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Original Article

Safety and effectiveness of apatinib in patients with previously treated metastatic gastric cancer: a sub-analysis from the real-world study of apatinib for gastric cancer treatment (AHEAD-G202)

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Abstract: Apatinib, a VEGFR2 receptor tyrosine kinase inhibitor, showed survival benefits in Asian patients with heavily pretreated advanced gastric cancer. However, the adverse event (AEs) profile of apatinib has limited its use. Dosing schedules are used to alleviate toxicities despite no supportive evidence. This study aimed to analyze the toxicity and effectiveness of apatinib alone, especially with different dosing strategies in advanced gastric cancer patients under a real-world setting. Data from the subpopulation of patients who failed ≥2 chemotherapy regimens enrolled in the AHEAD-G202 trial were analyzed. The primary endpoint was safety. The secondary endpoints were overall survival (OS) and progression-free survival (PFS). Totally 120 patients were included into three groups by the initial daily doses: 43 (35.8%) patients in the low-dose (250 mg) group, 67 (55.8%) patients in the mid-dose (425 mg to 500 mg) group, and 10 (8.3%) patients in the high-dose (675 to 850 mg) group. Grade 3/4 treatment-emergent AEs were infrequent (<5%), with the most commonly reported grade 3/4 AEs being hand-foot syndrome (4.2%),

hypertension (4.2%,), fatigue (4.2%), and difficulty in swallowing (4.2%) which gradually decreased among the high-, mid-, and low-dose groups. The median OS and PFS were 6.33 months (95% CI, 4.57-7.73) and 3.83 months (95% CI: 1.40-4.20), respectively and were comparable among the three doses groups. We found heavily pretreated advanced gastric cancer patients can tolerate and benefit from lower-doses of apatinib therapy. The lower initial daily dosing strategy represents an alternative approach for optimizing apatinib dosing in clinical practice.

Keywords: Apatinib, advanced gastric cancer, toxicity, effectiveness, dosing strategy, real-world

Introduction

Gastric cancer is the third most common cause of cancer-related death worldwide [1] and has higher incidence in East Asian than European populations, with East Asians accounting for over 70% of total global cases [2]. First- and second-line chemotherapy has been shown to significantly improve the survival of patients with advanced or metastatic gastric cancer [3, 4]. However, nearly all patients with advanced disease develop disease progression following treatment, and no standard treatment modality has been accepted as third-line treatment to date. Some studies have evaluated the efficacy of different modalities, including chemotherapy, anti-PD1, and anti-angiogenesis strategies, and reported varying results [5]. TAS102 was proven to prolong progression-free survival (PFS) and overall survival (OS) compared with best supportive care [6]. The anti-PD1 antibody pembrolizumab has also showed higher efficacy in PD-L1-positive disease, tumors with high microsatellite instability, or mismatch-repair-deficient chemotherapy-refractory tumors [7]. Nivolumab, another anti-PD1 antibody, has also demonstrated a statistically significant survival benefit irrespective of PD-L1 status [8].

Anti-angiogenesis is an important anti-cancer strategy [9], and several anti-angiogenic agents have been evaluated in clinical trials in gastric cancer to date. The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab has been shown to improve PFS and overall response rate (ORR), but not OS [10]. Ramucirumab, another VEGF monoclonal antibody, was also proven to prolong OS in REGARD and RAINBOW trials [11, 12]. Meanwhile, vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitors (TKIs) such as sunitinib and sorafenib only showed limited clinical benefit in gastric cancer [13, 14]. Regorafenib, an oral small-molecule multikinase inhibitor targeting signaling pathways including VEGFR1-3, significantly prolonged PFS and tended to improve OS in the phase II INTEGRATE study [15].

Apatinib, also known as YN968d1, is a novel TKI selectively targeting the intracellular ATP-binding site of VEGFR2. Apatinib prolonged PFS and OS by approximately 1 and 2 months, respectively, in patients with advanced gastric cancer who have previously failed second-line chemotherapy [16]. In the phase III trial [16], the therapeutic effect of apatinib on OS was mainly derived from prolonged PFS [17]. These results indicate that apatinib is a new option for third-line treatment of gastric cancer [18]. Despite the observed survival benefits, the emergence of toxicities, such as proteinuria, hypertension, hand-foot syndrome and fatigue has limited the use of apatinib. The standard daily dose of apatinib used in the registration trial was 850 mg/day. In clinical practice, however, physicians have commonly adopted various dosing or interval schedules and topical agents to counteract the toxicities, despite the lack of supportive clinical data. Therefore, we previously conducted an open label, non-interventional trial (AHEAD-G202 [clinical trial ID: NCT02668380]) to obtain more clinical evidence on the safety and effectiveness of apatinib in patients with gastric cancer in the real world.

The current study aimed to evaluate the toxicity and effectiveness of apatinib alone therapy in the subgroup of patients with heavily pretreated metastatic gastric cancer in the AHEAD-G202 trial. Further, we aimed to investigate the optimal dose of apatinib and the actual incidence and grade of adverse events (AEs) during the course of treatment.

Materials and methods

Patients

Data from patients who received apatinib as third- or higher-line treatment in the AHEAD-G202 trial were analyzed. The AHEAD-G202 trial was an open label, multicenter, non-interventional study which was conducted in 29 centers in China between September 2015 and March 2018. Eligible patients had histologically

proven advanced gastric cancer or gastroesophageal junction adenocarcinoma (advanced disease was defined as primary tumor or local recurrence not eligible for complete surgical resection or the presence of metastatic disease).

The study protocol received a centralized review at the institutional review board of the leader institution who also served as the reviewing board for the participating sites and was approved by the institutional review board of the leader institution and all participating sites obtained institutional review board or ethics committee approval of the study protocol prior to local initiation of the study (Supplementary List I). The trial followed the guiding principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and according to the laws and guidelines in China. The diagnostic and therapeutic practices were implemented according to the clinical practice of each participating center. All patients provided written informed consent.

Treatment

Apatinib (Jiangsu Hengrui Medicine) was initially administered orally at a dosage of 850 mg once daily for 4 weeks per cycle. However, as the trial proceeded, physicians reported higher incidences of AEs, and thus the drug manufacturer recommended lower doses at the discretion of the attending oncologists. Therefore, the initial dosage of apatinib could be range from 250 mg to 850 mg once daily according to the physician's discretion with consideration of the patients' physical condition. The daily dosage could be also adjusted due to AEs. The necessity of concurrent chemotherapy or targeted therapy combined during treatment was decided by the physician according to the patients' condition. Patients received apatinib until disease progression, unacceptable toxicities, or at the physician's discretion. If apatinib was discontinued for any reason, the date of the last dosage and the primary reason for discontinuation were documented, and the patient was withdrawn from the study.

Data collection and treatment-related evaluations

Data were obtained from the patients' medical and laboratory records or from telephone follow-up. The clinicodemographic characteristics and AEs were evaluated in all patients. Data on AEs were collected and coded to a preferred term using the Medical Dictionary for Regulatory Activities. Further, AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Treatment response and progression was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST v 1.1). Physician evaluations were conducted, but was not mandatory. Meanwhile, clinical assessment of treatment response was conducted using computed tomography and/or magnetic resonance imaging during follow-up visits at approximately 8-12-week intervals, according to routine practice.

Statistical analysis

All the data were analyzed via SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). The primary outcome measures of this study were safety and apatinib-emergent AEs. The secondary outcome measures included OS, PFS, ORR, and disease control rate (DCR). Treatment responses and AEs were both aggregated in the form of frequency counts and percentages. The ORR included complete response (CR) and partial response (PR), which were assessed using the RECIST v 1.1. DCR was calculated as the percentage of patients with stable disease (SD), CR, or PR. PFS and OS were measured from the date of apatinib initiation to the time of disease progression as determined by the physician and death from any cause, respectively. OS and PFS and their corresponding 95% confidence intervals (CIs) were estimated via the Kaplan-Meier method. Survivors at the time of data collection were censored at the date of last contact. The ORR and DCR analyses were based on frequency counts. The hazard ratios (HRs) and corresponding 95% CIs were estimated using the Cox's proportional hazards regression model. All statistical analyses were two sided. The statistical significance cutoff of P=0.05 was used to retain the variables in the final model.

Results

Patient and tumor characteristics

A total of 173 patients with advanced gastric cancer or advanced gastroesophageal junction adenocarcinoma received third- or higher-line

Table 1. Patient demographic and baseline characteristics for patients receiving third line or higher apatinib alone therapy

Variables	Apatinib				χ^2	P
	All	250 mg	425-500 mg	675-850 mg		
No. (%)	120	43 (35.8)	67 (55.8)	10 (8.3)		
Male gender, N (%)	81 (67.5)	29 (67.4)	46 (68.7)	6 (60)	0.2973	0.8619
Age, years, N (%)					0.0090	0.9955
≥65	47 (39.2)	17 (39.5)	26 (38.8)	4 (40)		
AJCC staging, N (%)						0.8410*
III	7 (5.8)	2 (4.7)	5 (7.5)	0 (0.0)		
IV	113 (94.2)	41 (95.3)	62 (92.5)	10 (100)		
ECOG performance score, N (%)						0.0497*
0	8 (6.7)	2 (4.7)	6 (9.0)	0 (0.0)		
1	73 (60.8)	21 (48.8)	46 (68.6)	6 (60)		
≥2	34 (28.3)	19 (44.2)	12 (17.9)	3 (30)		
N/A	5 (4.2)	1 (2.3)	3 (4.5)	1 (10)		
No. of metastatic sites, N (%)					0.5642	0.7542
>2	32 (26.7)	13 (30.2)	17 (25.4)	2 (20)		
Lauren classification, N (%)						0.5763*
Intestinal	26 (21.7)	14 (32.6)	11 (16.4)	1 (10)		
Diffuse	27 (22.5)	9 (20.9)	16 (23.9)	2 (20)		
Mixed	7 (5.8)	4 (9.3)	3 (4.5)	0 (0.0)		
N/A	60 (50)	16 (37.2)	37 (55.2)	7 (70)		
Prior radiotherapy, N (%)					3.0906	0.2132
Yes	20 (16.7)	6 (14.0)	14 (20.9)	0 (0.0)		
Prior surgery, N (%)						0.0487*
Yes	52 (43.3)	21 (48.8)	31 (46.3)	0 (0.0)		
No	48 (40)	15 (34.9)	28 (41.8)	5 (50)		
N/A	20 (16.7)	7 (16.3)	8 (11.9)	5 (50)		
Line of therapy, N (%)					2.0327	0.3619
3	85 (70.8)	29 (67.4)	47 (70.1)	9 (90)		
>3	35 (29.2)	14 (32.6)	20 (29.9)	1 (10)		

*Fisher's exact test.

apatinib. Of these, 120 patients who received apatinib alone were included in the analysis. The patients' baseline clinicodemographic characteristics are shown in **Table 1**. Majority of patients were male (67.5%), and 39.2% of the population were aged at least 65 years. Moreover, 94.2% of them had stage IV gastric cancer. The Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) score was 0 or 1 in 67.5% and 2 or above in 28.3% of the patients. In total, 16.7% of the patients received prior radiotherapy, and 43.3% underwent prior surgery. The initial dose of apatinib ranged from 250 to 850 mg once daily. The starting dose of apatinib was 250 mg in 43 patients (35.8%) (the-low dose group), 425 mg to 500 mg in 67 (55.8%) patients (the mid-dose group), and from 675 to 850 mg in 10 (8.3%) patients (the high-dose group). There was a significant difference in the rate of prior surgery (P=0.0487) and ECOG-PS score (P=0.0497) between the three groups.

Safety

In total, 120 patients were evaluated for apatinib alone-emergent AEs. The most commonly reported any-grade AEs (≥10%) included hypertension (40.8%), fatigue (30%), hand-foot syndrome (17.7%), nausea (16.7%), and proteinuria (14.2%) (**Table 2**). Grade 3/4 AEs were infrequent (<5%), and the most commonly reported

Table 2. Third line or higher apatinib alone-emergent adverse events, N (%)

AEs	All, N=120		250 mg, N=44		425-500 mg, N=66		675-850 mg, N=10	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic								
Leukopenia	4 (3.3)	0	2 (4.6)	0	2 (3.0)	0	0	0
Neutropenia	3 (2.5)	0	1 (2.3)	0	2 (3.0)	0	0	0
Anemia	1 (0.8)	0	0	0	1 (1.5)	0	0	0
Thrombocytopenia	6 (5.0)	2 (1.7)	3 (6.8)	0	3 (4.6)	2 (3.0)	0	0
Non-hematologic								
Proteinuria	17 (14.2)	4 (3.3)	3 (6.8)	1 (2.3)	11 (16.7)	3 (4.6)	3 (30)	0
Hypertension	49 (40.8)	5 (4.2)	19 (43.2)	1 (2.3)	26 (39.4)	3 (4.6)	4 (40)	1 (10)
Hand-foot syndrome	20 (17.7)	5 (4.2)	5 (11.4)	1 (2.3)	14 (21.2)	4 (6.1)	1 (10)	0
Elevated-transaminase	2 (1.7)	0	0	0	2 (3.0)	0	0	0
Hyperbilirubinemia	1 (0.8)	0	0	0	1	0	0	0
Bleeding	11	2 (1.7)	2 (4.6)	1 (2.3)	8	1 (1.5)	1	0
Fatigue	36 (30)	5 (4.2)	13 (29.6)	0	20 (30.3)	4 (6.1)	3 (30)	1 (10)
Alkaline phosphatase increased	0	0	0	0	0	0	0	0
Abdominal pain	2 (1.7)	0	2 (4.6)	0	0	0	0	0
Decreased appetite	3 (2.5)	1 (0.8)	2 (4.6)	1 (2.3)	1 (1.5)	0	0	0
Hypoalbuminemia	0	0	0	0	0	0	0	0
Diarrhea	9	2 (1.7)	3 (6.8)	0	6 (9.1)	2 (3.0)	0	0
Arrhythmia	0	0	0	0	0	0	0	0
Nausea	20 (16.7)	3 (2.5)	10 (22.7)	2 (4.6)	8 (12.1)	1 (1.5)	2 (20)	0
Vomiting	6 (5.0)	2 (1.7)	4 (9.1)	1 (2.3)	2 (3.0)	1 (1.5)	0	0
Intestinal obstruction	2 (1.7)	1 (0.8)	1 (2.3)	0	1 (1.5)	1 (1.5)	0	0
Oral mucositis	2 (1.7)	0	1 (2.3)	0	1 (1.5)	0	0	0
Urinary tract infection	1 (0.8)	0	0	0	1 (1.5)	0	0	0
Headache	2 (1.7)	0	2 (4.6)	0	0	0	0	0
Dizziness	1 (0.8)	0	1 (2.3)	0	0	0	0	0
Lumbar pain	0	0	0	0	0	0	0	0
Difficulty in swallowing	8 (6.7)	5 (4.2)	2 (4.6)	2 (4.6)	6 (9.1)	3 (4.6)	0	0
Hoarse voice	0	0	0	0	0	0	0	0
Stomach pain	1 (0.8)	0	0	0	1 (1.5)	0	0	0

were hand-foot syndrome (4.2%), hypertension (4.2%), fatigue (4.2%), difficulty in swallowing (4.2%), and proteinuria (3.3%). In the low-dose group, grade 3/4 nausea and difficulty in swallowing were each reported in 2 (4.6%) patients, and proteinuria, hypertension, hand-foot syndrome, bleeding, decreased appetite, and vomiting occurred each in 1 (2.3%) patient. No other grade 3/4 AEs were reported. In the mid-dose group, grade 3/4 hand-foot syndrome and fatigue occurred each in 4 (6.1%) patients; hypertension, proteinuria, and difficulty in swallowing occurred each in 3 (4.6%) patients. Furthermore, in the high-dose group, grade 3/4 hypertension and fatigue each occurred in 1/10 (10%) patient.

Dose interruption and adjustments occurred in 68 (56.7%) and 27 (22.5%) patients, respectively. The dose was reduced in 2, 10, and 5 patients in the low-, mid-, and high-dose groups, respectively, while it was increased in 8, 2, and 0 patients, respectively.

Effectiveness

The median PFS was 3.03 months (95% CI, 1.93-3.83) in the overall population (**Figure 1A**), while it was 3.83 months (95% CI: 1.40-4.20), 2.93 months (95% CI: 1.73-3.87), and 2.40 months (95% CI: 0.80-2.87) for the low-, mid-, and high-dose groups, respectively (χ^2=0.7736, *P*=0.6792) (**Figure 1B**). The median OS was 6.33 months (95% CI: 4.57-7.73) in

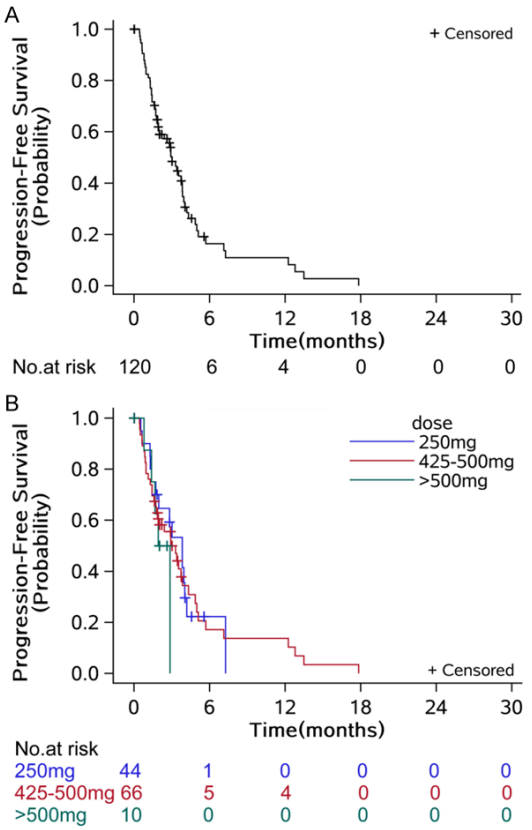

Figure 1. Kaplan-Meier estimates of progression-free survival (PFS). A. PFS for the overall population. The median PFS was 3.03 months (95% CI, 1.93-3.83). B. PFS stratified by dosing levels of apatinib. The median PFS was 3.83 months (95% CI: 1.40-4.20), 2.93 months (95% CI: 1.73-3.87) and 2.40 months (95% CI: 0.80-2.87) for the low, mid and high dose group, respectively (χ^2=0.7736, *P*=0.6792).

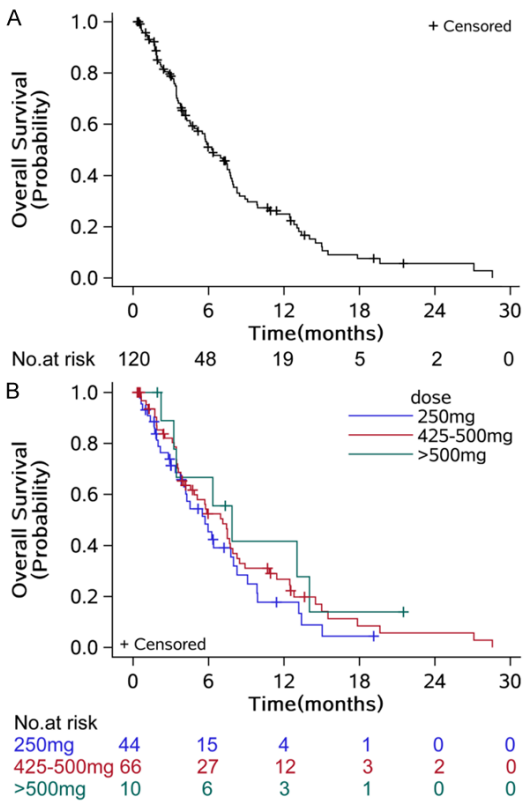

Figure 2. Kaplan-Meier estimates of overall survival (OS). A. OS for the overall population. The median OS was 6.33 months (95% CI: 4.57-7.73). B. OS stratified by dosing levels of apatinib. The median OS was 5.73 (95% CI: 3.77-8.00), 7.13 (95% CI: 4.57-7.93) and 7.87 months (95% CI: 2.23-14.03) for the low, mid and high dose group, respectively (χ^2=1.8872, *P*=0.3892).

the overall population (**Figure 2A**), while it was 5.73 months (95% CI: 3.77-8.00), 7.13 months (95% CI: 4.57-7.93), and 7.87 months (95% CI: 2.23-14.03) for the low-, mid-, and high-dose groups, respectively (χ^2=1.8872, *P*=0.3892) (**Figure 2B**). Multivariate Cox regression analysis showed no significant difference in PFS and OS among the three dose groups (**Table 3**).

Tumor response to apatinib was evaluable for 90 patients. CR/PR was achieved in 5.8% and SD in 55% of the patients. The ORR was 5.8%, and the DCR was 60.8%.

Discussion

Effective treatment modalities for patients with heavily pretreated advanced gastric cancer are yet to be identified to date. Although three more drugs (i.e., trifluridine/tipiracil[6], pembrolizumab[7], and nivolumab[8]) have been approved as third-line treatment for gastric cancer in some countries since apatinib has been approved in China in 2014, apatinib remains to have several advantages over other drugs. For example, apatinib is less expensive and an oral alternative. The oral treatment modality could have an important benefit of convenience over frequent infusions needed with nivolumab and pembrolizumab. However, apatinib-related AEs profile has greatly limited its use so various dosing strategies are being adopted in clinical practice.

In this report, we report the analysis of data from the third or higher lines subpopulation with apatinib alone therapy in the open label, non-interventional AHEAD-G202 trial. To the best of our knowledge, this study is the biggest real-world observation to investigate the safety and effectiveness of apatinib in the third- or

Table 3. Efficacy measures for patients receiving third line or higher apatinib alone therapy

Variables	Apatinib				χ^2	*P*
	All	250 mg	425-500 mg	675-850 mg		
No. (%)	120	44 (36.7)	66 (55.0)	10 (8.3)		
OS						
Median (95% CI), months	6.33 (4.57-7.73)	5.73 (3.77-8.00)	7.13 (4.57-7.93)	7.87 (2.23-14.03)	1.8872	0.3892
PFS						
Median (95% CI), months	3.03 (1.93-3.83)	3.83 (1.40-4.20)	2.93 (1.73-3.87)	2.40 (0.80-2.87)	0.7736	0.6792

higher-line setting for metastatic gastric cancer. The results of this subanalysis showed consistency in the safety and effectiveness of apatinib between the heavily pretreated subgroup and the pivotal phase III study reported previously [16]. It is worth nothing that lower daily doses (250-500 mg) of apatinib achieve comparable overall and progression-free survival versus higher daily doses (675-850 mg) of apatinib while maintaining a more benign safety profile.

The primary endpoints of our study were safety. As reported in the registration phase III study, apatinib, in which the initial daily dose was 850 mg, yielded grade 3 to 4 hand-foot syndrome (8.5%), with approximately one of two patients experiencing proteinuria (generally grade 1 to 2) and 5.7% of patients experiencing grade 3 to 4 neutropenia, this despite the exclusion of elderly patients (age >70 years) from the trial and the median age (58 years) in the two arms being lower than that in routine practice. Among the 40 cases of treatment discontinuation, 22 (55%) were due to toxicity. Further, the dose was reduced in 21% of patients who completed the apatinib treatment [16]. Thus, many physicians have adopted an empirical titration approach to manage toxicities. The current study demonstrated that although treatment-emergent toxicities of any grade are common among patients with heavily pretreated advanced gastric cancer, they are generally well tolerated even though 28.3% of patients had a baseline ECOG-PS >1, whereas in the registration phase III study [16], all patients were ECOG-PS 0-1 at baseline. Grade 3 or worse AEs were reported in less than 5% of the overall population, and only hand-foot syndrome and fatigue occurred in more than 5% of patients in the mid-dose group. Hypertension, hand-foot syndrome, nausea, and proteinuria were the most common AEs in our study, which are also well-known and common in antiangiogenic therapy. Rates of grade 3 or 4 hypertension, hand-foot syndrome, and proteinuria increased in mid-dose group compared with low-dose group, which can be explained by its dose-dependent toxicity [19]. Due to the small ratio of high-dose group, we didn't make further comparisons on this issue. In addition, there were no new unreported AEs in the current study compared with previous studies [10-16, 20, 21].

In total, 56.7% of patients required at least one dose interruption, and 14.2% had at least one dose reduction. The incidences of AEs were markedly lower than in the phase III study except hypertension (40.8% *vs.* 35.2%) [16]. The difference in apatinib dosage in the two studies may also partially explain the overall more benign profile of our study patients because 93.3% patients received daily dosages of apatinib lower than 850 mg. A phase II trial that used apatinib for the treatment of 25 patients with breast cancer showed that a dose of 750 mg once daily resulted in a dose delay of at least once cycle, with dose reductions in 84% of patients. Almost all patients experienced grade ≥3 toxicity, and treatment-related death occurred in two patients. The incidence of AEs markedly decreased when the apatinib dose was reduced to 500 mg once daily [22]. Collectively, these studies indicate that among Chinese cancer patients, lower doses of apatinib may be more preferable due to safety concerns. Thus, more and more published articles and ongoing trials selected initial dosages lower than 850 mg daily [20, 23-28].

Effectiveness is another crucial aspect of our study. In this study, apatinib therapy led to an overall median PFS of 3.03 months (95% CI: 1.93-3.83), which is slightly higher than that reported in the pivotal phase III trial [2.6 months (95% CI: 2.0 to 2.9)] [16]. Compared to that of the phase III trial, the median PFS was

higher in the low-dose group (3.83 months [95% CI: 1.40-4.20]) and the mid-dose group (2.93 months [95% CI: 1.70-3.87]), while it was slightly lower in the high-dose group (2.40 months [95% CI: 1.40-14.10]). The median OS of the overall population was similar to that of the phase III trial (6.33 months (95% CI: 4.57-7.73] *vs* 6.5 months (95% CI: 4.8-7.6]), but our mid-dose group (7.13 months [95% CI: 4.57-7.93]) and the high-dose group (7.87 months [95% CI: 2.23-14.03]) had higher OS than that in the trial. Moreover, our patients also had a higher ORR than in the phase III trial (5.8% *vs.* 2.84%) and a higher DCR (60.8% *vs.* 42.05%). Our study showed the effectiveness profile was similar between the heavily pretreated subgroup and the previously registration phase III study [16]. It also found prolonged PFS did not bring longer OS in low-dose group which meant patients' performance status was an important prognostic factor for apatinib therapy because up to 44.2% of patients had a baseline ECOG-PS >1 in this group.

In addition, due to no supportive evidence though many physicians have adopted a personalized apatinib dose and schedule adjustments in clinical practice, our study also focused on the optimal dose of apatinib during the course of treatment. Our data support the use of a feasible dose-modification strategy during apatinib treatment to optimize treatment outcomes and manage toxicities in a real-world setting. Considering the more benign safety profile in low-dose group, we think a lower starting dose of 250 mg/day is a feasible alternative in patients with poor performance status. Meanwhile, initial daily doses of 425 to 500 mg might be a good choice for heavily pretreated advanced gastric cancer patients with good performance status because this dosing schedule yielded clinical outcomes comparable to those of higher doses and incur lower incidences of grade 3 to 4 AEs *versus* 850 mg apatinib in the registration phase III study [16]. A previous real-world study that used initial daily doses of 500 mg and 250 mg apatinib for the treatment of 36 patients with gastric cancer also showed that lower doses of apatinib could be beneficial to advanced gastric cancer patients [21]. However, these findings should be interpreted with caution because this is an observational study which mingled with some complicated factors. There is still some dissimilitude between our study and the pivotal phase III study [16]. On one hand, only 6.7% patients received daily dosages of 850 mg in our trail, likely to reduce AEs. That meant a lack of a control group. On the other hand, dose titration was more flexibly in our study due to under real-world conditions. Some patients experienced a dose-escalation strategy due to well tolerance. However, no patients could have dose up-regulation to the high-dose group.

This study has several limitations including potentially missing data and possible information bias. Nevertheless, as a prospective real world study, we present first-hand safety and effectiveness data of apatinib in the third- or higher-line setting in advanced gastric cancer, which are valuable for deciding the appropriateness of apatinib in this setting in clinical practice.

In conclusion, our study revealed that heavily pretreated advanced gastric cancer patients can tolerate and benefit from lower-doses of apatinib therapy. Our data also support the use of a lower starting dose of 250 mg/day in patients with higher ECOG-PS, and daily initial doses of 425 to 500 mg might be a good choice in patients with good performance status. Therefore, physicians might view these strategies, which also will lower the patients' economic burden, as a welcome alternative approaches for optimizing apatinib dosing in the management of patients with heavily pretreated advanced gastric cancer. However, the optimal dose still needs further investigation in a larger population.

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Disclosure of conflict of interest

None.

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Supplementary List I

List of ethics committees for the AHEAD-G202 study

The study protocol was approved by the ethics committees or institution review boards of the following institutions (Approval number: HS-806):

Peking Union Medical College Hospital, Chinese Academy of Medical Sciences
The Fourth Hospital of Hebei Medical University
Fourth Medical Center of PLA General Hospital
Shanxi Tumor Hospital
Affiliated Hospital of Hebei University
Shanxi Provincial Hospital of Traditional Chinese Medicine
Peace Hospital of Changzhi Medical College
Cangzhou Central Hospital
Shanxi Academy of Medical Sciences, Shanxi Dayi Hospital
First Hospital of Qinhuangdao
Yangquan First People's Hospital
Peking University Third Hospital
Xingtai People's Hospital, Hebei Medical University Affiliated Hospital
Affiliated Hospital of Chengde Medical University
Chinese PLA General Hospital, Medical School of Chinese PLA
Air Force General Hospital, PLA
Second Hospital of Shanxi Medical University
Handan Central Hospital
Shijiazhuang People's Hospital
Peking University Binhai Hospital
Seventh Medical Center of PLA General Hospital
Datong Second People's Hospital
First Hospital of Shanxi Medical University
Fifth Medical Center of PLA General Hospital
Tianjin People's Hospital
Strategic Support Force Characteristic Medical Center/Former The 306 Hospital of PLA
Sixth Medical Center of PLA General Hospital
Tianjin Medical University Cancer Institute and Hospital
Tianjin Medical University General Hospital