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Original Article

Apatinib as a Third-Line Treatment for HER2-Positive Metastatic Gastric Cancer: A Multi-Center Single-Arm Cohort Study

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ABSTRACT

Purpose: Treatment options are limited after the failure of first-and second-line treatments in patients with HER2$^+$ metastatic gastric cancer (mGC). The present study aimed to explore the efficacy, safety, and prognostic factors of apatinib efficacy as a third-line therapy for patients with human epithelial growth factor receptor 2-positive (HER2$^+$) mGC.
Materials and Methods: A total of 59 HER2$^+$ mGC patients who received apatinib as third-line therapy were retrospectively enrolled in this two-center, single-arm, cohort study; the clinical response, survival data, and adverse events were retrieved.
Results: The median progression-free survival (PFS) was 5.2 months (95% confidence interval [CI], 3.9–6.5), and the median overall survival (OS) was 8.2 months (95% CI, 6.6–9.8) Furthermore, forward stepwise multivariate Cox regression analysis showed that a higher Eastern Cooperative Oncology Group performance status score and multiple metastases were independently correlated with decreased PFS and OS (both $P<0.05$). The main adverse events were leukopenia (45.8%), hypertension (44.1%), thrombocytopenia (39.0%), hand-foot syndrome (37.3%), and elevated transaminase (33.9%). Grade 3 adverse events mainly included hypertension (5.1%) and neutropenia (5.1%); grade 4 adverse events did not occur.
Conclusions: Apatinib is efficient and well tolerated in patients with HER2$^+$ mGC as a third-line treatment, suggesting that it may be a candidate of choice for these patients.

Keywords: Apatinib; Gastric cancer; Prognosis; Mortality; Safety

INTRODUCTION

Gastric cancer (GC) is one of the most prevalent carcinomas and ranks as the third leading cause of cancer-related deaths globally [1]. In China, both the incidence and mortality of GC are much higher than the global average, with approximately 400,000 new cases diagnosed each year, accounting for 13% of all cancer-related deaths [2,3]. With the availability of diagnostic techniques, such as gastroscopy screening, an increasing proportion of patients with GC are diagnosed at an early stage and have a relatively favorable prognosis [4,5]. However, some patients are diagnosed with metastatic GC (mGC) [6-8].

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Z.Z.; Data curation: Z.X., H.H., X.J., Y.Z.; Formal analysis: Z.X., N.Y., Z.Z.; Investigation: Z.X.; Supervision: Z.Z.; Writing - original draft: Z.X., H.H., X.J., Y.Z.; Writing - review and editing: N.Y., Z.Z.

One of the most prevalent genetic variants in patients with mGC is the human epidermal growth factor receptor 2-positive (HER2+) cancer. Currently, first-line and second-line treatments for patients with HER2+ mGC mainly include anti-HER2 agent regimens, such as trastuzumab combined with chemotherapy [3,9]. Nevertheless, some patients with HER2+ mGC may fail to respond to these treatments [10-14]. In addition, therapeutic options are limited after the failure of first- and second-line treatments in patients with HER2+ mGC [9,15]. Thus, effective treatment is urgently required to enhance the management of these patients.

Apatinib, a small-molecule tyrosine kinase inhibitor independently developed in China, can effectively inhibit tumor angiogenesis [16,17]. Apatinib has shown satisfactory efficacy and safety profiles in several malignancies such as non-small cell lung cancer, hepatocellular carcinoma, and GC [18-20]. This drug slightly extends the progression-free survival (PFS) and overall survival (OS) of these patients and has recently been recommended as a third-line salvage treatment for mGC in China [3,16,21,22]. Furthermore, anti-angiogenic therapies combined with chemotherapy have achieved favorable efficacy in HER2+ mGC [23-25]. Inspired by the abovementioned data, we speculated that apatinib might also be an effective and safe third-line therapy for patients with HER2+ mGC. To date, few investigations have focused on the role of apatinib in these patients.

The present study aimed to assess the efficacy of apatinib as third-line therapy in patients with HER2+ mGC and its prognostic factors in real clinical settings, with the aim of improving the management of HER2+ mGC.

MATERIALS AND METHODS

Patients

This multicenter, single-arm, cohort study retrospectively reviewed 59 patients with HER2+ mGC who received third-line apatinib between January 2016 and December 2020. The screening criteria were as follows: 1) diagnosis of mGC; 2) identification of HER2+; 3) treatment failure or disease progression after first- and second-line chemotherapy combined with anti-HER2 drugs, such as trastuzumab, pertuzumab, and lapatinib; 4) administration of apatinib as a third-line treatment; 5) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; and 6) complete data of treatment response and survival. Patients with other cancers or malignancies were excluded from this study. This study was approved by the Institutional Review Board of Handan Central Hospital with number of 2022004.

Data collection

Data including age, sex, ECOG PS score, primary lesion, prior surgery of primary lesion, tumor differentiation degree and metastasis status were obtained from medical records. In addition, adverse events that occurred during treatment were also collected and graded for toxicity assessment according to the standard toxicity criteria of the National Cancer Institute (version 4.0).

Treatment

Treatment information was collected from the clinical documents. Patients received apatinib as third-line therapy at different doses according to the ECOG PS score. Briefly, apatinib was administered orally at a dose of 250 mg daily to patients with an ECOG PS score of 2 and at a dose of 500 mg daily to patients with an ECOG PS score of 0–1. The dose of apatinib was

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adjusted (250–500 mg daily) depending on the patient's actual tolerance, and 22 (37.3%) patients in the study received dose adjustment. Apatinib administration was continued until disease progression, intolerable toxicity, or death.

Treatment response assessment

Treatment responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [26]: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR; CR + PR), disease control rate (DCR; CR + PR + SD). An imaging examination was performed every month to check the status of the tumor; in addition, the treatment response at week 8 was evaluated based on imaging data from a previous study [22].

Survival assessment

Disease progression status was assessed monthly using imaging examinations. Survival data were collected from the follow-up records, and the final follow-up date was December 31, 2021. The median, mean, and range of the follow-up were 8.2, 8.2, and 0.5–18.7 months, respectively. PFS and OS were calculated using survival data. PFS was estimated from the start of treatment to progressive disease, death, or the last follow-up date, whichever came first; OS was estimated from the treatment to death or the last follow-up date.

Statistical analysis

Continuous data are shown as mean with standard deviation, and categorical data are presented as counts (percentages). Survival data are displayed using Kaplan-Meier curves. Cox proportional hazards regression was used to analyze the factors related to PFS and OS. *S*tatistical significance was set at $P<0.05$. SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, CA, USA) were used to analyze the data and construct the figures.

RESULTS

Clinical features

Among the 59 patients with HER2+ mGC, the age was 62.2±8.1 years; 22 (37.3%) were females, and 37 (62.7%) were males. Regarding the ECOG PS score, 22 (37.3%) patients had a score of 0, 27 (45.8%) had a score of 1, and 10 (16.9%) had a score of 2. Furthermore, 8 (13.6%) patients had good tumor differentiation, 24 (40.6%) patients had moderate tumor differentiation, and 27 (45.8%) patients had poor tumor differentiation. Additionally, the numbers of patients with and without lung metastasis were 16 (27.1%) and 43 (72.9%), respectively. Moreover, 23 (39.0%) patients had multiple metastases and 36 (61.0%) patients had a single metastasis (**Table 1**).

Treatment response

After apatinib treatment, the rates of CR, PR, SD, and PD were 0%, 22.0% (95% confidence interval [CI], 11.4%–32.6%), 45.8% (95% CI, 33.1%–58.5%), and 32.2% (95% CI, 20.3%–44.1%), respectively. The ORR was 22.0% (95% CI, 11.4%–32.6%), and the DCR was 67.8% (95% CI, 52.3%–76.7%) among patients (**Table 2**).

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Table 1. Clinical features

Characteristic	Patients with mGC (n=59)
Age (yr)	62.2±8.1
Sex	
Female	22 (37.3)
Male	37 (62.7)
ECOG PS score	
0	22 (37.3)
1	27 (45.8)
2	10 (16.9)
Primary lesion	
Gastroesophageal junction	14 (23.7)
Gastric	45 (76.3)
Prior surgery of primary lesion	
No	26 (44.1)
Yes	33 (55.9)
Differentiation	
Well	8 (13.6)
Moderate	24 (40.6)
Poor	27 (45.8)
Liver metastasis	
No	34 (57.6)
Yes	25 (42.4)
Peritoneal metastasis	
No	50 (84.7)
Yes	9 (15.3)
Retroperitoneal LNM	
No	29 (49.2)
Yes	30 (50.8)
Lung metastasis	
No	43 (72.9)
Yes	16 (27.1)
Other metastases	
No	46 (78.0)
Yes	13 (22.0)
Multiple metastases	
No	36 (61.0)
Yes	23 (39.0)

Values are presented as mean with standard deviation or number (%).
mGC = metastatic gastric cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; LNM = lymph node metastasis.

Table 2. Treatment responses

Type of response	Number of patients	Percentage (%)	95% CI
Total			
CR	0	0.0	-
PR	13	22.0	11.4–32.6
SD	27	45.8	33.1–58.5
PD	19	32.2	20.3–44.1
ORR	13	22.0	11.4–32.6
DCR	40	67.8	52.3–76.7

CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; DCR = disease control rate.

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PFS and OS

During follow-up, 59 (100.0%) patients had disease progression and 57 (96.6%) patients died. Survival data were collected from follow-up records, which revealed that the median PFS (95% CI) was 5.2 (3.9–6.5) months (**Fig. 1A**) and the median OS (95% CI) was 8.2 (6.6–9.8) months (**Fig. 1B**).

Univariate Cox regression analysis showed that age (≥65 vs. <65 years) (hazard ratio [HR], 1.792; P=0.036), high ECOG PS score (HR, 1.591; P=0.018), poor differentiation (HR, 1.496; P=0.046), peritoneal metastasis (HR, 2.204; P=0.034), lung metastasis (HR, 2.235; P=0.011), and multiple metastases (HR, 2.661; P=0.001) were correlated with poor PFS (**Fig. 2A**). Furthermore, forward stepwise multivariate Cox regression analysis showed that age (≥65 vs. <65 years) (HR, 1.967; P=0.017), higher ECOG PS score (HR, 1.534; P=0.033), and multiple metastases (HR, 2.650; P=0.001) independently predicted decreased PFS (**Fig. 2B**).

Univariate Cox regression analysis demonstrated that a higher ECOG PS score (HR, 1.597; P=0.014), poor differentiation (HR, 1.880; P=0.003), peritoneal metastasis (HR, 2.677; P=0.009), lung metastasis (HR, 2.550; P=0.002), and multiple metastases (HR, 2.608; P=0.001) were correlated with unfavorable OS (**Fig. 3A**). Forward stepwise multivariate Cox regression analysis showed that a higher ECOG PS score (HR, 1.585; P=0.018) and multiple metastases (HR, 2.591; P=0.001) independently estimated decreased OS (**Fig. 3B**).

In addition, peritoneal metastasis was negatively correlated with PFS and OS (P=0.028 and P=0.006, respectively; **Supplementary Fig. 1**).

Adverse events

The most prevalent adverse events were leukopenia (45.8%), hypertension (44.1%), thrombocytopenia (39.0%), hand-foot syndrome (37.3%), elevated transaminase (33.9%), neutropenia (32.2%), proteinuria (30.5%), and fatigue (30.5%). Most adverse events were mild (grades 1 and 2). Grade 3 adverse events included hypertension (5.1%), hand-foot syndrome (5.1%), neutropenia (5.1%), thrombocytopenia (3.4%), anemia (3.4%), elevated

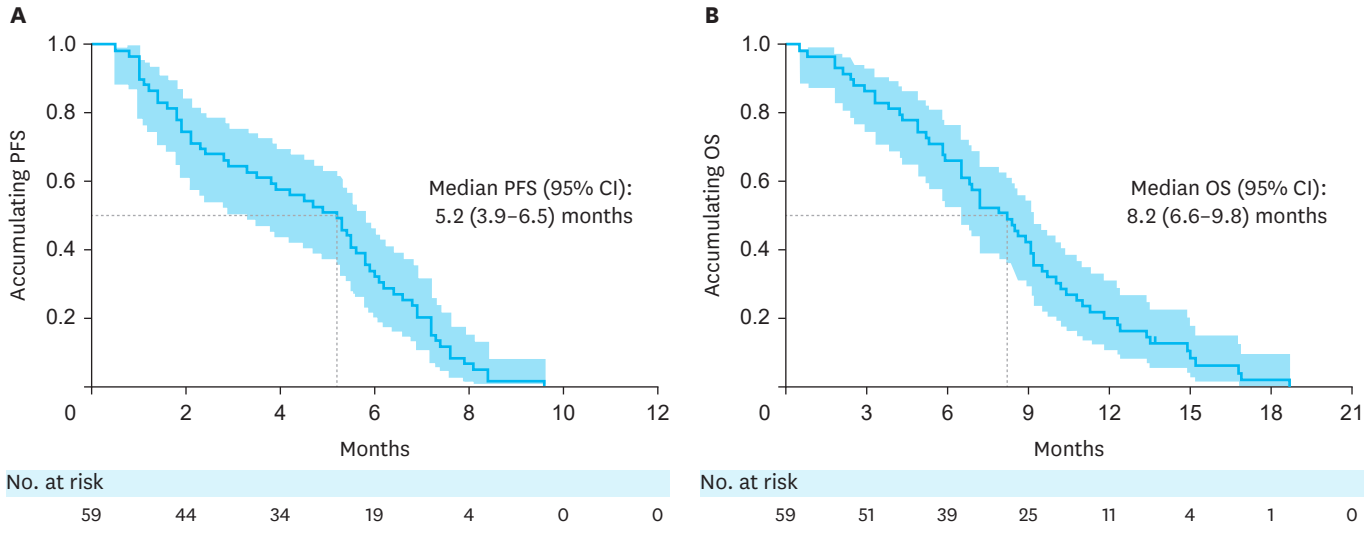

Fig. 1. Survival profile. Cumulative PFS (A) and OS (B) in patients with HER2+ mGC receiving apatinib. Red pattern, 95% CI of PFS/OS.
PFS = progression-free survival; OS = overall survival; HER2+ = human epithelial growth factor receptor 2-positive; mGC = metastatic gastric cancer; CI = confidence interval.

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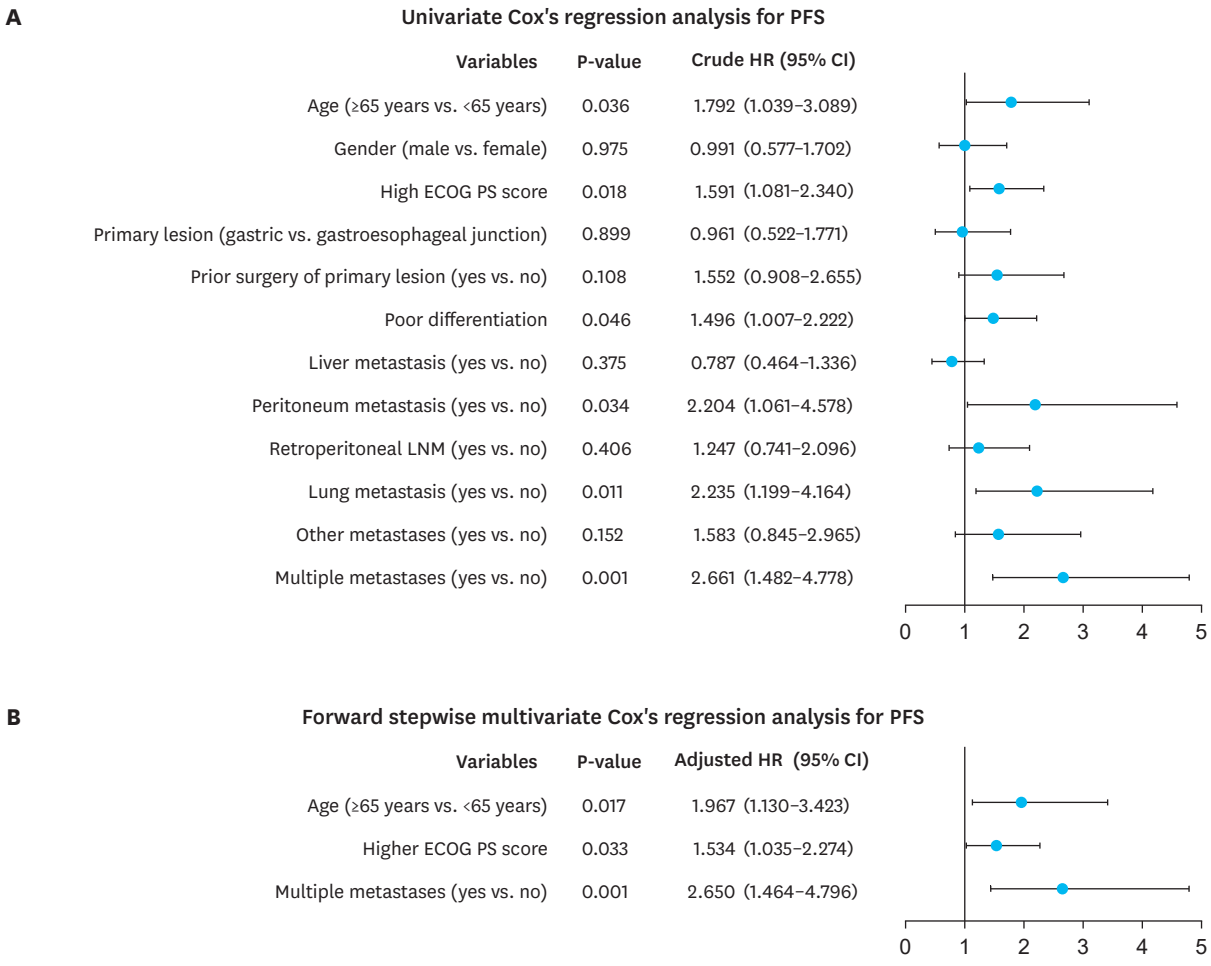

Fig. 2. Cox regression analysis for PFS. (A) Univariate and (B) multivariate Cox regression analyses for PFS in patients with HER2+ mGC receiving apatinib.
PFS = progression-free survival; HER2+ = human epithelial growth factor receptor 2-positive; mGC = metastatic gastric cancer; HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LNM = lymph node metastasis.

Table 3. Adverse events

Type of adverse event	Total	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	27 (45.8)	22 (37.3)	5 (8.5)	0 (0.0)	0 (0.0)
Hypertension	26 (44.1)	16 (27.1)	7 (11.9)	3 (5.1)	0 (0.0)
Thrombocytopenia	23 (39.0)	17 (28.8)	4 (6.8)	2 (3.4)	0 (0.0)
Hand-foot syndrome	22 (37.3)	15 (25.4)	4 (6.8)	3 (5.1)	0 (0.0)
Elevated transaminase	20 (33.9)	13 (22.0)	6 (10.2)	1 (1.7)	0 (0.0)
Neutropenia	19 (32.2)	11 (18.6)	5 (8.5)	3 (5.1)	0 (0.0)
Proteinuria	18 (30.5)	16 (27.1)	2 (3.4)	0 (0.0)	0 (0.0)
Fatigue	18 (30.5)	14 (23.7)	3 (5.1)	1 (1.7)	0 (0.0)
Nausea and vomiting	17 (28.8)	11 (18.6)	5 (8.5)	1 (1.7)	0 (0.0)
Anemia	16 (27.1)	11 (18.6)	3 (5.1)	2 (3.4)	0 (0.0)
Pruritus	15 (25.4)	11 (18.6)	4 (6.8)	0 (0.0)	0 (0.0)
Diarrhea	12 (20.3)	10 (16.9)	2 (3.4)	0 (0.0)	0 (0.0)
Anorexia	12 (20.3)	11 (18.6)	1 (1.7)	0 (0.0)	0 (0.0)
Increased bilirubin	8 (13.6)	6 (10.2)	2 (3.4)	0 (0.0)	0 (0.0)
Fever	5 (8.5)	4 (6.8)	1 (1.7)	0 (0.0)	0 (0.0)

Values are presented as number (%).

transaminase levels (1.7%), fatigue (1.7%), nausea, and vomiting (1.7%). No grade 4 adverse events occurred in any patient (**Table 3**).

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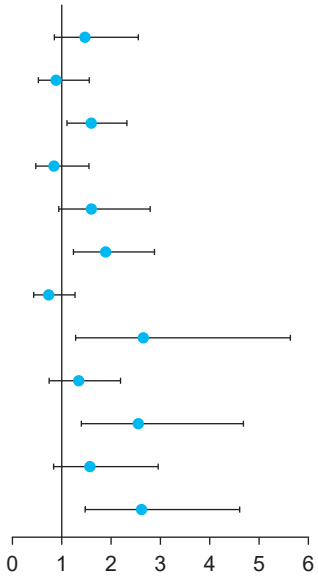
A Univariate Cox's regression analysis for OS

Variables	P-value	Crude HR (95% CI)
Age (≥65 years vs. <65 years)	0.171	1.470 (0.847–2.549)
Gender (male vs. female)	0.702	0.898 (0.517–1.559)
High ECOG PS score	0.014	1.597 (1.098–2.325)
Primary lesion (gastric vs. gastroesophageal junction)	0.589	0.845 (0.460–1.555)
Prior surgery of primary lesion (yes vs. no)	0.089	1.608 (0.930–2.781)
Poor differentiation	0.003	1.880 (1.232–2.870)
Liver metastasis (yes vs. no)	0.282	0.739 (0.426–1.282)
Peritoneum metastasis (yes vs. no)	0.009	2.677 (1.273–5.632)
Retroperitoneal LNM (yes vs. no)	0.386	1.271 (0.739–2.184)
Lung metastasis (yes vs. no)	0.002	2.550 (1.391–4.673)
Other metastases (yes vs. no)	0.164	1.566 (0.833–2.944)
Multiple metastases (yes vs. no)	0.001	2.608 (1.478–4.603)



B Forward stepwise multivariate Cox's regression analysis for OS

Variables	P-value	Adjusted HR (95% CI)
Higher ECOG PS score	0.018	1.585 (1.083–2.320)
Multiple metastases (yes vs. no)	0.001	2.591 (1.457–4.607)

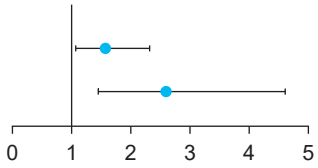


Fig. 3. Cox regression analysis for OS. (A) Univariate and (B) multivariate Cox regression analyses for OS in patients with HER2+ mGC receiving apatinib.
OS = overall survival; HER2+ = human epithelial growth factor receptor 2-positive; mGC = metastatic gastric cancer; HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LNM = lymph node metastasis.

DISCUSSION

In terms of the treatment response to third-line treatment in patients with HER2+ mGC, a previous study showed that in patients undergoing chemotherapy alone, CR, PR, SD and PD rates were 0%, 14%, 48%, and 30%, respectively [27]. Furthermore, another study also illustrated that in patients with HER2+ mGC receiving nivolumab as third-line treatment after previous treatment with trastuzumab, the rates of PR and SD were 16.9% and 25.4%, respectively, while the ORR and DCR were 16.9% and 42.4%, respectively [28]. In the present study, the rates of CR, PR, SD, and PD patients with HER2+ mGC receiving third-line apatinib therapy were 0.0%, 22.0%, 45.8%, and 32.2%, respectively, and the ORR and DCR were 22.0% and 67.8%, respectively, which were numerically higher than those of the abovementioned chemotherapy and immunotherapy regimens [27,28]. A possible reason might be that angiogenesis plays a crucial role in tumor growth of HER2+ mGC; thus, apatinib, as an effective angiogenesis inhibitor, could have better efficacy in patients HER2+ mGC [29,30].

Regarding the survival profile of HER2+ mGC patients receiving third-line treatment, it has been shown that among patients who received chemotherapy alone, the median PFS (95%

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CI) was 3.5 (2.0–4.3) months, and the median OS (95% CI) was 8.4 (6.9–10.7) months [27]. To explore the survival profile of patients with HER2+ mGC patients receiving apatinib as a third-line treatment, median PFS and OS were also calculated in the present study, which revealed that the median PFS (95% CI) and OS (95% CI) were 5.2 (3.9–6.5) and 8.2 (6.6–9.8) months, respectively. PFS was longer, while OS was shorter in patients with HER2+ mGC receiving third-line apatinib than in those receiving chemotherapy alone [23]. The potential explanation might be that the treatment response and enrolled patients could result in different survival profiles for patients with HER2+ mGC. Furthermore, we also found that a higher ECOG PS score and multiple metastases were independent predictive factors for poor PFS and OS, indicating that patients with HER2+ mGC with a higher ECOG PS score and multiple metastases require more attention. These patients may benefit from apatinib in combination with other drugs or other treatment options.

Previous studies have shown that the main adverse events associated with apatinib treatment in patients with cancer are hypertension, diarrhea, proteinuria, and hand-foot syndrome [18,31]. In the present study, the most common adverse events in patients with HER2+ mGC receiving apatinib as third-line treatment were hypertension, leukopenia, thrombocytopenia, and hand-foot syndrome; the incidence of adverse events was low, and the majority of them were tolerable and manageable, which was partly consistent with previous studies [18,31]. The data indicated that apatinib was well-tolerated as a third-line treatment in patients with HER2+ mGC.

The current study had several limitations, including not addressing the following points: 1) whether apatinib in combination with chemotherapy could promote efficacy compared with apatinib alone in patients with HER2+ mGC, and the acceptability of toxicity; 2) given the great progress in the development of immune checkpoint inhibitors such as programmed death receptor-1 (PD-1), the efficacy and safety of apatinib combined with PD-1 in patients with HER2+ mGC could be explored; 3) the present single-arm study did not include a control group; thus, a randomized controlled trial could be performed to further confirm the efficacy and safety of apatinib as a third-line treatment in patients with HER2+ mGC; and 4) the previous second-line treatment might have affected the outcome in the current study.

In conclusion, apatinib is efficient and reasonably well-tolerated in patients with HER2+ mGC as a third-line treatment, suggesting that it may be a potential choice for these patients.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

Correlation of peritoneal metastasis with survival. Correlation of peritoneal metastasis with (A) PFS and (B) OS.

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