactions, but it has the disadvantages of limited treatment effect, and looking for more reasonable and effective chemotherapy regimens is the key of the research on treatment of gastric cancer. S-1 capsule is oral fluorouracil-type drug that includes FT, gimeracil (CDHP) and Oxo, FT is the pro-drug of 5-FU, and CDHP can restrain the catabolism of 5-FU, and helps the long-term effective 5-FU depth in blood and tumor tissue[6]. Oxo can block the phosphorylation of 5-FU, has the very high distributing concentration in the gastrointestinal tissue, and reduces the toxicity of 5-FU[7]. In the study, S-1 chemotherapy was introduced in the postoperative treatment of observation group and mainly compared with FP chemotherapy in control group, and differences in prognosis and serum-related parameters were observed.

With in-depth development of molecular biological technology in cancer research, many tumor markers have been found and used for the judgment of tumor prognosis. Levels of tumor markers are significantly different in patients with different stages and likelihood of recurrence, this is the basis for them to evaluate the treatment effect and prognosis in patients, differences in serum levels of MMP-9, MMP-2, MG7-Ag, malignant TSGF, CA72-4 and CA19-9 levels of two groups after treatment were mainly observed in the study, and the results showed that the values of above parameters of observation group were lower. MMP-9 and MMP-2 play an important role in decomposing matrix and promoting the basement membrane breakthrough and blood vessel metastasis of tumor, and many studies have confirmed that they are closely related to tumor metastasis. MG7-Ag is one of the new tumor-associated antigens, and studies have shown that serum MG7-Ag has positive significance for the diagnosis of gastric cancer and monitoring of the condition and its specificity is as high as 70%[8,9]. TSGF is the material basis of large proliferation of malignant tumors and surrounding blood vessels, and can be released into the peripheral blood with the tumor formation, causing that cells secrete angiogenesis-promoting factors and tumor angiogenesis is exuberant. CA72-4 is a high molecular-weight glycoprotein abnormally expressed in various kinds of digestive tract tumors, there is increased CA72-4 level in only about 1% of patients with benign gastric disease, and the proportion is as high as 42.6% in gastric cancer[10]. Study shows that the CA19-9 sensitivity for the diagnosis of gastric cancer is 18%-60%, the specificity is 80%-85%, and it has positive effect on the diagnosis of gastric cancer and detection of its recurrence. TP and DpD are the catalyzing enzymes involved in the synthesis of DNA in cells, can promote DNA synthesis and cell proliferation, have increased expression in the occurrence of malignant tumors and are secreted into the blood. The research results showed that S-1chemotherapy after operation for gastric carcinoma could significantly reduce the dangerous level of disease and reduce the possibility of recurrence.

In addition to the well known tumor markers, there are still some factors in serum that are closely associated with gastric cancer conditions, and their levels can change with patients′ conditions. DKK1 is a glycoprotein with molecular weight of 24 kDa, and can antagonize Wnt/ β -catenin signaling pathway to play the roles such as degrading β -catenin protein and reducing T cell regulator expression[11]. MK can promote cell differentiation, promote mitosis and tumor angiogenesis, resist apoptosis, and so on, is highly expressed in a variety of different human malignant tumors, and

Table 3
Comparison of serum values of nutrition indexes and T cell immune function indexes between two groups after treatment.

Groups	Nutrition indexes			T cell immune function		
	TP (g/L)	ALB (mg/L)	PA (g/L)	$CD4^+$ T (mmol/L)	$CD8^+$ T (mmol/L)	$CD4^+$ T/ $CD8^+$ T
Observation group	67.27±8.38	41.27±4.38	261.25±32.94	734.82±85.11	632.84±70.79	2.16±0.32
Control group	54.91±6.93	32.91±3.74	209.88±25.47	629.54±73.83	691.27±75.88	1.81±0.21
t	8.932	7.384	8.182	7.394	9.372	5.382
P	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

it directly involved in the development and metastasis of tumor. Leptin is an obese gene-encoded protein widely existing in adipose tissue of human and mammals, and can promote angiogenesis and vascular permeability increase. Under normal circumstances, the expression of leptin is under strict regulation, and this balance is broken in cancer tissue and tends to angiogenesis[12]. Exosome has an obvious tumorigenic tendency, induces tumor cell migration and participates in tumor angiogenesis as well as tumor cell infiltration and metastasis[13]. OPN is a kind of secretory p-glycoprotein with a variety of biological functions, it is involved in the development of a variety of tumors, and studies in recent years have found that peripheral blood concentration of OPN can predict tumor recurrence and metastasis. In the study, serum DKK1, MK, Leptin, Exosome and OPN values of observation group after chemotherapy were all lower, indicating that S-1 chemotherapy had more advantages in reducing the recurrence of gastric cancer.

Gastrointestinal tumor optimizes digestive function inhibition and disease consumption, which will cause different degree of malnutrition and immunosuppression, especially cell immunosuppression. After operation for gastric cancer, the body's catabolism is more exuberant and serum protein degradation increases, and at the same time, immune function is further damaged, which increases the risk of infection, and increases the probability of tumor recurrence and metastasis[14]. TP, ALB and PA are typical serum nutrition-related proteins, and in this study, serum TP, ALB and PA levels of observation group after chemotherapy were higher, indicating that effective chemotherapy could further contain the malignant degree of residual tumor lesions and reduce the catabolism caused by tumor. Cellular immunity is the main immune system involved in the occurrence and development of tumor, there is different degree of immunosuppression in patients with tumor, and poor immune function is one of the main reasons for rapid tumor progress[15]. $CD4^+$ T/ $CD8^+$ T is a marker indicator of the judgment of cellular immune status, the higher the ratio, the better the immune function, and in the study, $CD4^+$ T and $CD4^+$ T/ $CD8^+$ T values of observation group after chemotherapy were higher, indicating that after S-1 chemotherapy, the immunosuppression in patients was relieved, and it helped to reduce the risk of long-term tumor recurrence[16].

To sum up, it is concluded that S-1 chemotherapy after operation for gastric carcinoma can inhibit the tumor activity and optimize patients' overall condition, and it's worth popularization and application in clinical practice in the future.

References

[1] He S, Liao G, Liu Y, et al. Overexpression of STAT3/pSTAT3 was associated with poor prognosis in gastric cancer: a meta-analysis. *Int J Clin Exp Med* 2015; **8**(11): 20014-20023.

[2] Bao JQ, Zhao XS, Wu-yun-gao-wa, et al. S-1 plus oxaliplatin versus FOLFOX6 as perioperative chemotherapy for resectable gastric cancer of stage II/III:a retrospective study. *Oncol Prog* 2014; **12**(1): 70-74.

[3] Liu WJ, Zhao YQ, Hu XF, et al. Effectiveness and safety evaluation of paclitaxel liposome combined with S-1 in treatment of advanced gastric cancer. *J Zhengzhou Univ (Med Sci)* 2014; **49**(6): 783-785.

[4] Cai LY, Yin WJ, Xu MY. Clinical significance of serum and tissue Dickkopf-1 levels in patients with gastric cancer. *Chin J Modern Med* 2014; **24**(6): 1-3.

[5] Shoda K, Komatsu S, Ichikawa D, et al. Thrombocytosis associated with poor prognosis in patients with gastric cancer. *Gan To Kagaku Ryoho* 2015; **42**(12):1980-1982.

[6] Zheng JR, Zhang M, Xu R, et al. Clinical application of tumor markers combined with motion detection in diagnosis and treatment monitoring in gastric cancer. *Chin J Clin (Electronic Edition)* 2015; **9**(3): 382-384.

[7] Hasegawa H, Fujitani K, Nakazuru S, et al. Optimal treatment change criteria for advanced gastric cancer with non-measurable peritoneal metastasis: symptom/tumor marker-based versus CT-based. *Anticancer Res* 2014; **34**(9): 5169-5174.

[8] Gong AA, Miao K. Effect of glutamine on serum CEA, AFP and T cell immune function in postoperative patients with gastric cancer. *Chin J Biochem Pharm* 2015; **10**(35): 90-92.

[9] Lee JC, Lee SY, Kim CY, et al. Clinical utility of tumor marker cutoff ratio and a combination scoring system of preoperative carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 72-4 levels in gastric cancer. *J Korean Surg Soc* 2013; **85**(6): 283-289.

[10]Zhang LG. Factors affecting the prognosis of gastric cancer after radical resection. *J Hainan Med Univ* 2013; **19**(10): 1438-1440.

[11]Men HT, Gou HF, Liu JY, et al. Prognostic factors of intraperitoneal chemotherapy for peritoneal carcinomatosis of gastric cancer: A retrospective study from a single center. *Oncol Lett* 2016; **11**(5): 3501-3507.

[12]Ma J, Shen H, Kapesa L, et al. Lauren classification and individualized chemotherapy in gastric cancer. *Oncol Lett* 2016; **11**(5): 2959-2964.

[13]Huang TC, Qiu XG. Detection of osteopontin as a potential biomarker for metastasis and recurrence in gastric cancer. *Med J Wuhan Univ* 2013; **34**(2): 280-282.

[14]Jiang W, Wang FJ, Kang Y. The distribution and clinical significance of Th17 cells in the tumor microenvironment of gastric cancer. *Oncol Progr* 2015; **13**(4): 396-399.

[15]Zhang K, Tan HX, Lu JG, Hu XH. Combined detection of serum CA72-4, MG-Ag and CA19-9 in predicting postoperative recurrence of patients with early gastric cancer. *J Hainan Med Univ* 2014; **20**(6): 773-775.

[16]Mokmeli S, Tehrani GA, Zamiri RE, et al. Investigating the frequency of the *ERCC1* gene C8092A polymorphism in Iranian patients with advanced gastric cancer receiving platinum-based chemotherapy. *Asian Pac J Cancer Prev* 2016;**17**(3): 1369-1372.