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ORIGINAL ARTICLE

Analysis on safety and efficacy of low-dose apatinib combined with paclitaxel as second-line treatment for advanced gastric cancer

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Summary

Purpose: *To investigate the safety and efficacy of low-dose apatinib combined with chemotherapy in the second-line treatment of advanced gastric cancer.*

Methods: *After retrospectively analyzing the clinical data of 96 patients with advanced gastric cancer admitted to the cancer center of Shanxi Bethune hospital from January 2016 to January 2020, and after progression to first-line chemotherapy, we used low-dose apatinib (250mg and 500mg respectively) combined with chemotherapy as second-line treatment. Compared with simultaneous simple chemotherapy, we analyzed the objective effective rate (ORR), disease control rate (DCR), progression-free survival (PFS) as well as overall survival (OS) of the combination treatment to evaluate the effect and related adverse reactions.*

Results: *Among the 96 patients, the most common adverse reactions were hypertension, hand-foot skin reaction and proteinuria in the targeted combined chemotherapy group. The ORR and DCR values of the targeted combined chemotherapy group were higher. The mPFS of 250 and 500 mg combined chemotherapy group and chemotherapy-alone were 5.8, 6.1 and 4.3 months, mOS were 7.2, 7.5 and 6.7 months, respectively. The results showed that mPFS and mOS of apatinib combined with chemotherapy were significantly better than that of chemotherapy with statistical significance.*

Conclusion: *Second-line chemotherapy in the treatment of advanced gastric cancer, with low dose of apatinib combined with chemotherapy not only offers good survival benefits, but does not increase the drug-related adverse reactions comparing with the simple chemotherapy group.*

Key words: *apatinib; advanced gastric cancer; low dose; adverse event*

Introduction

As a malignant tumor with the fifth incidence rate and the third mortality rate, gastric cancer occurs in about 1 million cases each year with incidence rate being highest in East Asia [1], and kills 783,000 patients [2]. The cancer has already metastasized at diagnosis in the majority of the patients, who have lost the chance of radical surgery. Therefore, the primary goal of treatment is to prolong the survival of patients and possibly improve their quality of life. In the clinic, radiotherapy and chemotherapy are still the main treatment methods for advanced gastric cancer. Studies have shown that the formation of tumor angiogenesis is one of the main factors in the progress and metastasis of malignant tumors [3]. Therefore, the clinical application of anti-tumor angiogenesis drugs plays an increasingly important role in the treatment of tumors.

Vascular endothelial growth factor and receptor-mediated signal transduction pathway are important pathways of tumor angiogenesis. As a small molecule anti angiogenic agent developed by China Hengrui Pharma Company, apatinib can effectively

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inhibit tumor angiogenesis as well as tumor angiogenesis and metastasis [4,5]. Apatinib was listed in China in 2015 for use in advanced gastric cancer or carcinoma of gastroesophageal junction with failure in second-line chemotherapy, of which the standard dose is 850 mg/d. However, in clinical practice, because most of them with advanced gastric cancer are in poor physical condition after the initial line treatment and have also poor tolerance due to advanced age, most of them treated with conventional dose of apatinib experienced intolerable adverse reactions, leading to the termination of treatment and unsatisfactory therapeutic effect [6].

We found that low-dose apatinib combined with chemotherapy can improve the disease control rate (DCR) and achieve good tolerance [7]. Therefore, the clinical data of patients with different low-dose apatinib combined with chemotherapy were collected and compared to chemotherapy alone, evaluating the safety and effectiveness of the treatment scheme, providing a reference for the treatment of advanced gastric cancer.

Methods

Clinical data

We retrospectively analyzed the clinical data of 96 patients with advanced metastatic gastric cancer who visited the cancer center of Shanxi Bethune hospital from January 2016 to June 2020. All of the patients were

Table 1. Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
ECOG score 0-2 points.	Hypertension could not be reduced to normal by antihypertensive drug (systolic blood pressure>140mmHg/ diastolic blood pressure> 90mmHg)
Objective imaging examination such as CT or MR can measure the lesions.	Cardiac insufficiency≥grade II
Blood routine, coagulation as well as liver and kidney function were normal.	Occurred active bleeding within 3 months
The function of bone marrow, heart, liver and kidney were normal.	Coagulation dysfunction (INR>1.5×ULN, APTT>1.5×ULN)
	Pregnant or lactating women

Table 2. Basic information of patients

Parameters	*Aparinib (500mg) +chemotherapy group*	*Aparinib (250mg) +chemotherapy group*	*Chemotherapy group*
Number of cases	35	29	32
Gender			
Male	20	19	15
Female	15	10	17
Average age	61 (39-76)	58 (35-78)	3 (36-71)
ECOG PS score			
0-1	28	16	18
2	7	13	14
Tumor types			
Adenocarcinoma	23	22	25
Mucinous adenocarcinoma	10	8	6
Adenosquamous carcinoma	2	1	1
Differentiation grade			
G1 (well differentiated)	6	2	1
G2 (moderately differentiated)	8	5	3
G3 (poorly differentiated or undifferentiated)	21	22	28
Metastasis (distant metastasis)			
Liver metastasis	14	11	12
Peritoneal carcinomatosis	8	5	4
Pulmonary metastasis	7	8	9
Pancreatic metastasis	2	0	1
Adrenal metastases	1	2	1
Bone metastases	3	3	5

ECOG PS: Eastern Cooperative Oncology Group performance status

to receive second-line treatment. The inclusion and exclusion criteria are shown in Table 1. According to the dosage of apatinib, the patients were divided into 500 mg combined chemotherapy group, 250 mg combined chemotherapy group and simple chemotherapy group, respectively. The basic clinical information of patients is shown in Table 2, who were followed up until June 30, 2020.

Treatment

The study included 96 patients with advanced gastric cancer confirmed by histopathology, whose disease progression was made after first-line treatment. According to the clinical treatment plan, they were divided into three groups: 500 mg combined with chemotherapy group, 250 mg combined with chemotherapy group and chemotherapy alone. The therapeutic schedule of apatinib was: oral, once a day; single drug paclitaxel dose was 135 mg/m^2, repeated every 21 days, with efficacy evaluated every 2 cycles. Disease progression or intolerable adverse reactions dictated stoppage of medication. The data of all patients were collected retrospectively. Informed consents of antitumor target and chemotherapy were signed during treatment.

Safety evaluation

The safety evaluation of treatment was evaluated according to NCI CTCAE 4.0 for all treated patients. The adverse events during treatment were observed and clinical manifestations along with occurrence, duration, severity and treatment of adverse drug reactions were recorded.

Efficacy evaluation

At least one measurable lesion (≥10 mm) should had been observed by imaging examination for all patients. RECIST criteria (RECIST1.1) were used to evaluate the objective efficacy. The evaluation with every two cycles of chemotherapy was divided into complete remission (CR), partial remission (PR), disease stability (SD) and disease progression (PD). Objective remission rate (ORR) was calculated by CR and PR, while disease control rate (DCR)was the sum of CR, PR and SD . Progression-free survival (PFS) was defined as the time from the beginning of medication to progression or death. Overall survival (OS) was the time from the beginning of medication to death. The follow-up time ranged from 2 to 18 months, and the last follow-up was June 2020.

Statistics

IBM SPSS Statistics 20 software was used to analyze the data. Descriptive statistical analysis was conducted for safety evaluation, Chi square test was used to compare adverse events between three groups. The Kaplan-Meier method was used to estimate the median PFS and OS. $P<0.05$ was considered statistically significant.

Results

Safety analysis

Among the 96 patients, there were 35 patients in the 250 mg apatinib combined with the chemotherapy group, as well as 29 patients in the 500 mg apatinib combined with the chemotherapy

Table 3. Comparison of adverse reactions in each group (%)

Feature	*Adverse event incidence n (%)*					*Adverse event incidence of grade III and above*				
	Aparinib (250mg) +chemotherapy group (n=35)	*Aparinib (500mg) +chemotherapy group (n=29)*	*Chemotherapy (n=32)*	x^2	*p*	*Aparinib (250mg) +chemotherapy group (n=35)*	*Aparinib (500mg) +chemotherapy group (n=29)*	*Chemotherapy (n=32)*	x^2	*p*
AE: non- hematologic toxicities										
Hypertension	9 (25.7)	13 (44.8)	0 (0)	15.834	0.000	2 (5.7)	3 (11.5)	0 (0)	3.326	0.190
Hand-foot skin reactions	8 (22.8)	11 (37.9)	0 (0)	14.114	0.001	1 (2.8)	2 (6.9)	0 (0)	2.403	0.301
Proteinuria	14 (40.0)	13 (44.8)	0 (0)	18.965	0.001	1 (2.8)	4 (13.7)	0(0)	6.479	0.039
Fatigue / loss of appetite	17 (48.5)	19 (65.5)	14 (43.7)	3.160	0.206	3 (8.5)	4 (13.7)	2 (6.2)	1.061	0.588
Diarrhea	8 (22.8)	9 (31.0)	2 (6.2)	6.213	0.045	2 (5.7)	6 (20.6)	2 (6.2)	4.704	0.095
Elevated liver enzymes	11 (31.4)	10 (34.4)	6 (18.7)	2.160	0.340	2 (5.7)	5 (17.2)	1 (3.1)	4.463	0.107
Hyperbilirubinemia	8 (22.8)	10 (34.4)	4 (12.5)	4.162	0.125	1 (2.8)	4 (13.7)	0 (0)	6.479	0.039
Hematology AE										
Leukopenia	16 (45.7)	16 (55.1)	10 (31.2)	3.624	0.163	6 (17.1)	8 (27.5)	5 (15.6)	1.615	0.446
Hemoglobin reduction	11 (21.1)	8 (28.2)	5 (17.3)	2.375	0.305	3 (8.5)	4 (13.7)	2 (6.2)	1.061	0.588
Thrombocytopenia	17 (48.3)	23 (65.0)	9 (28.7)	16.084	0.000	6 (17.1)	9 (31)	3 (9.3)	4.778	0.092

Table 4. Comparison of clinical efficacy of patients in the three groups

Group	*Aparinib (250mg) +chemotherapy group (n=35)*	*Aparinib (500mg) +chemotherapy group (n=29)*	*Chemotherapy (n=32)*	x^2	*p*
CR	0	0	0		
PR	4	5	2		
SD	10	9	6		
PD	21	15	24		
ORR (95%CI)	11.4	17.2	6.2	1.812	0.404
DCR (95%CI)	40.0	48.2	25.0	6.282	0.160

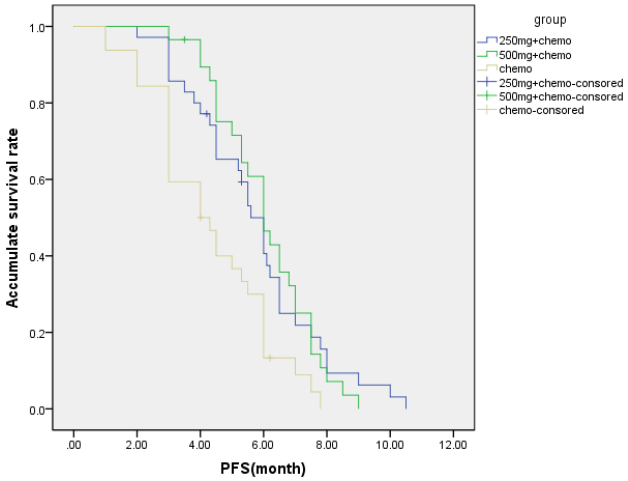

Figure 1. Kaplan-Meier survival curves. The progression-free survival rate of patients in the apatinib (250mg/500mg)+ chemotherapy group was significantly higher than that of the chemotherapy group (p=0.003).

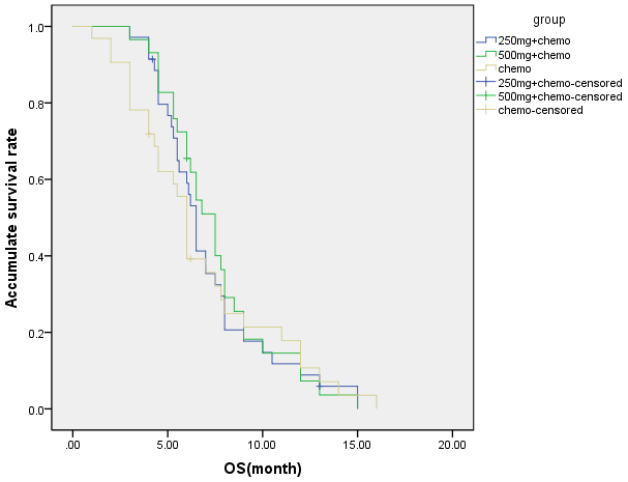

Figure 2. Kaplan-Meier survival curves. The difference between overall survival rate of patients in the three groups was not significantly different (p=0.820).

group and 32 patients in the chemotherapy-alone group. The drug-related adverse reactions in the targeted combined chemotherapy group mainly focused on non-hematologic toxicity, with hypertension (25.7%, 44.8%), hand-foot skin reaction (22.8%, 37.9%) and proteinuria (40%, 44.8%) as the most common, of which the incidence of non-hematological drug-related adverse event (AE) with grade III and above mainly consisted of hypertension, proteinuria and diarrhea (x^2=6.479, p<0.05). The adverse reactions of hematologic drug-related mainly included leukopenia (45.7, 55.1, 31.2%), decreased hemoglobin (21.1%, 28.2%, 17.3%) and thrombocytopenia (48.3, 65, 28.7%), of which thrombocytopenia was more obvious in the targeted combined chemotherapy group, with significant difference among the three groups (x^2=16.084, p<0.05), Leucopenia and thrombocytopenia were the most common in hematological drug-related adverse reactions with grade III and above.

Efficacy

After treatment, there was no case of complete remission, 11 cases had partial remission, 25 cases stable disease 60 cases progressive disease in the three groups, of which the ORR was 11.4%, 17.2%, 6.2%, while the DCR was 40.4%, 48.2%, and 25.0%, respectively. The ORR and DCR in the targeted combined chemotherapy group were significantly higher than in the chemotherapy group (Table 4).

Of 96 patients 5 were lost to follow up and 8 are still alive. The mPFS was 5.8 months (95% CI: 5.062-6.446) in the 250 mg dose combined chemotherapy group and 6.1 months (95% CI: 5.509-6.620) in the 500 mg dose combined chemotherapy group and 4.3 months (95% CI: 3.672~5.001) in the chemotherapy group, while the mOS was 7.2 months (95% CI: 6.148-8.165) in the 250 mg dose combined chemotherapy group and 7.5 months (95% CI: 6.148-8.165) in the 500 mg dose combined chemotherapy group 585 as well as 6.7 months

(95% CI: 5. 350- 8.108) in the chemotherapy group. Therefore, apatinib combined with chemotherapy showed advantages in mPFS and mOS compared with the chemotherapy group. For PFS log rank test showed p = 0.003 and OS p = 0.820 (Figures 1 and 2).

Discussion

It is very hard to deal with those patients with advanced metastatic gastric cancer in the clinic because of their poor condition, heavy tumor burden, drug resistance after multiline treatments and other problems. The primary aim of our clinical oncologists was to increase the long-term patient survival along with the improvement of their quality of life. In recent years, anti-vascular therapy has become a hot spot in the field of tumor research. The target of apatinib is vascular endothelial growth factor receptor-2 (VEGFR-2), which can not only selectively bind with VEGFR-2, but also competitively inhibit the binding of VEGF and VEGFR-2. In addition, it can inhibit the tyrosine kinases such as PDGFR - β, Ret, c-kit and c-src to decrease their activities [8,9] , so as to play an anti-tumor role by inhibiting the proliferation as well as migration of tumor cells and the formation of vascular endothelial cells.

So far, chemotherapy always has been the standard treatment for advanced gastric cancer. According to the international standard clinical guidelines, the first-line treatment is chemotherapy based on fluorouracil combined with platinum, while the second-line treatment is mainly single drug chemotherapy based on paclitaxel. We have found that anti-vascular drugs combined with paclitaxel as second-line treatment of metastatic gastric cancer after first-line treatment failure has achieved good results [10-12]. However, most patients with the recommended dose (850mg/d) developed intolerable adverse reactions. Through a number of clinical observations, low-dose apatinib combined with chemotherapy can also significantly improve the disease control rate [13,14].

The clinical data of 96 patients with advanced metastatic gastric cancer was retrospectively analyzed. After the first-line treatment with disease progression, the second-line patients were given two different low-dose therapies with 250 mg and 500 mg of apatinib combined with paclitaxel chemotherapy. Comparing the single-drug paclitaxel chemotherapy group with the control group, we found that ORR was 11.4%, 17.2%, 6.2%, and DCR was 40.4%, 48.2%, 25.0%, respectively. The ORR and DCR in the targeted combined chemotherapy group were significantly higher than in the chemotherapy-alone group. Meanwhile, we analyzed the PFS and OS of the targeted combined chemotherapy group, which revealed that the mPFS in the 250 mg dose combined chemotherapy group was 5.8 months, in the 500 mg dose combined chemotherapy group was 6.1 months, as well as in the chemotherapy-alone group was 4.3 months, clearly showing the mPFS of the combination treatment was more prolonged than the chemotherapy-alone group with significant results. In addition, the mOS was 7.2 months in the 250 mg dose combined chemotherapy group, 7.5 months in the 500 mg dose combined chemotherapy group and 6.7 months in the paclitaxel chemotherapy group. Therefore, the mOS of patients in the combination chemotherapy group was superior to the chemotherapy-alone group. The overall survival time of patients in the combination chemotherapy group was longest, contrary to the chemotherapy-alone group which was shortest, which meant the survival time of patients in the combination chemotherapy group was significantly longer than in the chemotherapy-alone group. The overall survival time of the 500 mg group was not different from the 250 mg group. Compared with previous studies on the first-line treatment [15], the second-line treatment had achieved satisfactory survival benefits, which provided a good clinical basis for the second-line treatment of advanced metastatic gastric cancer.

In addition to the observation of clinical efficacy, drug-related adverse reactions were another major target of this study. Adverse reactions of apatinib include hypertension, hand-foot skin reactions (HFSR), proteinuria, bleeding tendency, fatigue, diarrhea, transient elevated aminotransferase, thrombocytopenia, leucopenia, etc. Other rare adverse reactions include bleeding, arteriovenous thrombosis, rash, loss of appetite, nausea and vomiting, oral ulcers, hoarseness, and paronychia [16-18]. In this study, we monitored and analyzed the adverse reactions in the treatment process of patients to find out the overall adverse reactions and adverse reactions above III. The drug-related adverse reactions in the targeted combined chemotherapy group mainly consisted of non-hematologic toxicity, with hypertension, hand-foot skin reactions and albuminuria as the most common, which were in line with the common adverse reactions of anti-vascular targeted therapies. In addition, the incidence of adverse reactions of the 500 mg group was higher than that of 250 mg group. Hematologic drug-related adverse reactions mainly included leucopenia, hemoglobin reduction and thrombocytopenia, among which the thrombocytopenia was more obvious in the 500mg combined with the chemotherapy

group, with statistical difference. Based on the efficacy evaluation results of the 500mg and 250mg apatinib groups, we found that PFS and OS tended to be prolonged, but without statistical difference, so we adopted low-dose apatinib (250 mg) combined with chemotherapy to treat the elderly patients with poor physical condition score, which can decrease side effects and achieve good survival benefit.

To sum up, problems exist with the low effective rate of second-line treatment of advanced gastric cancer. Anti-vascular targeted drugs combined with chemotherapy and small molecule targeted drugs for anti-tumor angiogenesis are one of the optional strategies, by which most patients have achieved good clinical benefits [11,12,19]. Meanwhile, a number of clinical studies have confirmed that apatinib has certain therapeutic effect in malignant tumors such as lung cancer, liver cancer, ovarian cancer, sarcoma, colorectal cancer, etc [20-24]. Yet, this approach can also lead to drug-related adverse reactions for most patients receiving conventional dose.

Conclusions

Our study suggests that low-dose apatinib combined with chemotherapy as second-line treatment of advanced gastric cancer has achieved better disease control rate than chemotherapy-alone, becoming one of the safe and effective strategies in the second-line treatment of advanced gastric cancer because of its low incidence of adverse reactions and good tolerance.

Conflict of interests

The authors declare no conflict of interests.

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