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Treatment effect of apatinib combined chemotherapy as second-line or above therapy in patients with advanced gastric cancer or adenocarcinoma of the gastroesophageal junction

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Received March 9, 2020, accepted April 3, 2020

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Pharmazie 75: 389-394 (2020) *doi: 10.1691/ph.2020.0403*

This study aimed to compare the therapeutic effects between apatinib combined chemotherapy and chemotherapy alone as second-line or above therapy in advanced gastric cancer (GC) or adenocarcinoma of the gastroesophageal junction (AGEJ). The clinical data of advanced GC or AGEJ patients, including sex, age, Eastern Cooperative Oncology Group (ECOG) grading, chemotherapy regimen, pathological grading, location of primary lesion, previous gastrectomy, metastases, previous chemotherapy or radiotherapy were retrospectively collected, and the progression-free survival (PFS) was recorded. 127 patients underwent apatinib combined chemotherapy and 60 patients underwent chemotherapy regimen alone. Disease control rate (DCR) of patients with apatinib combined chemotherapy was higher than that of chemotherapy alone (P=0.033). A Kaplan-Meier (KM) plot showed that PFS was significantly longer in patients receiving apatinib combined chemotherapy than those treated by chemotherapy alone (P = 0.002). The PFS of patients with a number of metastatic lesions ≤ 2 was obviously longer than that of patients with a number of metastatic lesions > 2 (P < 0.001). Cox regression analysis revealed that PFS was independently associated with the number of metastatic lesions >2 (HR=2.129, 95% CI: 1.256-3.608, P=0.005) and treatment methods (chemotherapy alone or apatinib combined chemotherapy) (HR=1.427, 95% CI: 1.055-1.930, P=0.021). Compared with chemotherapy alone, apatinib combined chemotherapy could significantly improve DCR and prolong the PFS in advanced GC or AGEJ cases who had failed in at least first-line chemotherapy with acceptable tolerance.

1. Introduction

Gastric cancer (GC) remains one of the most serious malignant tumors in the world. More than 70% of patients are from Southeast Asia, and half of them are Chinese. The incidence rate and mortality rate rank the third place among all malignant tumors in China. Chemotherapy-based comprehensive treatment is usually applied to prolong the survival time of GC patients (Hamashima 2014). Although a variety of chemotherapeutic drugs have been used for standard first- or second-line treatment of advanced GC, there is still lack of accepted standard treatment regimen after second-line treatment failure (Johnston and Beckman 2019).

Angiogenesis is one of the crucial processes in the malignant growth of tumors. Persistent angiogenesis is associated with the occurrence, development and metastasis of tumors. Anti-angiogenesis is an effective way and important method for tumor treatment (Chen et al. 2017; Takahari 2017). Apatinib belongs to a new generation of tyrosine kinase inhibitors. The main target of apatinib is vascular endothelial growth factor receptor-2 (VEGFR2). Apatinib could inhibit the binding of VEGF and autophosphorylation, suppress angiogenesis, reduce tumor microvessel density, and effectively prevent the growth, proliferation and migration of tumor blood vessels (Zhao et al. 2018). A multicenter, randomized, double-blind trial (NCT01512745) included 267 patients with advanced GC or adenocarcinoma of the gastroesophageal junction (AGEJ) who underwent prior failure to second-line chemotherapy, with 176 patients in the apatinib group, and 91 cases in the placebo group. Median overall survival (OS) time in the two groups were 6.5 months and 4.7 months, respectively. And median progression free survival (PFS) were 2.6 months and 1.8 months, respectively. The adverse reactions of patients in each group were controllable (Qin 2014).

However, the clinical efficacy of anti-angiogenic drugs in combination with chemotherapy for advanced GC remained unclear. A previous study had indicated that compared with paclitaxel alone, ramucirumab combined with paclitaxel could increase the OS rate of patients with advanced GC or AGEJ who failed in their first-line treatment (Wilke et al. 2014). The mechanism of ramucirumab, which was the tumor angiogenesis inhibitor against the VEGFR-2, was like that of apatinib in the treatment of advanced GC or AGEJ, and was included in NCCN Clinical Practice Guidelines (October 2015) as second-line drug for advanced GC (Fornaro et al. 2016). Therefore, our study aimed to explore the treatment effect of apatinib combined chemotherapy and chemotherapy alone as second-line or above therapy in advanced GC or AGEJ patients.

2. Investigations and results

2.1. Baseline clinical characteristics of the study participants

A total of 187 cases with advanced GC or AGEJ met the inclusion and exclusion criteria, of which 127 received apatinib combined chemotherapy and 60 patients received chemotherapy alone..

Table 1: Baseline clinical characteristics of the study participants

Variables	Apatinib combined chemotherapy (n=127)	Chemotherapy alone (n=60)	P value
Sex			
Male	87(68.5%)	42(70.0%)	0.836
Female	40(31.5%)	18(30.0%)	
Age (years old)			
<65	80(63.0%)	37(61.7%)	0.861
≥65	47(37.0%)	23(38.3%)	
ECOG			
0	65(51.2%)	28(46.7%)	0.564
1	62(48.8%)	32(53.3%)	
Chemotherapy regimens			
FU	42(33.0%)	19(31.7%)	0.401
PTX	34(26.8%)	14(23.3%)	
FU, PTX/DOC, platinum	32(25.2%)	12(20.0%)	
CPT-11	19(15.0%)	15(25.0%)	
Pathological results			
High differentiation	47(37.0%)	18(30.0%)	0.738
Moderate differentiation	24(18.9%)	14(23.3%)	
Poor differentiation	50(39.4%)	24(40.0%)	
Signet-ring cell carcinoma	6(4.7%)	4(6.7%)	
Primary lesions			
Gastric area	57(44.9%)	22(36.7%)	0.201
Gastroesophageal junction	70(55.1%)	38(63.3%)	
Previous gastrectomy			
Ye	65(51.2%)	29(48.3%)	0.756
No	62(48.8%)	31(51.7%)	
Metastases			
Peritoneal metastasis	57(44.9%)	21(35.0%)	0.201
Other organ metastases	70(55.1%)	39(65.0%)	
Number of metastatic lesions			
≤ 2	83(65.4%)	44(73.3%)	0.275
>2	44(34.6%)	16(26.7%)	
Previous chemotherapy			
First line	57(44.9%)	23(38.3%)	0.398
Second line or above	70(55.1%)	37(61.7%)	
Radiotherapy			
Yes	25(19.7%)	14(23.3%)	0.566
No	102(80.3%)	46(76.7%)	
ORR	21(16.5%)	9(15.0%)	0.789
DCR	72(56.7%)	24(40.0%)	0.033

ECOG: Eastern Cooperative Oncology Group; FU: fluorouracil; PTX: taxanes; CPT-11: irinotecan; DOC: docetaxel; ORR: Objective response rate; DCR: Disease control rate.

Baseline data of the two groups were comparable, including gender, age, ECOG grading, chemotherapy regimen, pathological results, location of primary lesion, previous gastrectomy, metastases, number of metastatic lesions, previous chemotherapy and radiotherapy (all $P > 0.05$). The results are shown in Table 1.

2.2. Short-term efficacy and survival analysis

ORR was 16.5% in the apatinib combined chemotherapy group and 15.0% in the chemotherapy alone group, respectively. No significant difference was observed between the two groups. The DCR of patients in the apatinib combined chemotherapy group was higher than that of chemotherapy alone group (56.7% vs 40.0%, P=0.033). A Kaplan-Meier plot indicated that the PFS of apatinb combined chemotherapy group (10.0 months, 95% CI: 8.54-11.57) was obviously longer than that of chemotherapy alone group (8.0 months, 95% CI: 6.50-9.51, $P = 0.002$), see Fig. 1. It also became obvious that the PFS of patients with metastatic lesions ≤ 2 (10.0 months, 95% CI: 8.54-11.47) was significantly longer than that of patients with metastatic lesions > 2 (8.0 months, 95% CI: 7.47-8.54, $P < 0.001$), see Fig. 2.

2.3. Multivariate analyses

Cox regression analysis revealed that after adjusting for other confounding factors, PFS was independently associated with the

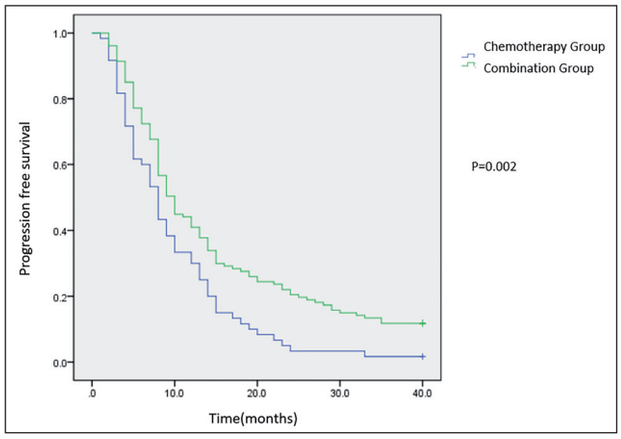

Fig. 1: KM curve of PFS. The PFS of patients in apatinib + chemotherapy group was obviously longer than that of cases in the chemotherapy alone group.

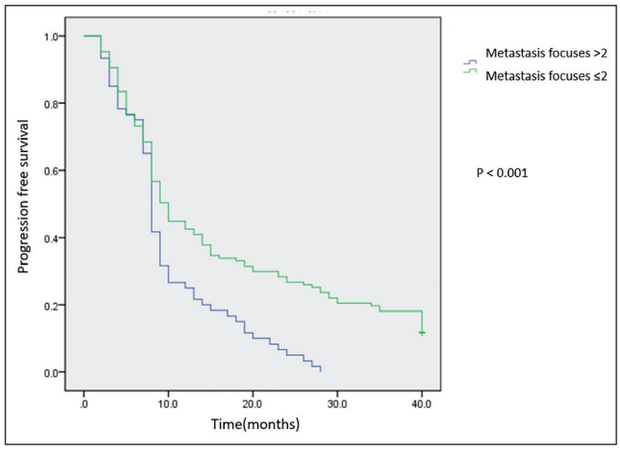

Fig. 2: KM curve of PFS. The PFS of patients with number of metastatic lesions ≤ 2 was significantly longer than that of patients with number of metastatic lesions > 2

number of metastatic lesions >2 (HR=2.129, 95% CI: 1.256-3.608, P=0.005) and treatment methods (chemotherapy alone or apatinib combined chemotherapy) (HR=1.427, 95% CI: 1.055-1.930, P=0.021), as shown in Table 2.

2.4. Safety analysis

All the 187 patients underwent at least two cycles of chemotherapy. Safety data for both are listed in Table 3. Common adverse reactions included leukopenia, neutropenia, anemia, thrombocytopenia, proteinuria, hypertension, hand-foot syndrome, elevated transaminases, hyperbilirubinemia, hemorrhage, sensory neuropathy, abdominal pain, vomiting or loss of appetite, hypoproteinemia and diarrhea. Compared with the chemotherapy alone group, the proportions of patients with grade III or IV hand-foot skin reactions, proteinuria, and hypertension were higher in the apatinib combined chemotherapy group (all $P < 0.05$). All above-mentioned toxic reactions were within the tolerable range.

3. Discussion

Our study indicated that PFS of the apatinb combined chemotherapy group (10.0 months, 95% CI: 8.54-11.57) was longer than that of the chemotherapy alone group (8.0 months, 95% CI: 6.50-9.51, $P = 0.002$). The apatinb combined chemotherapy group extended PFS for about 2 months. Cox regression analysis revealed that after adjusting for other confounding factors, PFS was independently associated with the number of metastatic lesions >2 (HR=2.129, 95% CI: 1.256-3.608, P=0.005) and treatment methods (chemotherapy alone or apatinib combined chemotherapy) (HR=1.427, 95% CI: 1.055-1.930, P=0.021).

Recently, China has applied taxanes, oxaliplatin and irinotecan as the main chemotherapy regimens to rescue patients with advanced GC or AGEJ who fail in their first-line treatment. However, due to the AEs of chemotherapy drugs, drug resistance of tumor cells and other factors, the treatment effects of chemotherapy were still not satisfied (Nie et al. 2017). Angiogenesis played the indispensable role in the development and progression of solid tumors. Combined chemotherapy with small molecule targeted drugs showed unique advantages, bringing hopes for patients with advanced GC or AGEJ who failed in their first-line treatment (Tomasello et al. 2016). VEGFR-2 was considered as a receptor that was closely related to angiogenesis (Shi et al. 2016). Wilke et al. (2014) found that the VEGFR-2 antagonist ramucirumab combined with paclitaxel significantly increased the mPFS compared with placebo plus paclitaxel (5.5 months vs 2.8 months, $P < 0.001$) in GC cases. Tong et al. (2012) observed that apatinib significantly enhanced the efficacy of paclitaxel against murine xenograft tumors. Both REGARD and RAINBOW clinical trials showed that, as the second-line drug, ramucirumab could improve survival in GC patients, and increased the OS of 1.40 and 2.27 months, respectively (Fuchs et al. 2014; Wilke et al. 2014). However, phase II clinical trials revealed that ramucirumab combined with FOLFOX chemotherapy could not prolong PFS or OS in patients with GC or AGEJ (Yoon et al. 2016; Bai and Zhang 2018). Compared with ramucirumab, apatinib was more convenient in administration leading to better patients' compliance (Chen et al. 2017).

Our results revealed that compared with the chemotherapy alone group, the PFS in the group of chemotherapy combined with apatinib showed a trend to prolongation in patients with advanced GC or AGEJ who failed in at least first-line chemotherapy. The difference was statistically significant and patients' tolerance was acceptable. AEs related to apatinib were controllable. This was consistent with previous clinical trials of apatinib combined with docetaxel as second-line chemotherapy for advanced GC (Zhang et al. 2017). In addition, our study also showed that apatinib in combination with chemotherapy and less than two metastatic lesions were independent prognostic factors for advanced GC, which were consistent with previous clinical trials of apatinib monotherapy (Li et al. 2016; Guo et al. 2019). Previous randomized controlled clinical trials indicated that PFS of 3.67 months (95% CI: 2.17-6.80 months) was observed in 144 advanced GC patients receiving 425 mg twice daily (Li et al. 2013). The large-scale clinical trial for third-line treatment of advanced GC had been completed, and apatinib had been approved by State Food and Drug Administration (SFDA) of China for advanced GC or AGEJ patients as the third-line or above treatment. Guo Y et al. (2019) demonstrated that apatinib had relatively better DCR and survival benefit in the treatment of advanced GC who failed in second-line or above treatment, and adverse reactions were controllable.

As a small molecule tyrosine kinase inhibitor that specifically targets VEGFR2, apatinib has achieved valuable therapeutic effects in the fields of GC, colorectal cancer, and lung cancer (Zhao et al. 2018). In terms of safety, the occurrences of AEs were generally consistent with phase II and phase III apatinib clinical studies. Common AEs include leukopenia, neutropenia, thrombocytopenia, hypertension, proteinuria, hand-foot skin reaction, fatigue, loss of appetite, and diarrhea. No unexpected AEs occurred in the patients of apatinib combined chemotherapy group. The majority of AEs could be controlled and reversed by drug withdrawal, down-regulation of dose, and symptomatic treatment (Scott et al. 2015; Roviello et al. 2016). Since apatinib entered the market at the end of 2014, there had been few studies on the biomarkers, mainly focusing on the prediction of treatment effect through the AEs caused by apatinib. For example, the early occurrence of hypertension, high expression of phosphorylated VEGFR-2, proteinuria, hand-foot syndrome and other clinical manifestations after taking apatinib may potentially have a predictive value in anti-angiogenic therapy (Fan et al. 2014, Liu et al. 2017).

Table 2: Cox regression analysis of prognostic factors for PFS

Variables		Multivariate analysis		
		HR	95%CI	P
Gender	Female	1	reference	
	Male	0.582	0.068-4.975	0.631
Age (years)	< 65 years	1	reference	
	≥ 65 years	0.251	0.012-5.287	0.374
ECOG	0	1	reference	
	1	1.078	0.627-1.884	0.792
Primary lesions	Gastric area	1	reference	
	Gastroesophageal junction	1.216	0.730-2.024	0.452
Pathological results	High differentiation	1	reference	
	Moderate differentiation	0.925	0.611-1.401	0.713
	Poor differentiation	1.047	0.994-1.103	0.086
	Signet-ring cell carcinoma	2.126	0.963-4.694	0.062
Previous gastrectomy	Yes	1	reference	
	No	0.627	0.124-3.179	0.573
Previous chemotherapy	First line	1	reference	
	Second line or above	0.879	0.519-1.490	0.632
Chemotherapy regimens	FU	1	reference	
	PTX	0.218	0.020-2.409	0.214
	FU, PTX/DOC, platinum	1.324	0.712-2.461	0.375
	CPT-11	1.355	0.570-3.223	0.492
Number of *metastatic lesion*s	≤2	1	reference	
	>2	2.129	1.256-3.608	0.005
Metastases	Peritoneal metastasis	1	reference	
	Other organ metastases	0.749	0.229-2.453	0.633
Radiotherapy	Yes	1	reference	
	No	0.867	0.245-3.072	0.824
Previous chemotherapy	First line	1	reference	
	Second line or above	1.432	0.697-2.940	0.328
Treatment	Chemotherapy alone	1	reference	
	Apatinib combined chemotherapy	1.427	1.055-1.930	0.021

ECOG: Eastern Cooperative Oncology Group; FU: fluorouracil; PTX: taxanes; CPT-11: irinotecan; DOC: docetaxel.

This study had several limitations. First, this was a retrospective study of a single center with a small sample size. Second, report bias and selective bias were unavoidable, and we could not establish a control group due to the nature of the retrospective cohort. Third, we did not assess the quality of life during the treatment period, which could offer more valuable messages about AEs of apatinib. Fourth, for issues such as which chemotherapeutic regimen combined with apatinib could obtain better clinical effects and patients' tolerance, and whether early administration of apatinib for second-line or earlier treatment could lead to more clinical benefits, high-quality prospective randomized controlled clinical trial with large-sample, multicenter, long-term follow-up are needed.

In conclusion, compared with chemotherapy alone, apatinib combined chemotherapy could significantly improve DCR and prolong the PFS in advanced GC or AGEJ cases who had failed in at least first-line chemotherapy with acceptable tolerance.

4. Experimental

4.1. Patients

This was a retrospective analysis of advanced GC or AGEJ patients that were treated with apatinib combined chemotherapy or chemotherapy alone between January 2015 and December 2017 in the Traditional Chinese and Western Oncology Department of The First Affiliated Hospital of Anhui Medical University. Inclusion criteria were: 1) 18-75 years old; 2) ECOG/PS scores 0-1; 3) advanced GC or AGEJ confirmed by gastroscopy and pathology (local advanced stage, recurrent GC or AGEJ with no indications of surgical resection; or metastatic lesions); 4) at least first-line chemotherapy failed; 5) at least one target lesion could be measured by CT or MRI; 6) estimated survival period ≥ 3 months. Exclusion criteria were: 1) hypertension could not return to the normal range with antihypertensive drugs (≥140/90 mmHg); 2) bleeding tendency, abnormal coagulation function, taking hemostatic agents or anticoagulants; 3) heart, brain, liver, kidney and other organ dysfunction, or hematological examination did not meet the basic requirements of chemotherapy; 4) presence of various factors affecting oral medication (dysphagia, nausea, vomiting, chronic diarrhea or intestinal obstruction); 5) clear tendency to gastrointestinal bleeding, such as local active ulcers, fecal occult blood; melena stool or hematemesis within 2 months; 6) other chemotherapy-related contraindications. The study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee and Institutional Review Board of The First Affiliated Hospital of Anhui Medical University. Written informed consent to take part in this retrospective study was not regarded necessary by the Ethics Committee.

4.2. Treatment regimens

Patients received simultaneous oral apatinib treatment at a dose of 500 mg/d in the apatinib combined chemotherapy group. One cycle lasted for 28 days. When grade III or above adverse reactions associated with apatinib occurred, the dose of abatinib could be reduced to 250 mg/d. All patients received chemotherapy regimens based on taxanes (PTX) or irinotecan (CPT-11) or fluorouracil (FU) or three drug regimens (FU, PTX/DOC, platinum) (Lordick et al. 2014). These regimens lasted for 21-28

Table 3: Advers effects of patients

Advers effects	Apatinib combined chemotherapy (n=127)		Chemotherapy alone (n=60)		P value
	Any grade	Grade III or IV	Any grade	Grade III or IV	
Hematologic System					
Leukopenia	78(61.4%)	46(36.2%)	38(63.3%)	19(31.7%)	0.542
Neutropenia	68(53.5%)	53(41.7%)	38(63.3%)	23(38.3%)	0.750
Anemia	39(30.7%)	10(7.9%)	14(23.3%)	4(6.7%)	0.999
Thrombocytopenia	43(33.9%)	18(14.2%)	21(35%)	8(13.3%)	0.877
Non-hematologic system					
Proteinuria	38(29.9%)	12(9.4%)	3(5.0%)	0(0%)	0.010
Hypertension	40(31.5%)	17(13.4%)	4(6.7%)	2(3.3%)	0.030
Hand-foot syndrome	52(40.9%)	27(21.3%)	11(18.3%)	5(8.3%)	0.028
Elevated transaminases	34(26.8%)	12(9.4%)	12(20.0%)	5(8.3%)	0.804
Hyperbilirubinemia	29(22.8%)	21(16.5%)	15(25.0%)	4(6.7%)	0.064
Hemorrhage	24(18.9%)	11(8.7%)	9(15.0%)	3(5%)	0.554
Sensory neuropathy	65(51.2%)	26(20.5%)	32(53.3%)	13(21.7%)	0.851
Abdominal pain	52(40.9%)	13(10.2%)	31(51.7%)	9(15.0%)	0.345
Vomiting or loss of appetite	96(75.6%)	16(12.6%)	43(71.7%)	8(13.3%)	0.888
Hypoproteinemia	34(26.8%)	10(7.9%)	12(20.0%)	5(8.3%)	0.999
Diarrhea	33(26.0%)	19(15.0%)	14(23.3%)	5(8.3%)	0.206

AEs: adverse effects.

d as one cycle and were expected to complete 2-6 cycles. Patients with stable and effective treatment continued to receive the original chemotherapy regimen (dose increase was not allowed) until progression or the intolerable toxicity, or the patient refused to receive chemotherapy. The doses of chemotherapy drugs were reduced by 25-50% for patients with grade III-IV toxicity and supportive treatments were given or chemotherapy was stopped.

4.3. Evaluation criteria for treatment effect and adverse reaction

On the basis of the RECIST 1.1 criteria, tumor responses were performed and classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Disease control rate (DCR) and objective response rate (ORR) were also calculated (Eisenhauer et al. 2009). CT or MRI were performed every two cycles of chemotherapy to evaluate the treatment effect until disease progression. PFS referred to the time of patients treated with apatinib combined chemotherapy or chemotherapy alone to disease progression or the last follow-up. All adverse events (AEs) were assessed on the basis of National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (Trotti et al. 2003).

4.4. Statistical analysis

Statistical analyses were carried out using SPSS 21.0 for Windows (IBM Corp., Chicago, IL, USA). Distribution of continuous data was conducted by the Kolmogorov-Smirnov test. Continuous data are presented as the mean±standard deviation or median (range) and were compared between groups using student t test or Mann-Whitney U test. Count data are presented as *n* (%) and were compared between groups using the chi-squared test or Fisher's exact test. Survival curve (PFS) was plotted by Kaplan-Meier method with Log-rank test. Cox analysis was further performed to explore the association between PFS and potential risk factors. Statistical significance was defined as $P < 0.05$.

Conflicts of interest: The authors report no relationships that could be construed as a conflict of interest.

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