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ORIGINAL ARTICLE

Efficacy of trastuzumab combined with SOX or IP chemotherapy regimen in the treatment of advanced gastric cancer

Dazhou Xu[1], Zhimei Zhang[2], Shuxian Zhang[1], Xinjian Fang[3], Lei Wang[4], Qiuling Li[5]

[1]Department of Gastroenterology, Lianyungang Clinical College of Nanjing Medical University, The First People's Hospital of Lianyungang, Lianyungang 222000, China. [2]Phase I Clinical Research Center ang Department of Gastroenterology, Lianyungang Clinical College of Nanjing Medical University, The First People's Hospital of Lianyungang, Lianyungang 222000, China. [3]Department of Oncology, The second People's Hospital of Lianyungang, Lianyungang 222000, China. [4]Department of Oncology, Lianyungang Clinical College of Nanjing Medical University, The First People's Hospital of Lianyungang, Lianyungang 222000, China. [5]Department of General Surgery, Donghai County People's Hospital of Lianyungang, Lianyungang 222000, China.

Summary

Purpose: *The purpose of this study was to compare the clinical efficacy and safety of S-1 + oxaliplatin (SOX) chemotherapy regimen combined with trastuzumab and irinotecan + cisplatin (IP) chemotherapy regimen combined with trastuzumab in treating human epidermal growth factor receptor 2 (HER-2)-positive advanced gastric cancer.*

Methods: *A total of 138 patients with HER-2-positive advanced gastric cancer were divided into SOX group (SOX chemotherapy regimen combined with trastuzumab; n=69) and IP group (IP chemotherapy regimen combined with trastuzumab; n=69). Then, the clinical efficacy, incidence rate of adverse reactions, quality-of-life score and other indicators were compared between the two groups of patients. Additionally, the levels of myeloid-related protein-14 (MRP-14), stromal cell-derived factor-1 (SDF-1), fibroblast-specific protein-1 (FSP-1) and CXC chemokine receptor-4 (CXCR4) in peripheral blood and the changes in neovascularization markers were detected, and the survival of patients was followed up and recorded.*

Results: *The disease control rate (DCR) was clearly better in SOX group than that in IP group. Serum levels of MRP-14, SDF-1, FSP-1 and CXCR4 were obviously lower in SOX group than those in IP group. The scores of physical function, behavioral function, role function and social function were higher in SOX group than those in IP group. Moreover, the follow-up results revealed that the PFS of patients was overtly longer in SOX group than that in IP group.*

Conclusions: *Trastuzumab combined with SOX chemotherapy regimen has an obvious curative effect in the treatment of advanced gastric cancer, which prominently improves the quality of life of patients, lowers the serum tumor marker levels in patients, delays tumor progression, and results in tolerable adverse reactions. Therefore, it is worthy of application in clinical practice.*

Key words: *trastuzumab, human epidermal growth factor receptor-2, SOX regimen, IP regimen, gastric cancer, advanced stage*

Introduction

Gastric cancer ranks second in terms of incidence rate and third in mortality rate among malignant tumors in China [1]. Since gastric cancer has obscure symptoms in the early stage, most patients tend to be diagnosed at the advanced stage and miss the best opportunity for surgical treatment. Consequently, the recurrence and metastasis rates are high (40-60%) after radical surgery, further leading to a low 5-year survival rate (only about 20%) [2,3].

Corresponding author: Zhimei Zhang, MD. Phase I Clinical Research Center and Department of Gastroenterology, Lianyungang Clinical College of Nanjing Medical University, The First People's Hospital of Lianyungang, 6 Zhenhua Rd, Haizhou District, Lianyungang, Jiangsu 222000, China.
Tel: +86 018961322299, Email: 1365360153@qq.com
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About 25-30% of patients with gastric cancer have positively expressed human epidermal growth factor receptor-2 (HER-2) that plays a vital role in the invasion, growth and metastasis of tumors, and highly expressed HER-2 indicates poor prognosis of patients in most cases [4,5]. Trastuzumab, a large-molecule monoclonal antibody highly selective for HER-2, is able to suppress the growth and metastasis of tumors by repressing HER-2 expression [6,7]. However, studies have proven that trastuzumab monotherapy or simple chemotherapy has no obvious efficacy in these patients, so chemotherapy combined with trastuzumab is the most common approach for the treatment of HER-2 positive gastric cancer [8,9]. As to the specific chemotherapy regimens, S-1 + oxaliplatin (SOX) scheme is mainly recommended by the National Comprehensive Cancer Network (USA), and irinotecan + cisplatin (IP) scheme is mainly advised by the European Association for Cancer Research. In this study, the clinical efficacy of SOX regimen combined with trastuzumab was compared with that of IP regimen combined with trastuzumab in the treatment of HER-2-positive advanced gastric cancer, hoping to provide a strong basis for the selection of clinical therapeutic regimens for such patients.

Methods

Study subjects

The clinical data of 138 patients with HER-2-positive advanced gastric cancer were collected. The inclusion criteria were set as follows: patients definitely diagnosed with HER-2-positive advanced gastric cancer according to the results of gastroscopy, iconography, histopathology, molecular biology and serum indicator tests, treatment-naive patients with measurable lesions, patients who were unable to or unwilling to receive surgical treatment, and patients with a KPS score of ≥60 points and expected survival time of ≥3 months. The exclusion criteria involved patients with critical diseases such as severe liver and kidney diseases, severe infection, severe cardiovascular diseases, severe coagulopathy and severe mental illness, those with other gastric diseases like gastric adenomatous polyps, or those with other types of malignant tumors including non-small cell lung cancer and primary liver cancer. There were 74 males and 64 females aged 38-79 years old, with an average of (55.63±9.45) years old. The general data like age, gender, pathological type, treatment site and clinical stage showed no statistically significant differences between the two groups (p>0.05), which were comparable (Table 1). All patients enrolled were informed of this study and signed the informed consent in accordance with *Declaration of Helsinki*. This study was approved by the Ethics Committee of The First People's Hospital of Lianyungang.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Indicators	*SOX group (n=69)* *n (%)*	*IP group (n=69)* *n (%)*	*p*
Age, years	54.75±9.73	56.21±9.89	0.384
Gender (male/female)	39/30	35/34	0.495
Pathological type			0.583
Adenocarcinoma	43 (62.3)	37 (53.6)	
Mucinous adenocarcinoma	7 (10.1)	9 (13.0)	
Signet-ring cell carcinoma	19 (27.5)	23 (33.3)	
Tumor location			0.777
Gastric cardia	16 (23.2)	14 (20.3)	
Gastric fundus	28 (40.6)	26 (37.7)	
Gastric antrum	25 (36.2)	29 (42.0)	
Differentiation degree			0.603
High	2 (2.9)	3 (4.3)	
Moderate	22 (31.9)	17 (24.6)	
Low	45 (65.2)	49 (71.0)	
TNM stage			0.571
IIIA	18 (26.1)	20 (29.0)	
IIIB	21 (30.4)	25 (36.2)	
IV	30 (43.5)	24 (34.8)	
KPS score			0.576
80-90	22 (31.9)	19 (27.5)	
60-80	47 (68.1)	50 (72.5)	

TNM: tumor, lymph node, metastasis; KPS: Karnofsky performance status.

Therapeutic methods

The same basic treatment and application method of trastuzumab were adopted in the two groups. Trastuzumab (Shanghai Roche Pharmaceutical Ltd., diluent batch number: N3885, subpackage batch number: SH0176) was intravenously injected at the initial dose of 8 mg/kg and thereafter 6 mg/kg on the first day of each week. SOX chemotherapy regimen was performed in SOX group: Oxaliplatin injection (Jiangsu Aosaikang Pharmaceutical Co., Ltd., specification: 50 mg/vial) was added to 500 mL of 5% glucose solution and then intravenously infused for 3 h on the first day at 130 mg•m^2/time, while S-1 capsule (Qilu Pharmaceutical Co., Ltd., specification: 20 mg/capsule) were given orally from day 1 to day 14 (2 tablets/time, twice a day). With 21 d as 1 cycle, a total of 4 treatment cycles were carried out. The patients in IP group were treated with IP chemotherapy: Irinotecan hydrochloride injection (Jiangsu Hengrui Medicine Co., Ltd., specification: 100 mg: 5 mL/vial) was intravenously infused on day 1 and day 8 at 60 mg/m^2/time, and cisplatin (Qilu Pharmaceutical Co., Ltd., specification: 20 mg/vial) was intravenously infused from day 1 to day 3 at 30 mg•m^2/time. With 21 d as 1 cycle, a total of 4 treatment cycles were carried out.

Observation indexes

Clinical efficacy was evaluated as follows: after treatment, the total length and width of lesions were measured through magnetic resonance imaging (MRI) and gastroscopy, with the complete disappearance of lesions for >28 days as complete remission (CR). The reduction of ≥30% in the total length and width of lesions for >28 days was determined as partial remission (PR), the reduction of <30% in the total length and width of lesions for >28 days was judged as stable disease (SD), and the reduction below the criterion of SD was classified as progressive disease (PD). Overall response rate (ORR) = (CR + PR)/total number of cases ×100%, and disease control rate (DCR) = (CR + PR + SD)/ total number of cases ×100%.

Before treatment and after the four courses of treatment, 2 venous blood samples (5 mL) were collected from every patient in the two groups and centrifuged at 3000 rpm using a low-speed centrifuge for 10 min. Then, the serum was collected and stored in a refrigerator at -80°C. Thereafter, enzyme-linked immunosorbent assay (ELISA) was conducted to detect the levels of tumor markers [myeloid-related protein-14 (MRP-14), stromal cell-derived factor-1 (SDF-1), fibroblast-specific protein-1 (FSP-1) and CXC chemokine receptor-4 (CXCR4)] and neovascularization markers [vascular endothelial growth factor (VEGF), Angiopoietin-2 (Ang-2), Endostatin (ES) and pigment epithelium-derived factor (PEDF)] in patients with gastric cance.

Besides, the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (30 version) was employed to assess the quality of life of patients before and after treatment, in which the functional module mainly includes physical function, behavioral function, role function, emotional function, social function and cognitive function, with a score of 100 points for each item. The higher the score is, the better the quality of life will be. The toxic and side effects including liver toxicity, renal toxicity, neurotoxicity, cardiotoxicity, myelosuppression and gastrointestinal reaction were evaluated in the two groups of patients during treatment as per the World Health Organization uniform criteria for toxic and side effects of chemotherapy drugs.

All patients were followed up *via* enhanced MRI or CT at 1 month after treatment and at every 3 or 6 months. The follow-up was ended in December 2019. Overall survival (OS, the time interval from the start of treatment to the death or the deadline of follow-up) and progression-free survival (PFS, the time interval from the start of treatment to the tumor progression or death) were used as observation indicators.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was employed for the comparison between groups. Enumeration data were expressed as ratio (%), and x^2 test or Fisher's exact test was used for their comparison. The t-test was used for analyzing measurement data. Differences between two groups were analyzed by using the Student's t-test. Comparison between multiple groups was done using One-way ANOVA test followed by *post hoc* test (least significant difference). Moreover, survival curves were plotted using Kaplan-Meier method, and log-rank test was adopted. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups of patients after treatment

In SOX group, there were 11 cases of CR, 24 cases of PR, 23 cases of SD and 11 cases of PD, with an ORR of 50.7% (35/69) and a DCR of 84.1% (58/69). There were 7 cases of CR, 20 cases of PR, 19 cases of SD and 23 cases of PD, with an ORR of 39.1% (27/69) and a DCR of 66.7% (46/69) in IP group. The ORR showed no statistically significant difference between SOX group and IP group (p=0.171), whereas the DCR was clearly better in SOX group than that in IP group (p=0.018) (Table 2).

Comparisons of tumor markers and neovascularization markers in peripheral blood between the two groups before and after treatment

Before treatment, no statistically significant differences were found in serum MRP-14, SDF-1, FSP-1, CXCR4, VEGF, Ang-2, ES and PEDF levels between the two groups (p>0.05). After treatment, the levels of serum MRP-14, SDF-1, FSP-1 and CXCR4 declined to (6.87±0.83) mg/L, (1.71±0.16) ng/L, (4.04±0.35) ng/L and (0.43±0.06) pg/L in SOX group and (10.64±1.02) mg/L, (3.63±0.54) ng/L,

(7.10±0.66) ng/L and (0.72±0.08) pg/L in IP group, respectively, and SOX group had evidently lowered levels of serum MRP-14, SDF-1, FSP-1 and CXCR4 in comparison with IP group (p<0.001). In addition, the levels of serum VEGF, Ang-2, ES and PEDF were reduced to (82.29±30.37) ng/L and (89.73±28.90) ng/L, (336.16±60.43) ng/L and (348.30±61.34) ng/L, (85.67±23.54) μg/L and (93.64±25.51) μg/L, and (46.58±13.47) μg/L and (50.65±16.69) μg/L, respectively, in both groups after treatment, and they were prominently lower in SOX group than those in IP group after treatment, showing no statistically significant differences (p=0.149, p=0.244, p=0.059, p=0.117) (Figure 1 and Figure 2).

Comparison of improvement of quality of life between the two groups of patients

The scores of physical function, behavioral function, role function, emotional function, social function and cognitive function showed no statistically significant differences between the two groups of patients before treatment (p>0.05), while they were distinctly increased after treatment in both groups and higher in SOX group than those in IP group after treatment (p<0.05). Meanwhile, there were statistically significant differences in the scores of physical function, behavioral function, role function and social function (p<0.05), whereas no statistically significant differences were observed in the scores of emotional function and cognitive function (p>0.05) (Table 3).

Comparison of incidence rate of adverse reactions between the two groups of patients

There were 10 and 13 cases of leukopenia, 7 and 11 cases of anemia, 10 and 8 cases of thrombocytopenia, 15 and 18 cases of gastrointestinal reaction, 7 and 10 cases of live function damage,

Table 2. Comparison of tumor response between the two groups of patients

Indicators	*SOX group (n=69)* *n (%)*	*IP group (n=69)* *n (%)*	*p*
Complete response (CR)	11 (15.9)	7 (10.1)	
Partial response (PR)	24 (34.8)	20 (29.0)	
Stable disease (SD)	23 (33.3)	19 (27.5)	
Progressive disease (PD)	11 (15.9)	23 (33.3)	
ORR (CR + PR)	35 (50.7)	27 (39.1)	0.171
DCR (CR + PR+SD)	58 (84.1)	46 (66.7)	0.018

ORR: objective response rate; DCR: disease control rate.

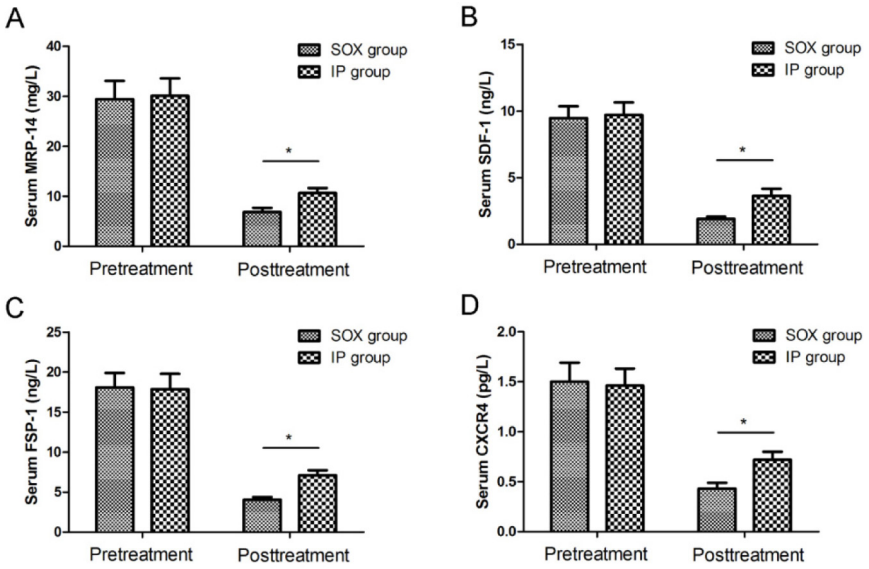

Figure 1. Comparison of pretreatment and posttreatment serum tumor markers of the studied patients. The differences in pretreatment serum MRP-14 **(A)**, SDF-1 **(B)**, FSP-1 **(C)** and CXCR4 **(D)** levels of patients between SOX group and IP group had no statistical significance. Serum MRP-14, SDF-1, FSP-1 and CXCR4 levels of patients were significantly decreased after treatment Posttreatment serum MRP-14, SDF-1, FSP-1 and CXCR4 levels of patients in sox group were significantly lower than those of IP group (*p<0.05).

6 and 8 cases of renal function damage, 4 and 7 cases of peripheral neurotoxicity, 5 and 8 cases of mucositis, and 5 and 3 cases of cardiotoxicity in SOX group and IP group, respectively. Most of the adverse reactions were grade I-II, relieved after symptomatic treatment and tolerable of continuing treatment, and severe adverse reactions (grade III-IV) were fewer. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups of patients (p>0.05) (Table 4).

Follow-up results of survival status of patients

The patients were followed up for 3-12 months until December, 2019. The median OS and PFS were (9.8±2.6) and (5.5±2.1) months in SOX group and (8.3±2.4) and (4.9±1.9) months in IP group, respectively. Survival curves were plotted by Kaplain-Meier method (Figure 3). Based on log-rank test, there was no statistically significant difference in the OS of patients between the two groups (p=0.190), whereas the PFS of patients was overtly superior in SOX group to that in IP group (p=0.027).

Table 3. Comparison of posttreatment EORTC-QLQ-C30 scale scores between two different groups of patients

Parameters	*SOX group (n=69)*	*IP group (n=69)*	*p*
QLQ-C30 Functioning scales			
Physical			
Pretreatment	61.62±7.41	59.97±8.07	0.213
Posttreatment	73.07±9.17	69.22±8.96	0.014
Behavioral			
Pretreatment	58.14±6.98	56.90±7.09	0.302
Posttreatment	70.43±7.64	64.16±8.19	0.001
Role			
Pretreatment	55.51±8.65	54.14±7.90	0.333
Posttreatment	68.79±9.27	63.11±9.67	0.001
Emotional			
Pretreatment	50.73±8.15	52.02±8.54	0.366
Posttreatment	71.09±9.89	68.24±9.35	0.084
Social			
Pretreatment	58.35±7.26	56.94±7.02	0.248
Posttreatment	68.57±8.45	64.63±8.33	0.007
Cognitive			
Pretreatment	55.39±8.45	54.04±8.63	0.355
Posttreatment	72.10±9.15	69.28±9.23	0.074

EORTC: European Organization for Research and Treatment of Cancer.

Table 4. Comparison of adverse reactions between the two groups of patients

Indicators	*SOX group (n=69)*		*IP group (n=69)*		*p*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Leukopenia	8 (11.6)	2 (2.9)	10 (14.5)	3 (4.3)	0.649
Anemia	7 (10.1)	0 (0)	11 (15.9)	0 (0)	0.449
Thrombocytopenia	9 (13.0)	1 (1.4)	6 (8.7)	2 (2.9)	0.801
Nausea and vomiting	14 (20.3)	1 (1.4)	16 (23.2)	2 (2.9)	0.690
Live function damage	6 (8.7)	1 (1.4)	9 (13.0)	1 (1.4)	0.606
Renal function damage	5 (7.2)	1 (1.4)	7 (10.1)	1 (1.4)	0.779
Peripheral neurotoxicity	4 (5.8)	0 (0)	6 (8.7)	1 (1.4)	0.532
Mucositis	5 (7.2)	0 (0)	8 (11.6)	0 (0)	0.562
Cardiotoxicity	5 (7.2)	0 (0)	3 (4.3)	0 (0)	0.718

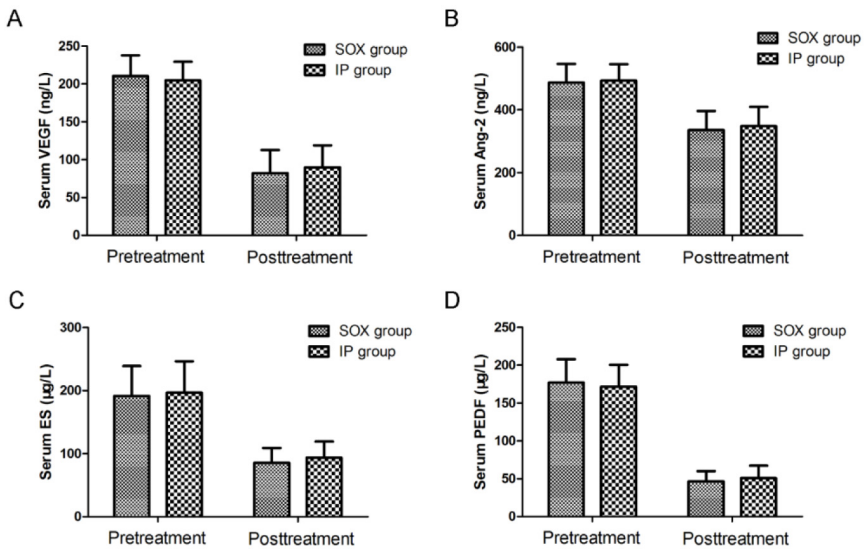

Figure 2. Comparison of pretreatment and posttreatment serum VEGF **(A)**, Ang-2 **(B)**, ES **(C)** and PEDF **(D)** levels of the studied patients. The differences in pretreatment serum VEGF, Ang-2, ES and PEDF levels of patients between SOX group and IP group had no statistical significance. Serum VEGF, Ang-2, ES and PEDF levels of patients were significantly decreased after treatment. The differences in posttreatment serum VEGF, Ang-2, ES and PEDF levels of patients between SOX group and IP group had no statistical significance.

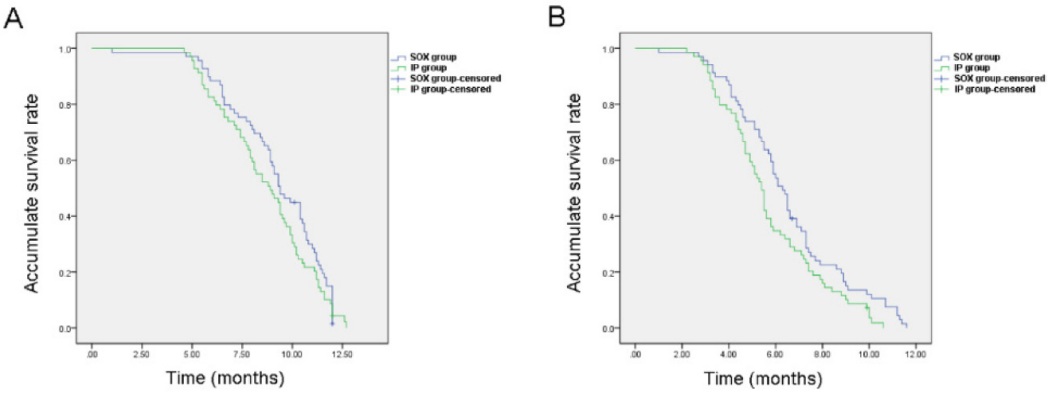

Figure 3. Kaplan-Meier survival curves of advanced gastric cancer patients. The difference in the overall survival rate **(A)** of patients between SOX group and IP group had no statistical significance (p=0.190). The progression free survival rate **(B)** of patients in SOX group was significantly higher than that of IP group (p=0.027).

Discussion

HER-2, a member of the HER superfamily, is expressed in a small quantity in human tissues under normal conditions and highly expressed in various cancer cells such as breast cancer cells, ovarian cancer cells and gastric cancer cells, which plays a crucial role in the proliferation, infiltration and metastasis of tumor cells [10-12]. The rate of HER-2-positive gastric cancer is about 12-20% [13]. Trastuzumab, a monoclonal antibody targeted against the extracellular part of the HER-2 cell membrane, binds to the extracellular IV region of the HER-2 cell membrane to block the transduction of downstream PI3K/AKT and Ras/MEK tumor cell signals, thereby exerting an anti-tumor effect [14,15]. In a randomized prospective phase III multicenter clinical study (ToGA study), the efficacy of the therapeutic regimen (HER-2 monoclonal antibody trastuzumab combined with 5-Fu + cisplatin) was compared with that of chemotherapy alone for the first time in the initial treatment of HER-2-positive gastric cancer. The results showed that the tumor response rate is prominently higher, and the disease progression time, response duration, and median PFS and OS are significantly longer in combination trastuzumab group than those in control group [16]. The ToGA study lays a basis for the fundamental role of trastuzumab in the first-line treatment of HER-2-positive gastric cancer. In recent years, increasing research results have manifested that

trastuzumab combined with XELOX, SOX, SP and other chemotherapy regimens are more effective than chemotherapy alone in the treatment of advanced gastric cancer [17-19].

Currently, anti-HER-2 drugs combined with chemotherapy are mainly recommended in major global guidelines for the treatment of HER-2-positive advanced gastric cancer. However, there is no consensus on the selection of specific chemotherapy methods. The treatment with anti-HER-2 drugs + SOX regimen is advised in guidelines of the National Comprehensive Cancer Network for the treatment of the disease. The IP regimen is mainly recommended by the European Association for Cancer Research for the treatment of the disease. The mFOLFOX6 or SOX regimen in combination with anti-HER-2 drugs is recommended in the *Japanese gastric cancer treatment guidelines* (the 4th edition). In this study, the clinical efficacy and safety of SOX regimen combined with trastuzumab were compared those of IP regimen combined with trastuzumab in the treatment of HER-2-positive advanced gastric cancer. The results revealed that no statistically significant difference was detected in the ORR between the two groups (p=0.171), whereas the DCR was significantly better in SOX group than that in IP group (p=0.018). Besides, the follow-up results demonstrated that there was no statistically significant difference in the OS of patients between two groups (p=0.190), whereas the PFS of patients was overtly longer in SOX group than that in IP group (p=0.027). In terms of safety, the adverse reactions were mainly in grade I-II, relieved after symptomatic treatment and tolerable of continuing treatment, and no statistically significant difference was detected in the incidence rate of adverse reactions (p>0.05). The scores of the of quality of life of all items were distinctly increased after treatment in both groups, and they were higher in SOX group than those in IP group after treatment. The scores of physical function, behavioral function, role function and social function showed statistically significant differences (p<0.05). These results suggest that trastuzumab combined with SOX regimen is effective and safe, which can also more effectively improve the quality of life of patients.

Studies have denoted that MRP-14 can promote the growth and metastasis of gastric cancer cells, and weaken the killing effect of chemotherapeutic drugs on cancer cells. SDF-1 is mainly detected in interstitial cells and can mediate cancerous inflammatory reactions and exacerbate the proliferation of malignant tumor cells. FSP-1 can specifically bind to cytoskeletal components in tumor cells such as tubulin, thus activating the backbone dynamics of gastric cancer cells and promoting the infiltration of cancer cells. CXCR4 is capable of facilitating the proliferation of cancer cells and the production of angiogenic factors including VEGF and VEGFR-2, thereby promoting tumor metastasis. As a result, MRP-14, SDF-1, FSP-1 and CXCR4 have close associations with the occurrence and development of HER-2-positive advanced gastric cancer, and their levels can effectively reflect the anti-tumor effect of chemotherapy [20-22]. It was discovered in this study that the levels of serum tumor markers in patients were clearly lower in SOX group than those in IP group after treatment (p<0.001), while the levels of serum neovascularization markers had no statistically significant differences between the two groups (p>0.05).

This study is a single-center retrospective study with certain limitations. It had limited number of patients enrolled, insufficient follow-up time, and incomprehensive content of the follow-up. Advanced gastric cancer has increased tumor load and poor prognosis. Hence, more rigorous, multicenter, prospective and randomized studies with a large sample size are needed in the future to verify the conclusion made in this study, so as to provide a stronger basis for the choice of chemotherapy regimens for such patients.

Conclusions

Trastuzumab combined with SOX chemotherapy regimen has an obvious curative effect in the treatment of advanced gastric cancer, which prominently improves the quality of life of patients, decreases the levels of serum tumor markers in patients, delays tumor progression, and results in tolerable adverse reactions. Therefore, it is worthy of application in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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