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ORIGINAL ARTICLE

Efficacy and prognosis analyses of apatinib combined with S-1 in third-line chemotherapy for advanced gastric cancer

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Summary

Purpose: *To explore the efficacy and safety of apatinib (an anti-angiogenic drug) combined with S-1 (a fluorouracil drug) in the third-line chemotherapy for advanced gastric cancer, and to analyze the factors influencing the prognosis.*

Methods: *Eighty-four patients with advanced gastric cancer, who did not respond to second-line or above chemotherapy and were treated in our hospital were enrolled and divided into Apatinib+S-1 group (n=42) and S-1 group (n=42), based on different treatments applied. Next, the clinical responses and adverse reactions of patients were observed and recorded. The patients were followed up through the outpatient service and telephone to record their survival and disease progression. Additionally, the factors affecting the prognosis of patients were analyzed.*

Results: *The objective response rate (ORR) and disease control rate (DCR) in the Apatinib+S-1 group were 9.5% (4/42) and 71.4% (30/42), respectively, which were significantly higher than those in the S-1 group. The main adverse reactions after therapy included neutropenia, thrombocytopenia, anemia, stomatitis, hypertension, proteinuria, hand-foot syndrome and gastrointestinal reaction, which were mostly of grade I-II. The incidence rates of hypertension, proteinuria and hand-foot syndrome were 42.9%, 26.2%, and 23.8%, respectively, in the Apatinib+S-1 group, which were overtly higher than those in the S-1 group. There was no statistically significant difference in the overall survival (OS) of patients between two groups (p=0.063), while the progression free survival (PFS) of patients was overtly longer in the Apatinib + S-1 group than that in S-1 group. Univariate analysis of PFS showed that the PFS of patients with high differentiation of tumor or post-treatment proteinuria or hand-foot syndrome was evidently higher than that of patients without high differentiation of tumor or post-treatment proteinuria or hand-foot syndrome.*

Conclusion: *Patients with advanced gastric cancer achieve relatively satisfactory short-term therapeutic effects after treatment with apatinib combined with S-1 in the third-line therapy, whose PFS is notably better than those treated with S-1 alone, and they are tolerant to adverse reactions. Highly differentiated tumors and post-treatment proteinuria and hand-foot syndrome are predictable factors for the PFS of patients.*

Key words: *apatinib, S-1, gastric cancer, advanced stage, efficacy, prognosis*

Introduction

Gastric cancer is a common malignancy all over the world. According to a new statistical report on cancers published by CA Cancer J Clin (an authoritative journal sponsored by the American Cancer Society) in 2015, there were over 950,000 new cases of gastric cancer around the world in 2012, second only to that of lung cancer, breast cancer, colorectal cancer and prostate cancer, with the highest incidence rate in East Asia, and there were about 730,000 deaths from gastric cancer, second only to lung cancer and liver cancer [1]. At present, the diagnostic rate of early gastric cancer is less than 10% in China due to atypical early symptoms. Sixty-five to 70% of gastric cancers are diagnosed

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in the middle or advanced stage, and the 5-year survival rate is relatively low (only 27.4%) [2-4]. There are many chemotherapeutic drugs used in standard first- or second-line treatment of advanced gastric cancer, but there is no recognized standard treatment regimen after the failure of second-line treatment. Besides, a considerable number of patients have good physical condition, can tolerate further treatment and urgently require safe and effective treatment to improve their quality of life and prolong their survival [5].

S-1 is mainly composed of three drugs including tegafur. Tegafur, a prodrug, is metabolized into 5-fluorouracil, of which the effect duration is prolonged by gemcitabine and the adverse reactions are attenuated by potassium oxonate. Hence, S-1 has the advantage of alleviating gastrointestinal toxicity and improving patient tolerance while ensuring the therapeutic effect compared with intravenous chemotherapy drugs [6,7]. Apatinib, a small-molecule vascular endothelial growth factor receptor 2 (VEGFR-2) tyrosine kinase inhibitor, blocks the VEGF signaling pathway to repress tumor angiogenesis. Its clinical efficacy has also been verified in phase II and III clinical trials: in apitidib group, the median progression-free survival (PFS) and disease control rate (DCR) are obviously improved, and the adverse reactions can be controlled through dose adjustment [8,9].

In this study, the clinical data of 84 patients with advanced gastric cancer treated with apatinib combined with S-1 or S-1 alone in our department from May 2015 to May 2017 were retrospectively analyzed, the clinical efficacy and safety of apatinib in the third-line chemotherapy for advanced gastric cancer were discussed, and the possible influencing factors for the prognosis of patients were analyzed.

Methods

General data

The clinical data of 84 patients with advanced gastric cancer, who did not respond to the second-line or above chemotherapy, were selected and randomly divided into two groups (Apatinib + S-1 group and S-1 alone group) to separately take apatinib combined with S-1 or S-1 alone, with 42 patients in each group. These patients were aged 23-73 years and definitely diagnosed with advanced gastric cancer via histology and/or cytology and had at least one measurable lesion (≥10 mm on spiral computed tomography (CT) scan images as per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 standard). As to gender, there were 47 males and 37 females. In terms of tumor location, there were 15 cases in fundus or cardia, 21 cases in gastric body and 44 cases

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

Parameters	*Apatinib+S-1 group (n=42)* *n (%)*	*S-1 group (n=42)* *n (%)*	*p value*
Age	58.78±10.84	60.43±10.13	0.473
Gender, n (%)			0.510
Male	25 (58.3)	22 (64.6)	
Female	17 (41.7)	20 (35.4)	
Tumor diameter (cm)	4.11±1.33	4.36±1.18	0.365
Tumor location			0.772
Gastric fundus and cardia	8 (20.8)	7 (16.7)	
Gastric body	11 (22.9)	14 (20.8)	
Gastric antrum	23 (56.2)	21 (62.5)	
Grade of differentiation			0.862
High	3 (43.8)	2 (37.5)	
Moderate	9 (25.0)	11 (29.2)	
Poor	24 (6.2)	22 (10.4)	
Undifferentiated	4 (14.6)	3 (16.7)	
Undetermined	2 (10.4)	4 (6.2)	
ECOG score			0.374
0	15 (12.5)	19 (20.8)	
1	27 (33.3)	23 (35.4)	
Previous chemotherapy			0.243
Second-line	31 (31.3)	26 (25.0)	
Second-line or more	11 (22.9)	16 (18.8)	

ECOG: Eastern Cooperative Oncology Group

in pylorus. As for tumor differentiation grade, tumors in 5 cases were highly differentiated, in 20 cases were moderately differentiated, in 46 cases were poorly differentiated, in 7 cases were undifferentiated, and in 6 cases were unclassified. According to Eastern Cooperative Oncology Group (ECOG) score, 34 cases had 0 point and 50 cases 1 point. Fifty-seven patients underwent chemotherapy below the second line, and 27 received chemotherapy above the second line. The baseline data including age, tumor size, tumor location, differentiation, ECOG score and history of chemotherapy had no statistically significant differences between two groups (p>0.05), which were comparable (Table 1). All patients enrolled were informed and signed informed consent in accordance with Declaration of Helsinki. This study was approved by the Ethics Committee of Liaocheng People's Hospital.

Exclusion criteria: hypertensive patients whose pressure level could not return to the normal range after treatment with antihypertensive drugs, patients with ≥ grade II coronary heart disease, arrhythmia or cardiac insufficiency, those with active digestive ulcers and occult blood in stool of (++), those with hematemesis or melena in the past 3 months, and those with abnormal coagulation and bleeding tendency, and those with symptomatic central nervous system metastasis, or pregnant or lactating women.

Therapeutic methods

S-1 group: S-1 dose: body surface area <1.25 m^2: 40 mg in the morning and evening, respectively; body surface area 1.25-1.50 m^2: 40 mg in the morning and 60 mg in the evening; and body surface area >1.50 m^2: 60 mg in the morning and evening, respectively, q3w, d1-14, po, with drug decrease or withdrawal at a deceleration rate of 20 mg in the case of grade III or above adverse reactions.

Apatinib+S-1 group: administration method and dose of S-1 were the same as above. In terms of apatinib, the initial dose was 500 mg/d, and the dose was increased to 850 mg/d if there were no severe adverse reactions after 1 week. In case of poor tolerance, drug decrease or withdrawal was performed according to the consensus on drug safety management of apatinib, q3w. Besides, for patients with elevated blood pressure, ACEI or ARB drugs were the preferred choices, and non-dihydropyridine calcium antagonists were forbidden.

Observation indexes

According to RECIST 1.1, routine CT, magnetic resonance imaging (MRI) and other examinations were performed at the prescribed time for efficacy evaluation: complete response (CR): tumor was completely subsided and tumor markers returned to normal for ≥ 4 weeks; partial response (PR): the sum of the longest diameter of all target lesions was decreased by ≥ 30% for ≥ 4 weeks; stable disease (SD): status between PR and PD; and progressive disease (PD): the sum of the longest diameter of all target lesions of the tumor was increased by ≥20% or new metastases were detected. Objective response rate (ORR) = CR+PR, and DCR = CR+PR+SD. Each patient should perform all the examinations to determine the baseline of the tumor lesions before enrollment, and the effect was evaluated once every 2 cycles. If the patient had discomfort, he/she should be admitted to the hospital for examination and effect evaluation. During chemotherapy, adverse reactions of patients were observed and evaluated, recorded and counted according to NCI-CTCAE version 4.0 in which the severity is classified into grade I-IV.

The patients were followed up to record the survival and tumor progression. Overall survival (OS): from the day when patients received treatment with apatinib mesylate to the day when they died or were lost to follow-up. PFS: from the day when patients received treatment with apatinib mesylate to the day when tumor progressed, or they died or were lost to follow-up. The follow-up included routine blood examination, serum biochemistry, full tumor markers evaluation (CEA, CA 19.9 and CA 72-4), gastroscopy and imaging examination, including MRI and PET-CT examinations if necessary, which ended in May 2019.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean±standard deviation (x±s), and t-test was employed for the comparison between two groups. Numerical data were expressed as ratio (%), and x^2 test was used for comparison among groups. P<0.05 suggested that the difference was statistically significant. Survival curves were plotted by Kaplain-Meier method and Log-rank test was used to compare the survival rates between groups. P<0.05 suggested a statistically significant difference.

Results

Comparisons of short-term effects

Apatinib+S-1 group had 0 case of CR, 4 cases of PR, 26 cases of SD and 12 cases of PD, and S-1 alone group had 0 case of CR, 0 case of PR, 17 cases of SD and 25 cases of PD. The ORR and DCR of patients were 9.5% (4/42) and 71.4% (30/42) in the Apatinib+S-1 group and 0% and 40.5% (17/42) in the S-1 alone group, showing statistically significant differences. The ORR and DCR of patients were remarkably higher in the Apatinib+S-1 group than those in the S-1 alone group (p=0.040, p=0.004) (Table 2).

Comparisons of adverse reactions

After treatment with Apatinib combined with S-1 group or S-1 alone group, the following major adverse reactions were observed in the 84 patients with gastric cancer: neutropenia, thrombocytopenia, anemia, stomatitis, hypertension, proteinuria, hand-foot syndrome and gastrointestinal reactions. The incidence rates of hypertension, proteinuria and hand-foot syndrome in the Apatinib+S-1 group were 42.9% (18/42), 26.2% (11/42), and 23.8% (10/42), respectively, which were markedly

higher than those in the S-1 alone group (p=0.001, p=0.002, p=0.013). There were no statistically significant differences in the remaining adverse reactions between two groups (p>0.05). Most adverse reactions were of grade I-II. The incidence rate of grade III-IV adverse reactions was slightly higher in the Apatinib+S-1 group than that in the S-1 alone group, but the differences were mostly not statistically significant (p>0.05). The incidence rate of grade III-IV hypertension was 10.2% (5/42) in the Apatinib+S-1 group, which was evidently higher than that in the S-1 group (p=0.021). When there were grade III-IV adverse reactions, symptomatic treatment or temporary withdrawal or administration after decreasing the dose of apatinib was carried out, so that no severe adverse reactions or deaths due to adverse reactions of drugs were registered in the patients (Table 3).

Table 2. Comparison of clinical efficacy of patients in the two groups

Parameters	*Apatinib+S-1 group (n=42)* *n (%)*	*S-1 group (n=42)* *n (%)*	*p value*
CR	0	0	
PR	4	0	
SD	26	17	
PD	12	25	
ORR (%)	4 (9.5)	0 (0)	0.040
DCR (%)	30 (71.4)	17 (40.5)	0.004

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate

Table 3. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Grade I-IV*		*p value*	*Grade III-IV*		*p value*
	Apatinib+S-1 group *n (%)*	*S-1 group* *n (%)*		*Apatinib+S-1 group* *n (%)*	*S-1 group* *n (%)*	
Anemia	27 (64.3)	24 (57.1)	0.503	7 (16.7)	5 (11.9)	0.533
Thrombocytopenia	28 (66.7)	25 (59.5)	0.498	8 (19.0)	5 (11.9)	0.366
Leukopenia	35 (83.3)	30 (71.4)	0.192	14 (33.3)	16 (38.1)	0.649
Nausea, vomiting	22 (52.4)	16 (38.1)	0.188	7 (16.7)	4 (9.5)	0.332
Diarrhea	23 (54.8)	15 (35.7)	0.080	7 (16.7)	6 (14.3)	0.763
Stomatitis	14 (33.3)	9 (21.4)	0.159	5 (11.9)	2 (4.8)	0.236
Hypertension	18 (42.9)	3 (7.1)	0.001	5 (10.2)	0 (0)	0.021
Proteinuria	11 (26.2)	1 (2.4)	0.002	0 (0)	0 (0)	1.000
Hand-foot syndrome	10 (23.8)	2 (4.8)	0.013	3 (7.2)	0 (0)	0.078

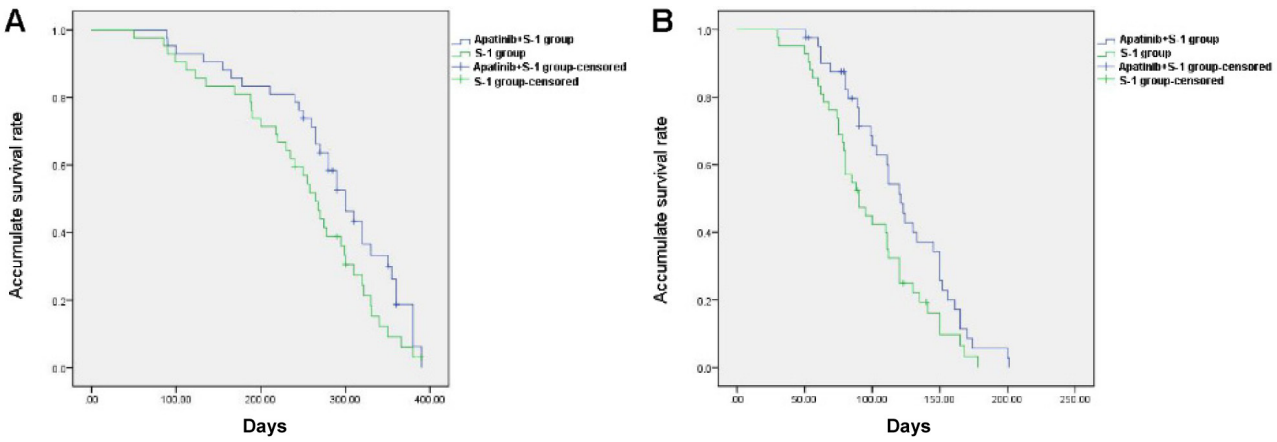

Figure 1. Kaplan-Meier survival curves of the studied patients. **A:** The difference between overall survival rate of patients in the Apatinib+S-1 group and S-1 alone group has no statistical significance (p=0.063). **B:** The progression-free survival rate of patients in the Apatinib+S-1 group was significantly higher than that of the S-1 group (p=0.020).

Results of patient survival follow-up

The median follow-up time of patients was 299 and 287 days, respectively, in the two groups. There was 1 case lost to follow-up (at 150 days after treatment) in the Apatinib+S-1 group and 2 cases lost to follow-up (at 180 and 240 days after treatment, respectively) in the S-1 alone group. The median OS of patients was 257 and 234 days, respectively, and the median PFS was 123 and 67 days, respectively, in the two groups. At the end of the follow-up, Kaplan-Meier survival curves in the two groups (Figure 1) were plotted, and the results of log-rank test revealed that the OS of patients exhibited no statistically significant difference between the two groups (p=0.063), while the PFS of patients displayed a statistically significant difference between the two groups (p=0.020), which was dramatically higher in the Apatinib+S-1 group than that in the S-1 alone group.

Table 4. Univariate analysis of predictors for PFS of patients in the Apatinib+S-1 group

Predictors	*n (%)*	*Median PFS (d)*	*95%CI*	*p value*
Age, years				0.520
>65	24 (25.3)	117	75.437-163.451	
≤65	18 (74.7)	145	15.741-311.349	
Tumor size, cm				0.391
≥5	15 (30.1)	87	39.652-148.965	
<5	27 (69.9)	129	89.034-163.940	
Tumor location				0.467
Gastric fundus and cardia	8 (20.8)	74	20.788-103.289	
Gastric body	11 (22.9)	105	33.413-202.656	
Gastric antrum	23 (56.2)	132	92.336-158.955	
Grade of differentiation				0.035
High	3 (43.8)	169	97.044-180.675	
Moderate	9 (25.0)	143	65.751-229.406	
Poor	24 (6.2)	79	22.147-115.633	
Undifferentiated	4 (14.6)	62	31.209-136.744	
Can not classified	2 (10.4)	91	41.256-153.363	
ECOG score				0.547
0	15 (12.5)	142	25.589-221-560	
1	27 (33.3)	110	30.798-230.124	
Previous chemotherapy				0.417
Second-line	31 (31.3)	133	83.397-158.702	
Second-line or more	11 (22.9)	94	66.523-127.532	
Hematologic toxicity				
Anemia	27 (64.3)	66	24.650-122.534	0.484
No anemia	15 (12.5)	129	98.320-155.387	
Thrombocytopenia	28 (66.7)	102	14.532-199.605	0.531
No thrombocytopenia	14 (33.3)	126	86.190-168.709	
Leukopenia	35 (83.3)	151	93.451-216.590	0.756
No leukopenia	7 (16.7)	103	77.513-134.520	
Non-hematologic toxicity				
Stomatitis	14 (33.3)	88	45.216-143.687	0.392
No stomatitis	28 (66.7)	130	112.304-153.898	
Hypertension	18 (42.9)	159	113.529-195.431	0.120
No hypertension	24 (57.1)	104	64.556-136.521	
Proteinuria	11 (26.2)	164	85.342-255.601	0.018
No proteinuria	31 (73.8)	97	80.813-119.894	
Hand-foot syndrome	10 (23.8)	148	93.519-210.938	0.041
No hand-foot syndrome	32 (76.2)	90	71.115-121.533	

PFS: progression free survival; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group

Univariate analysis of patient PFS

The relevant data like patient age, tumor location, tumor size, differentiation grade, ECOG score, history of chemotherapy and adverse reactions of patients in the Apatinib+S-1 group were collected to complete the univariate analysis of PFS in the Apatinib + S-1 group. The possible effects of the clinical status before enrollment and different responses after treatment of the 42 patients on PFS were analyzed to objectively reveal the predictive factors for PFS of patients with advanced gastric cancer treated with Apatinib combined with S-1. According to Table 4, the correlations of the basic conditions of patients before treatment such as age, tumor size, tumor location, history of chemotherapy and ECOG score with patient PFS were of no statistical significance (p>0.05), while tumor differentiation was significantly correlated with PFS, and the PFS of patients with highly differentiated tumor was overtly higher than that of those with poorly differentiated tumor (p=0.035). The adverse reactions of patients receiving Apatinib combined with S-1 were analyzed, and it was found that hematological toxicity, stomatitis and hypertension had no statistically significant relations with patient PFS (p>0.05), while proteinuria and hand-foot syndrome were evidently associated with patient PFS, and the PFS of patients with proteinuria or hand-foot syndrome after treatment was notably higher than that of patients without proteinuria or hand-foot syndrome after treatment (p=0.018, p=0.041).

Discussion

The prognosis of patients with advanced gastric cancer is poor, with a 5-year OS rate of only about 10.8% [10]. As to the treatment of advanced disease, the options are limited at present, with unsatisfactory therapeutic effects. Among them, chemotherapy is the basis for the treatment of advanced gastric cancer, but the side effects of chemotherapy drugs are great. Moreover, some patients are poorly tolerant and fail to complete the full course of treatment, which also affects the treatment efficacy. Meanwhile, chemotherapy has a certain bottleneck and limited selectivity. Given this, more precise treatment methods for advanced gastric cancer are needed to prolong the survival and improve the patient quality of life. Currently, the first-line chemotherapy regimen for patients with advanced gastric cancer is still a combination of fluorouracil and platinum drugs. For second-line chemotherapy, the chemotherapy with topoisomerase inhibitors and taxanes still displays a significant advantage in survival compared with BCS [11-13]. However, the efficacy of the advanced third-line chemotherapy drugs has a relatively significant reduction, which remains a major challenge in clinical work.

Apatinib is an oral small-molecule anti-angiogenic drug independently developed in China, of which the action target is mainly VEGFR-2, and it represses mitogen-activated protein by binding to VERFR-2 target, thereby inhibiting the proliferation of vascular endothelial cells [14]. Moreover, Apatinib has achieved certain effects in phase II and III clinical studies of advanced gastric cancer, proving its safety and efficacy in advanced disease, which, therefore, has been listed in 2014 for the third-line and above treatment of advanced gastric cancer [8,9,15,16]. Many studies have manifested that Apartinib alone remarkably prolongs the median OS and PFS of patients with advanced gastric cancer who did not respond to second-line chemotherapy. For solid tumors resistant to drugs, Apatinib is able to inhibit p-glycoprotein transmission, thus reversing the multi-drug resistance mediated by adenosine triphosphate-binding cassette, subfamily B, member 1 (ABCB1) and adenosine triphosphate-binding cassette transporter G2 (ABCG2), and it also acts on leukemia cells with overexpressed ABCG2 and ABCB1, thereby improving the efficacy of chemotherapeutic drugs [17,18]. These basic molecular biology studies have clearly pointed out that Apatinib is able to be combined with conventional ABCB1 and ABCG2 matrix chemotherapy drugs to overcome the multidrug resistance in clinical tumor chemotherapy, thus improving the efficacy of combined chemotherapy.

Therefore, this study retrospectively analyzed and compared the efficacy and safety of Apatinib combined with S-1 and S-1 alone in the third-line treatment of advanced disease, and was found that the ORR and DCR of patients in the Apatinib+S-1 group were 9.5% and 71.4%, respectively, which were markedly higher than those in the S-1 alone group (p=0.040, p=0.004). The follow-up results demonstrated that there was no statistically significant difference in the OS of patients between two groups (p=0.063), while the PFS of patients was overtly longer in the Apatinib+S-1 group than that in the S-1 alone group (p=0.020), which is basically in line with the findings of other researchers [19,20].

As to adverse reactions, no statistically significant differences were found in the incidence rates of neutropenia, thrombocytopenia, anemia, stomatitis and gastrointestinal reactions, most of which were grade I-II, between two groups, while the incidence rates of hypertension, proteinuria and hand-foot syndrome were significantly higher in the Apatinib+S-1 group than those in the S-1

alone group (p=0.001, p=0.002, p=0.013). Univariate analysis uncovered that the PFS of patients with high tumor differentiation grade or post-treatment proteinuria or hand-foot syndrome was evidently longer than that of those without high tumor differentiation or post-treatment proteinuria or hand-foot syndrome (p=0.035, p=0.018, p=0.041). The specific mechanism by which antiangiogenic inhibitors lead to hypertension remains unclear, and it may be related to declined N0/PGI2 secreted by endothelial cells/platelets, abnormal vascular density (small blood vessels and capillaries), vascular stiffness and endothelin dysfunction [21-23]. Antiangiogenic pathways can also affect the structure and function of glomerular endothelial cells, thereby resulting in changes in vascular permeability [24]. Such inhibitors may damage glomerular endothelial cells and podocytes, changing the structural and charging barriers of the glomerular filtration membrane and giving rise to increased protein filtration that exceeds the re-absorption of renal tubules, thus forming renal proteinuria. The mechanism of occurrence of hand-foot syndrome is unclear, which may be due to the excess Apatinib residue in the skin caused by damaged vascular repair of the dermis due to the inhibition of anti-vascular pathways [25].

There are still some shortcomings in this study. The sample size was small, the follow-up time was insufficient, the patients were not subgrouped to analyze for tumor stage and history of treatment, and flexible time for review of some patients and biased accurate tumor progression time produced an influence on the analysis of patient prognosis. Hence, multicenter randomized controlled trials with a large sample size are needed in the future to verify the conclusion of this study, so as to provide a more powerful basis for the third-line treatment of patients with advanced gastric cancer.

Conclusions

Patients with advanced gastric cancer achieve relatively satisfactory short-term therapeutic effects after treatment with Apatinib combined with S-1 in the third-line therapy, whose PFS is notably better than those treated with S-1 alone, and they are tolerant to adverse reactions. Highly differentiated tumor and post-treatment proteinuria and hand-foot syndrome are predictive factors for the PFS of patients.

Conflict of interests

The authors declare no conflict of interests.

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