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ORIGINAL ARTICLE

Efficacy of apatinib combined with tegafur gimeracil and oteracil potassium in the second-line treatment of advanced gastric cancer

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Summary

Purpose: *To investigate the clinical efficacy and safety of apatinib combined with tegafur-gimeracil-oteracil potassium (S-1) in the second-line treatment of advanced gastric cancer.*

Methods: *A total of 126 patients with advanced gastric cancer admitted to our hospital from January 2017 to September 2018 were enrolled as the research objects, none of whom underwent surgery. For these patients, second-line treatment was recommended due to the failure of first-line treatment. According to the different therapeutic options, patients were categorized into S-1 group (n=63) and Apatinib group (S-1 combined with apatinib, n=63), and drugs were administered orally. The clinical efficacy, serological indicators, adverse reactions and immune function were compared between the two groups. Besides, the survival status of patients was recorded through follow-up.*

Results: *In S-1 group and Apatinib group, the objective response rate (ORR) was 30.2% (19/63) vs. 50.8% (32/63) and the disease control rate (DCR) was 54.0% (34/63) vs. 74.6% (47/63), respectively. The results indicated that Apatinib group was superior to S-1 group in terms of ORR and DCR, suggesting statistically significant differences (p=0.018, p=0.016). Compared with those before treatment, the serum levels of carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and tumor supplied group of factors (TSGF) in the two groups of patients were prominently reduced after treatment (p<0.05). After treatment, CA19-9 and TSGF levels were remarkably lower in Apatinib group than those in S-1 group (p=0.008, p=0.023), and there was no statistically significant difference in the CEA level between the two groups (p=0.057). After treatment, the quality of life of patients was improved notably in Apatinib group compared with that in S-1 group (p=0.002). Adverse reactions mainly involved hematological toxicity, nausea and vomiting, abnormal renal function, impairment of hepatic function, neurotoxicity, hypertension and hand-foot syndrome, most of which were in grade I-II and relieved after symptomatic treatment and could be tolerated for continued treatment. Serious adverse reactions in grade III-IV occurred rarely. No statistically significant difference was found in the incidence rate of adverse reactions between the two groups of patients (p>0.05). Besides, according to the follow-up results, median overall survival (OS) was 8.1 months vs. 10.7 months and median progression-free survival (PFS) was 4.2 months vs. 5.3 months, respectively, in S-1 group and Apatinib group. The results of log-rank test demonstrated that Apatinib group was superior to S-1 group with respect to OS, showing a statistically significant difference (p=0.028), and no statistically significant difference was found in PFS between the two groups of patients (p=0.159).*

Conclusion: *In the second-line treatment of advanced gastric cancer, apatinib combined with S-1 is superior to S-1 alone in term of clinical efficacy, and its adverse reactions can be tolerated. Apatinib combined with S-1 can prominently improve the quality of life, reduce the serum tumor marker levels and prolong the OS of patients, but it cannot extend the PFS.*

Key words: *apatinib, tegafur-gimeracil-oteracil potassium, gastric cancer, advanced, efficacy*

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Introduction

Gastric cancer is a common malignant tumor in China, and there are more than 420,000 new cases each year, and it ranks fourth in the incidence of malignancies worldwide [1]. Most of patients lose surgery opportunity due to the progression of tumor into advanced stage, which increases the difficulty of treatment [2]. Chemotherapy-based comprehensive treatment is the main strategy for advanced gastric cancer. At present, two-drug or three-drug combination based on platinum, fluorouracil or taxane is considered as the first-line treatment option, but second-line treatment option has not yet reached a consensus [3,4]. As a new type of fluorouracil drug that possesses good oral tolerance, tegafur-gimeracil-oteracil potassium (S-1) is commonly used in the second-line treatment of stage III-IV gastric cancer, showing a positive effect on controlling the disease [5,6]. Recently, as the development of targeted therapy for gastric cancer, apatinib serving as a novel generation of small-molecule vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor has been marketed in China for the third-line treatment (and above) of advanced gastric cancer or gastroesophageal junction adenocarcinoma [7,8]. In this study, the clinical data of advanced gastric cancer patients administered with apatinib combined with S-1 or S-1 alone after the failure of first-line chemotherapy were retrospectively analyzed, and the clinical efficacy and adverse reactions of different options in second-line treatment were compared, so as to provide references for second-line treatment of advanced gastric cancer.

Methods

Research objects

The clinical data of 126 patients with advanced gastric cancer admitted to our hospital from January 2017 to September 2018 were collected. The inclusion criteria were as follows: a) patients diagnosed with advanced gastric cancer through pathological, cytological or imaging examination, b) those receiving failed first-line chemotherapy such as ECF, DCF and FOLFOX regimens, c) those with at least one measurable lesion, d) those with a Karnofsky performance status (KPS) score ≥60 points and expected survival time ≥3 months, and e) those with no contraindications

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

Parameters	*S-1 group (n=63)* *n (%)*	*Apatinib group(n=63)* *n (%)*	*p value*
Age, years	55.93±9.74	57.22±9.69	0.458
Gender (male/female)	41/22	36/27	0.465
Pathological type			0.408
Adenocarcinoma	55 (87.3)	52 (82.5)	
Mucinous adenocarcinoma	3 (4.8)	7 (11.1)	
Signet-ring cell carcinoma	5 (7.9)	4 (6.3)	
Tumor location			0.118
Gastric fundus	24 (38.1)	14 (22.2)	
Gastric body	29 (46.0)	33 (52.4)	
Gastric antrum	10 (15.9)	16 (25.4)	
Differentiation degree			0.311
Moderate	44 (69.8)	49 (77.8)	
Low	19 (30.2)	14 (22.2)	
TNM stage			0.463
IIIB	41 (65.1)	37 (58.7)	
IV	22 (34.9)	26 (41.3)	
Metastatic sites			0.619
Liver	6 (9.5)	8 (12.7)	
Peritoneum	9 (14.3)	11 (17.5)	
Multiple organs	48 (76.2)	44 (69.8)	
KPS score			0.271
80-90	21 (33.3)	27 (42.9)	
60-80	42 (67.7)	36 (57.1)	

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

for apatinib and S-1. The exclusion criteria involved: a) patients with severe chronic systemic diseases, or severe cardiac, renal, hepatic or pulmonary insufficiency, b) those with severe hypertension, or c) those with mental disorders. In all patients, there were 77 males and 49 females aged 36-79 years old, with an average of (56.67±9.65) years old. There were no statistically significant differences in general data such as age, gender, pathological type, treatment site and clinical stage between the two groups of patients (p>0.05) (Table 1). This study complied with the *Declaration of Helsinki* and was approved by the Medical Ethics Committee of our hospital. All the enrolled patients signed the informed consent.

Therapeutic options

Patients in S-1 group were administered with Tegafur Gimeracil Oteracil Potassium Capsule (20 mg/capsule), with dosage and usage as follows: 40 mg twice daily in the morning and evening for body surface area <1.25 m^2, 40 mg in the morning and 60 mg in the evening for body surface area ranged 1.25-1.50 m^2, and 60 mg twice daily in the morning and evening for body surface area >1.50 m^2, for 14 consecutive days followed by a 14-day rest, namely 28 days as a cycle.

Based on the treatment in S-1 group, patients in Apatinib group were treated with Apatinib Tablets (250 mg/tablet): initial dose of 500 mg once daily, followed by 850 mg once daily according to the patient's tolerance, for a cycle of 28 days. During the treatment, both groups were administered with antiemesis, acid suppression, gastric mucosa protection, protection of liver and kidney function, and increase of leukocytes or platelets. At least 2 cycles of chemotherapy was required for the two groups of patients.

Observation indicators

The curative effect was evaluated in line with the Response Evaluation Criteria in Solid Tumor, including: a) complete remission (CR): disappearance of tumor lesions for more than 1 month, b) partial remission (PR): at least 30% decrease in sum of diameters of tumor lesions for more than 1 month, and relief of clinical symptoms, c) stable disease (SD): less than 30% decrease or less than 20% increase in sum of diameters of tumor lesions, and no appearance of new lesions, d) progressive disease (PD): more than 20% increase in sum of diameters of tumor lesions, appearance of new lesions, and still obvious clinical symptoms. Objective response rate (ORR)=CR+PR, and disease control rate (DCR)=CR+PR+SD.

Adverse reactions were assessed according to the anti-tumor drug adverse reaction scoring standards formulated by the World Health Organization (WHO), and divided into stage 0-IV. Patient's quality of life was compared between the two groups before and after chemotherapy. Using KPS score as the criterion, the higher the score, the better the quality of life. The evaluation criteria involved: a) improvement: the score increased by more than 10 points compared with that before treatment, b) stability: the score changed within 10 points compared with that before treatment, and c) decline: the score decreased by more than 10 points compared with that before treatment.

A volume of 5 mL of fasting venous blood was extracted from every patient before and after treatment to separate serum. Later, serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and tumor supplied group of factors (TSGF) were detected *via* electrochemiluminescence immunoassay using a Beckman AU5800 automatic biochemical analyzer (USA). The kits were purchased from Roche (USA).

All patients were followed up through out-patient and in-patient medical record system and telephone from the start of treatment to September 2020. Overall survival (OS) referred to the period from the start of treatment to death or the last follow-up, and progression-free survival (PFS) was defined as the period from the start of treatment to PD or the last follow-up.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was adopted for statistical analysis. Measurement data were expressed by mean ± standard deviation, and t-test was used for comparison between the two groups. Enumeration data were expressed by percentage (%) and compared using chi-square test or Fisher's exact probability test. Data from paired samples of immunological indicators were analyzed by t-test, and two-way analysis of variance was utilized for multi-group comparison. Besides, the survival curves were plotted using the Kaplan-Meier method, and the difference was compared by the Log-rank test. P<0.05 indicated that the difference was statistically significant.

Table 2. Comparison of tumor response of patients in the two studied groups

Parameters	*S-1 group (n=63)* *n (%)*	*Apatinib group (n=63)* *n (%)*	*p value*
Complete response (CR)	1 (1.6)	3 (4.8)	
Partial response (PR)	18 (28.6)	29 (46.0)	
Stable disease (SD)	15 (23.8)	18 (28.6)	
Progressive disease (PD)	29 (46.0)	16 (25.4)	
ORR (CR + PR)	19 (30.2)	32 (50.8)	0.018
DCR (CR + PR+SD)	34 (54.0)	47 (74.6)	0.016

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

Results

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

There was 1 case of CR, 18 cases of PR, 15 cases of SD and 29 cases of PD in S-1 group, and 3 cases of CR, 29 cases of PR, 18 cases of SD and 16 cases of PD in Apatinib group. In S-1 group and Apatinib group, ORR was 30.2% (19/63) *vs.* 50.8% (32/63) and DCR was 54.0% (34/63) *vs.* 74.6% (47/63), respectively. The results indicated that Apatinib group was superior to S-1 group in terms of ORR and DCR, suggesting statistically significant differences (p=0.018, p=0.016) (Table 2).

Comparison of peripheral blood tumor marker levels before and after treatment between the two groups of patients

Before treatment, there were no statistically significant differences in the serum levels of CA19-9, CEA and TSGF between the two groups of patients (p>0.05). After treatment, the serum levels of CA19-9, CEA and TSGF were reduced to (14.63±6.79) U/mL *vs.* (11.48±6.36) U/mL, (3.03±0.88) ng/mL *vs.* (2.75±0.75) ng/mL and (68.47±13.68) U/mL *vs.* (63.18±12.14) U/mL in S-1 group and Apatinib group, respectively. The results revealed that the levels of these indicators were lower in Apatinib group than those in S-1 group. The differences in CA19-9 and TSGF levels were statistically significant (p=0.008, p=0.023), and there was no statistically significant difference in the CEA level between the two groups (p=0.057) (Table 3).

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

After treatment, according to the KPS score, there were 9 cases of improvement (14.3%), 21 cases of stability (33.3%) and 33 cases of decline (52.3%) in S-1 group, and 15 cases of improvement (23.8%), 34 cases of stability (54.0%) and 14 cases of decline (22.2%) in Apatinib group, indi-

Table 3. Comparison of serum tumor markers of patients in the two studied groups

	S-1 group (n=63)	*Apatinib group (n=63)*	*p value*
CA19-9 (U/ml)			
Pretreatment	40.34±9.36	39.59±9.19	0.651
Posttreatment	14.63±6.79	11.48±6.36	0.008
CEA (ng/ml)			
Pretreatment	4.24±0.91	4.13±1.05	0.531
Posttreatment	3.03±0.88	2.75±0.75	0.057
TSGF (U/ml)			
Pretreatment	82.61±15.19	83.91±14.87	0.628
Posttreatment	68.47±13.68	63.18±12.14	0.023

CEA: carcinoma embryonic antigen; TSGF: tumor specific growth factor.

Table 4. Comparison of adverse reactions of patients in the two studied groups

Parameters	*S-1 group (n=63)*		*Apatinib group (n=63)*		*p value*
	Grade I-II n (%)	*Grade III-IV* n (%)	*Grade I-II* n (%)	*Grade III-IV* n (%)	
Leukopenia	29 (46.0)	5 (7.9)	33 (52.4)	8 (12.7)	0.204
Thrombocytopenia	11 (17.5)	3 (4.8)	10 (15.9)	2 (3.2)	0.559
Nausea and vomiting	17 (27.0)	0 (0)	21 (33.3)	0 (0)	0.438
Diarrhea	4 (6.3)	0 (0)	3 (4.8)	0 (0)	0.697
Transaminase elevation	16 (25.4)	0 (0)	19 (30.2)	0 (0)	0.551
Proteinuria	4 (6.3)	0 (0)	6 (9.5)	2 (3.2)	0.225
Hematuria	3 (4.8)	0 (0)	4 (6.3)	0 (0)	0.697
Hypertension	18 (28.6)	0 (0)	22 (34.9)	6 (9.5)	0.064
Peripheral neurotoxicity	24 (38.1)	0 (0)	26 (41.3)	0 (0)	0.616
Oral ulcer	12 (19.0)	0 (0)	18 (28.6)	0 (0)	0.210
Hand-foot syndrome	7 (11.1)	0 (0)	13 (20.6)	2 (3.2)	0.061

cating statistically significant differences between two groups. After treatment, the quality of life of patients was improved notably in Apatinib group compared with that in S-1 group (p=0.002).

Comparison of adverse reactions between the two groups of patients

The adverse reactions of apatinib combined with S-1 mainly included hematological toxicity, nausea and vomiting, abnormal renal function, impairment of hepatic function, neurotoxicity, hypertension and hand-foot syndrome. Most of the adverse reactions were in grade I-II, which were relieved after symptomatic treatment and could be tolerated for subsequent treatment, and serious adverse reactions in grade III-IV occurred rarely. Adverse reactions in grade III-IV involved leukopenia in 5 cases and 8 cases, thrombocytopenia in 3 cases and 2 cases, hypertension in 0 cases and 6 cases, and hand-foot syndrome in 0 cases and 2 cases in S-1 group and Apatinib group, respectively. No statistically significant difference was found in the incidence rate of adverse reactions between the two groups of patients (p>0.05) (Table 4).

Follow-up results of survival

As of September 2020, the follow-up period was 3-24 months. According to the follow-up results, OS was 8.1 months *vs.* 10.7 months, and PFS was 4.2 months *vs.* 5.3 months, respectively, in S-1 group and Apatinib group. The survival curve was plotted using the Kaplan-Meier method (Figure 1), and the difference in OS was compared by the Log-rank test, which was statistically significant. The results demonstrated that Apatinib group was superior to S-1 group with respect to OS (p=0.028), and no statistically significant difference was found in PFS between the two groups of patients (p=0.159).

Discussion

Chemotherapy is beneficial to patients with advanced gastric cancer for the purpose of prolonging their survival time, but it is difficult to extend the median survival time above 12 months [9]. Nowadays, molecular targeted therapy involving tumor signaling pathways such as epidermal growth factor receptor, VEGF, c-MET gene, and serine-threonine kinase has brought new hope for patients with gastric cancer, and inhibiting these tumor signaling pathways may improve therapeutic effects [10,11]. At present, second-line treatment option has not yet reached a consensus due to unsatisfactory treatment effects. It has been proven that ORR, PFS and median OS of chemotherapy drugs in second-line treatment option are 12.5-17.1%, 2.5-3.6 months and 6.3-9.6 months, respectively [12-14]. Most patients with advanced gastric cancer, due to poor physical status, cannot tolerate chemotherapy in case of progression after first-line treatment [15].

Apatinib is a new oral small-molecule VEGF-2 tyrosine kinase inhibitor, and it exerts an anticancer effect through effectively inhibiting tumor vascular growth [16]. In a phase III randomized double-blind trial, apatinib is administered for advanced and metastatic gastric cancer and gastroesophageal junction adenocarcinoma patients after failure of second-line (and above) chemotherapy, and the results indicated that median OS (6.5 months *vs.* 4.7 months) and median PFS (2.6 months *vs.* 1.8 months) are significantly amelio-

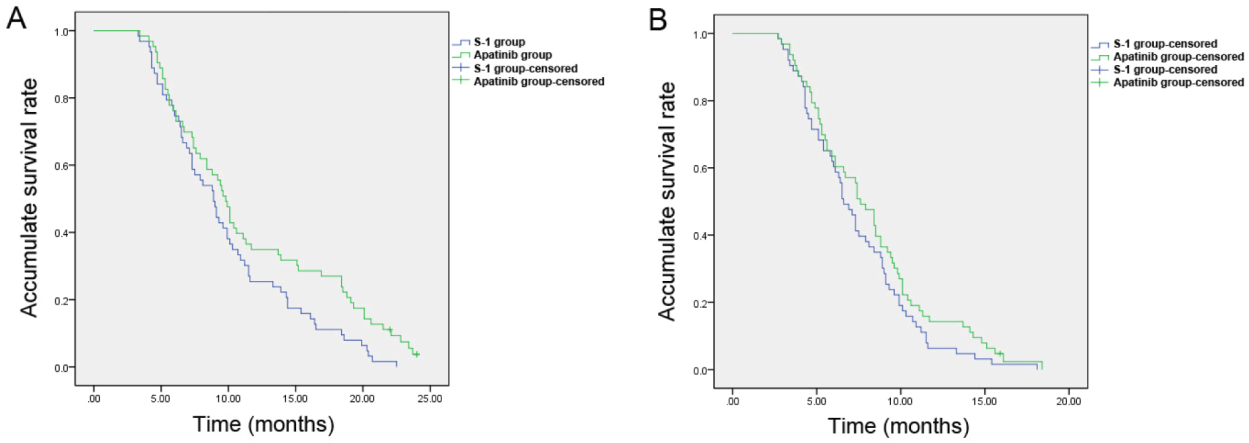

Figure 1. Kaplan-Meier survival curves of advanced gastric cancer patients. The overall survival rate **(A)** of patients in Apatinib group was significantly higher than that of S-1 group (p=0.028). The difference between progression free survival rate **(B)** of patients in S-1 group and Apatinib group had no statistical significance (p=0.159).

rated in apatinib group than those in placebo group [17]. Therefore, apatinib was approved for third-line (and above) treatment of advanced gastric cancer and gastroesophageal junction adenocarcinoma in China in 2014. S-1, consisting of tegafur, gimeracil and oteracil potassium, is kind of fluorouracil drugs with high efficiency, low toxicity and good tolerance [18]. In this study, the results displayed that apatinib combined with S-1 exhibited a synergistic effect of targeted drugs and chemotherapeutic drugs. Two-drug combination group was superior to single-drug group in terms of ORR and DCR. Two-drug combination group was superior to single-drug group with respect to OS, and no statistically significant difference was found in PFS between the two groups. The adverse reactions in grade I-II in this study mainly involved leukopenia, thrombocytopenia, oral mucositis, proteinuria, hematuria, hypertension, nausea and vomiting, diarrhea, hepatic injury and hand-foot syndrome, and those in grade III-IV included leukopenia, thrombocytopenia, proteinuria, hypertension and hand-foot syndrome. The incidence rate of adverse reactions was similar between the two groups.

As a broad-spectrum tumor marker, serum CEA is expressed in gastric cancer, lung cancer, pancreatic cancer, breast cancer and colorectal cancer, and has auxiliary reference value for clinical diagnosis, monitoring of therapeutic effects and prognostic evaluation [19]. CA19-9 is a mixture of glycoproteins with high molecular weight, and it is expressed in serum in the form of mucin. CA19-9 is abnormally highly expressed in the detection of gastric cancer, colorectal cancer, gallbladder cancer and liver cancer, and its positive rate is higher [20]. In this study, serum CEA, CA19-9 and TSGF levels were detected to assess the short-term efficacy on patients with advanced gastric cancer. The results elucidated that the serum levels of CA19-9 and TSGF were remarkably lower in two-drug combination group than those in single-drug group, and there was no statistically significant difference in the CEA level between the two groups, consistent with the conclusion of literatures, indicating that S-1 combined with apatinib has a prominent advantage in the treatment of stage III-IV gastric cancer.

The present study was a single-center retrospective study with certain limitations. For example, the number of patients enrolled was limited, the follow-up period was not long enough, and the follow-up content was not comprehensive enough. In the future, more rigorous multi-center, large-sample prospective randomized studies are recommended to verify the conclusions of this study, and the synergistic mechanism of apatinib combined with S-1 in the treatment of advanced gastric cancer needs to be further investigated.

Conclusion

In the second-line treatment of advanced gastric cancer, apatinib combined with S-1 is superior to S-1 alone in term of clinical efficacy, and its adverse reactions can be tolerated. Apatinib combined with S-1 can prominently improve the quality of life, reduce the serum tumor marker levels and prolong the OS of patients, but it cannot extend the PFS.

Conflict of interests

The authors declare no conflict of interests.

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