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An open label, multicenter, noninterventional study of apatinib in advanced gastric cancer patients (AHEAD-G202)

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Abstract

Background: Apatinib has been proved to be effective and well tolerated among patients in phase II and III studies. Here, we evaluated the safety and effectiveness of apatinib in advanced gastric cancer patients in a real-world setting.

Methods: This study enrolled advanced gastric cancer patients who had progressed or relapsed despite systemic chemotherapy. The primary outcome was safety and the secondary outcomes included overall survival (OS) and progression-free survival (PFS).

Results: A total of 337 patients were included. In total, 62 (18.4%), 102 (30.3%), and 173 (51.3%) patients received first, second, and third or higher line apatinib therapy, respectively. Grade 3/4 treatment-emergent adverse events (AEs) were infrequent (<5%), with hypertension (6.8%) being the only grade 3/4 AE occurring in more than 5% of the patients and across the low-dose (250 mg, 7.3%), mid-dose (425–500 mg, 6.1%), and high-dose group (675–850 mg, 2/15, 13.3%). The median OS and PFS were 7.13 months (95% CI, 6.17–7.93) and 4.20 months (95% CI, 4.60–4.77), respectively, and were comparable among the low-, mid-, and high-dose groups.

Conclusion: Lower daily doses of apatinib achieved comparable OS and PFS *versus* higher daily doses of apatinib while maintaining a more benign safety profile in advanced gastric cancer patients.

Clinical Trial Registration: ClinicalTrials.gov identifier: NCT02668380.

Keywords: apatinib, safety, effectiveness, gastric cancer, real world

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Introduction

Gastric cancer is one of the most frequent malignancies and currently the third leading cause of cancer-related mortality globally with approximately 723,000 deaths annually.[1,2] Despite the recent decline in the prevalence of gastric cancer in China, 498,000 gastric cancer deaths were estimated to have occurred in 2015 in the country,[3] with a mortality of 15.6 per 100,000.[4]

Gastric cancer is often diagnosed at an advanced stage (locally advanced or metastatic) when it is not amenable to curative surgical resection and palliative chemotherapy remains the principal therapeutic modality.[5] The outcome of advanced gastric cancer is rather dismal with an overall survival (OS) less than 12 months.[6] For advanced gastric cancer patients with a good performance status, chemotherapy is the standard first-line

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therapeutic option. A combination of a fluoropyrimidine (e.g. 5-fluorouracil, capecitabine, or S-1), a platinum agent (e.g. cisplatin, or oxaliplatin), and a taxane (e.g. docetaxel) are usually recommended in patients with human epidermal growth factor 2 (HER-2) negative tumors;[7–9] patients who have HER-2 positive tumors should also receive trastuzumab.[10] For further improvement of treatment outcomes, second-line chemotherapy is administered routinely.[7–9] Treatment options include docetaxel, paclitaxel, or irinotecan monotherapy,[11–14] or the antivascular endothelial growth factor receptor 2 antibody ramucirumab alone or in combination with paclitaxel.[15,16] However, nearly all patients with advanced disease continue to have disease progression following treatment. At present, new approaches are focusing on molecularly driven therapies and immunotherapy.

Apatinib, which was approved in 2014 by the China Food and Drug Administration (CFDA) for treating advanced gastric or gastroesophageal junction adenocarcinoma patients who failed second-line chemotherapy,[17,18] is an oral tyrosine kinase inhibitor of vascular endothelial growth factor receptor 2.[19] The drug has demonstrated antitumor activity in some solid tumors.[20] The phase III trial has shown that apatinib at the dose level of 850 mg once daily significantly improves the prognosis of advanced gastric cancer patients who have previously failed second-line chemotherapy, modestly extending progression-free survival (PFS) by 1 month and OS by 2 months.[17] However, lingering questions still remain regarding the safety of apatinib in the phase III trial;[21] 8.5% of the patients had grade 3/4 hand–foot syndrome and 5.7% had grade 3/4 neutropenia. In addition, the median age of the study population was 58 years and a smaller proportion of the study population were aged between 65 and 70 years, which is lower than the age of patients seen in the real-world setting. Furthermore, 40 patients in the phase III trial discontinued apatinib treatment, 22 (55%) of them owing to toxicity.

The goals of second-line and subsequent lines of treatment in advanced gastric cancer are to increase residual survival and gain symptomatic control, while minimizing toxicities.[13,22,23] Our current experience is limited with the use of apatinib for advanced gastric cancer and is based mostly on data from clinical trials in which the patient population is tightly controlled and homogeneous and a higher dose of apatinib (850 mg once daily) is used.[17,24–26] Only a small real-world study is available on the effectiveness and safety of apatinib in 36 patients with advanced gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction.[27] Therefore, as the first tyrosine kinase inhibitor approved in advanced gastric cancer, it is necessary to evaluate the treatment of apatinib more accurately in the real-world setting. In this noninterventional study, we investigated the safety and effectiveness of apatinib in 337 advanced gastric cancer patients in a real-world setting.

Methods

Patients

This noninterventional, real-world study was conducted across 29 centers in China between September 2015 and March 2018. We enrolled adult (⩾18 years old) patients with pathologically proven advanced gastric cancer. Patients with known allergy to apatinib, pregnant or lactating women, and patients with active bleeding, ulcers, intestinal perforation or obstruction within 30 days after major surgery, uncontrolled hypertension, NY functional class III–IV cardiac insufficiency, or severe liver and kidney dysfunction were excluded. 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. All participating sites obtained institutional review board or ethics committee approval of the study protocol prior to local initiation of the study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and according to the relevant laws and guidelines in China (Supplementary List I). Written informed consent to participation in the study was obtained from each patient before the start of the study. The diagnostic and therapeutic practices were implemented according to the clinical practice of each participating center. The trial is registered at www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02668380).

Treatment

Any dosing schedule and dose modification of apatinib were part of routine clinical practice. Apatinib was given orally at 850 mg once daily. One cycle of treatment consisted of 28 days. The dose was modified at the discretion of attending

oncologists to 250–850 mg once daily during the course of the study following recommendation by the drug manufacturer (Jiangsu Hengrui Medicine) and an expert consensus[28] based on feedback of treatment-emergent adverse events (AEs). The modification was approved by the appropriate ethics committee and updated in the protocol. Patients received apatinib until disease progression, unacceptable toxicities or at the physician's discretion. Dose interruptions or reductions were done to manage toxicities following the starting dose. Dose was increased if deemed necessary. 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.

Patient evaluation

We collected information on patient demographic and baseline characteristics including American Joint Committee on Cancer stage, Lauren classification and Eastern Cooperative Oncology Group performance status (ECOG-PS) score, treatment patterns by line of therapy, patient outcomes, and safety data. AEs were collected and coded to a preferred term using the Medical Dictionary for Regulatory Activities. AEs were reviewed and determined from the medical history and laboratory findings or from telephone follow up according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Safety analysis included all patients who received at least one dose of the study drug and had at least one follow-up safety assessment. The intention-to-treat (ITT) population included all patients who received at least one dose of the study drug, had a baseline assessment, and at least one post-baseline assessment. Evaluation of treatment response and progression was based on physician's assessment; response evaluation criteria in solid tumors (RECIST v1.1) evaluation was performed but not mandatory. In accordance with routine practice, clinical assessment of response to treatment and evaluation by computed tomography or magnetic resonance imaging were undertaken during regular visits at an interval of approximately 8–12 weeks.

Statistical analysis

Scientific conduct and safety reviews were supervised by a trained team of supervisors to assure adherence to the study protocol by each participating center and accuracy and integrity of trial data. The statistical analyses were prespecified before the database lock and followed the ITT principle. All analyses were descriptive and performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). No sample size calculation was required given that this was a registry study and the final total number of patients enrolled was the size of the study population. Both responses and AEs were aggregated in the form of frequency counts and percentages. The primary outcome of this study was safety and included treatment and apatinib alone-emergent AEs. The secondary outcomes included OS, PFS, objective response rate (ORR), and disease control rate (DCR). The ORR included complete response (CR) and partial response (PR) that were assessed using the RECIST v 1.1. DCR was the percentage of patients with stable disease (SD), CR, or PR. OS and PFS and their corresponding 95% confidence intervals (CIs) were evaluated using Kaplan–Meier method and measured from the date of apatinib initiation to the time of progression by physician assessment or death of any cause. Patients surviving or progressing at the time of data collection were censored at the date of last contact for OS and PFS, respectively. Date of the last contact was used for OS and date of last evaluable follow up was used for PFS of patients who dropped out of the study or were lost to follow up. The ORR and DCR were analyzed on the basis of frequency counts. 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 demographic, baseline, and treatment characteristics

The study flowchart is shown in Figure 1. Patient demographic and baseline characteristics are shown in Table 1. A total of 337 advanced gastric cancer patients received apatinib therapy at 29 participating centers. Male patients accounted for 68.5% of the study population and 36.8% of the patients were aged at least 65 years. Moreover, 95.2% of them had stage IV gastric cancer. The ECOG-PS score was 0 or 1 in 61.4% and 2 or above in 21.7% of the patients.

In total, 17.5% of the patients received prior radiotherapy, 43.6% underwent prior surgery, and 81.6% received prior chemotherapy. The number

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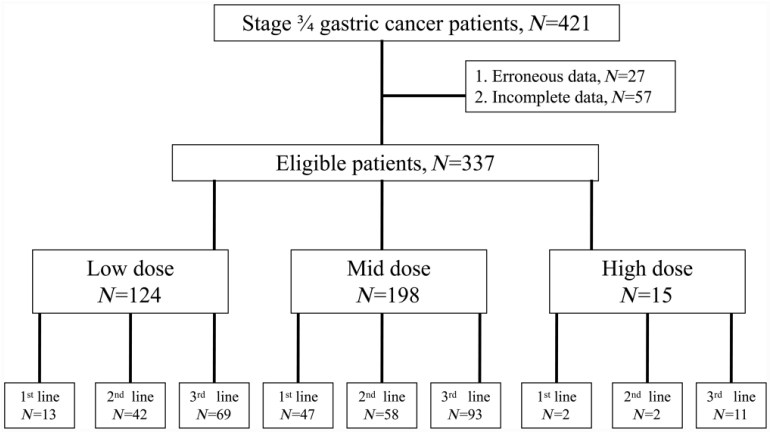

Figure 1. The study flowchart.

of patients who received single, double, and triple chemotherapy and their line of apatinib therapy are shown in Supplementary Table 1. All patients received apatinib therapy, including first-line apatinib in 62 (18.4%) patients, second-line apatinib in 102 (30.3%) patients, and third or higher line apatinib in 173 (51.3%) patients. The initial dose of apatinib ranged from 250 mg once daily to 850 mg once daily. The starting dose of apatinib was 250 mg in 124 patients (36.8%) (the low-dose group), 425–500 mg in 198 (58.7%) patients (the mid-dose group), and from 675 to 850 mg in 15 (4.4%) patients (the high-dose group). The three groups differed significantly in lines of apatinib treatment ($p = 0.0266$), prior surgery ($p = 0.0485$) and ECOG-PS score ($p = 0.0214$).

Treatment and apatinib emergent AEs

A total of 166 (49.3%) patients required at least one dose interruption, and 24.3% required at least one dose adjustment (Supplementary Table 2). At the study cutoff (30 October 2018), 327 patients had discontinued treatment. The primary reasons for discontinuation were death (31.8%), disease progression (23.3%), and AEs (22.9%). In total, 86.6% of the overall population reported treatment-emergent AEs of any grade and any cause (Table 2). Commonly reported treatment-emergent AEs (⩾10%) of any grade included, among others, hypertension (44.8%), fatigue (27.9%), and hand–foot syndrome (20.8%). Among grade 3/4 AEs, hypertension remained the most frequent treatment-emergent AE (6.8%), followed by fatigue (3.9%), thrombocytopenia (3.3%), and hand–foot syndrome (3.3%). Hypertension also remained the most frequent treatment-emergent AE in the low-dose group (7.3%), followed by thrombocytopenia (4.0%), fatigue (2.4%), nausea (2.4%), and intestinal obstruction (2.4%). Hypertension also remained the most frequent grade 3/4 treatment-emergent AE in the mid-dose group (6.1%), followed by hand–foot syndrome (4.6%), and fatigue (4.6%). Grade 3/4 hypertension was seen in 2 (2/15, 13.3%) patients and fatigue in 1 (1/15, 6.7%) patient in the high-dose group. No other grade 3/4 AEs were observed in the high-dose group.

A total of 166 patients were evaluated for AEs due to apatinib in combination with chemotherapy. Hypertension (14.2%) was the most common grade 3/4 AE in the study population and across the three dosing groups (Supplementary Table 3). Grade 3/4 hypertension occurred in 6 (14.0%) patients and thrombocytopenia in 4 (9.3%) patients in the low-dose group. Grade 3/4 hypertension occurred in 8 (13.1%) patients and thrombocytopenia, bleeding, and fatigue each occurred in 4 (6.6%) patients in the mid-dose group. Furthermore, grade 3/4 hypertension was reported in 1/2 patient in the high-dose group.

In total, 231 patients were evaluated for apatinib alone-emergent AEs. Commonly reported apatinib-emergent AEs (⩾10%) of any grade included hypertension (45.0%), fatigue (32.9%), nausea (17.3%), hand–foot syndrome (16.0%), and proteinuria (13.9%) (Table 3). All grade 3/4 apatinib-emergent AEs were <5%. Grade 3/4 AEs included hypertension and proteinuria each in 8 (3.5%) patients, and hand–foot syndrome and fatigue each in 7 (3.0%) patients. Grade 3/4 AEs included hypertension (3.6%), nausea (2.4%), and difficulty in swallowing (2.4%) in the low-dose group.

Table 1. Patient demographic and baseline characteristics.

Variables	Apatinib				χ^2	*p*
	All	250 mg	425–500 mg	675–850 mg		
***N* (%)**	337	124 (36.8)	198 (58.7)	15 (4.5)		
Male gender, *n* (%)	231 (68.5)	88 (70.2)	135 (68.7)	8 (53.3)	1.7619	0.4144
Age, years, (%)					4.2005	0.1224
⩾65	124 (36.8)	54 (43.5)	64 (32.3)	6 (40.0)		
AJCC staging, *n* (%)					3.1153	0.2106
III	16 (4.7)	4 (3.2)	12 (6.1)	0 (0.0)		
IV	321 (95.2)	120 (96.8)	186 (93.9)	15 (100.0)		
ECOG performance score, *n* (%)						0.0214*
0	41 (1.2)	8 (6.4)	32 (16.2)	1 (6.7)		
1	203 (60.2)	75 (60.5)	120 (60.6)	8 (53.3)		
>=2	73 (21.7)	35 (28.2)	34 (17.2)	4 (26.7)		
N/A	20 (5.9)	6 (4.8)	12 (6.1)	2 (13.3)		
Metastatic sites, *n* (%)					1.229	0.5409
>2	76 (22.5)	31 (25.0)	43 (21.7)	2 (13.3)		
Lauren classification, *n* (%)						0.6859*
Intestinal	59 (17.5)	24 (19.4)	33 (16.7)	2 (40.0)		
Diffuse	95 (28.2)	29 (23.4)	63 (31.8)	3 (60.0)		
Mixed	22 (6.5)	8 (6.4)	14 (7.1)	0 (0.0)		
N/A	161 (47.8)	63 (50.8)	88 (44.4)	10 (66.7)		
Prior radiotherapy, *n* (%)					3.2267	0.1992
Yes	59 (17.5)	21 (16.9)	36 (18.2)	2 (13.3)		
Prior surgery, *n* (%)						0.0485*
Yes	147 (43.6)	59 (47.6)	87 (43.9)	1 (11.1)		
No	159 (47.2)	52 (41.9)	99 (50.0)	8 (53.3)		
N/A	31 (9.2)	13 (10.5)	12 (6.1)	6 (40.0)		
Line of therapy, *n* (%)						0.0266*
1	62 (18.4)	13 (10.5)	47 (23.7)	2 (14.3)		
2	102 (30.3)	42 (33.9)	58 (29.3)	2 (14.3)		
>=3	173 (51.3)	69 (55.6)	93 (47.0)	11 (73.3)		

*Fisher's exact test.
AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

Table 2. Treatment-emergent adverse events (AEs) in the study population, *n* (%).

AEs	All, *n* = 337		250 mg, *n* = 124		425–500 mg, *n* = 198		675–850 mg, *n* = 15	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic toxicities								
Leukopenia	19 (5.6)	0	12 (9.7)	0	7 (3.5)	0	0	0
Neutropenia	8 (2.4)	1 (0.3)	4 (3.2)	1 (0.8)	4 (2.5)	0	0	0
Anemia	6 (1.8)	1 (0.3)	2 (1.6)	0	4 (2.0)	1 (0.5)	0	0
Thrombocytopenia	21 (6.2)	11 (3.3)	11 (8.9)	5 (4.0)	9 (4.6)	6 (3.1)	1 (6.7)	0
Nonhematologic toxicities								
Proteinuria	45 (13.4)	8 (2.4)	15 (12.1)	2 (1.6)	26 (26.5)	6 (3.0)	4 (26.7)	0
Hypertension	151 (44.8)	23 (6.8)	63 (50.8)	9 (7.3)	81 (40.9)	12 (6.1)	7 (46.7)	2 (13.3)
Hand–foot syndrome	70 (20.8)	11 (3.3)	22 (17.7)	2 (1.6)	46 (23.2)	9 (4.6)	2 (13.3)	0
Transaminase elevations	5 (1.5)	1 (0.3)	0	0	5 (2.5)	1 (0.5)	0	0
Hyperbilirubinemia	6 (1.8)	0	3 (2.4)	0	3 (1.5)	0	0	0
Bleeding	30 (8.9)	7 (2.1)	10 (8.1)	2 (1.6)	19 (9.6)	5 (2.5)	1 (6.7)	0
Fatigue	104 (27.9)	13 (3.9)	45 (36.3)	3 (2.4)	64 (32.3)	9 (4.6)	5 (33.3)	1 (6.7)
Alkaline phosphatase elevations	1 (0.3)	0	1 (0.8)	0	0	0	0	0
Abdominal pain	11 (3.3)	2 (0.6)	7 (5.6)	1 (0.8)	4 (2.0)	1 (0.5)	0	0
Loss of appetite	29 (8.6)	5 (1.5)	14 (11.3)	2 (1.6)	15 (7.6)	3 (1.5)	0	0
Hypoalbuminemia	4 (1.2)	0	2 (1.6)	0	2 (1.0)	0	0	0
Diarrhea	30 (8.9)	4 (1.2)	13 (10.5)	0	17 (8.6)	4 (2.0)	0	0
Arrhythmia	19 (5.6)	2 (0.6)	12 (9.7)	0	7 (3.5)	2 (1.0)	0	0
Nausea	55 (16.3)	4 (1.2)	26 (20.8)	3 (2.4)	25 (12.6)	1 (0.5)	4 (26.7)	0
Vomiting	20 (5.9)	4 (1.2)	14 (11.3)	2 (1.6)	6 (3.0)	2 (1.0)	0	0
Intestinal obstruction	9 (2.7)	4 (1.2)	5 (4.0)	3 (2.4)	4 (2.0)	1 (0.5)	0	0
Oral mucositis	18 (5.3)	4 (1.2)	10 (8.1)	2 (1.6)	8 (4.0)	2 (1.0)	0	0
Urinary tract infection	15 (4.5)	4 (1.2)	9 (7.3)	2 (1.6)	6 (3.0)	2 (1.0)	0	0
Headache	7 (2.1)	0	5 (4.0)	0	2 (1.0)	0	0	0
Dizziness	10 (3.0)	0	3 (2.4)	0	7 (3.5)	0	0	0
Lumbar pain	3 (0.9)	0	2 (1.6)	0	1 (0.5)	0	0	0
Difficulty in swallowing	12 (3.6)	6 (1.8)	3 (2.4)	2 (1.6)	9 (4.6)	4 (2.0)	0	0
Hoarse voice	9 (2.7)	1 (0.3)	3 (2.4)	0	6 (3.0)	1 (0.5)	0	0

Table 3. Apatinib alone-emergent adverse events, *n* (%).

AEs	All, *n* = 231		250 mg, *n* = 83		425–500 mg, *n* = 135		675–850 mg, *n* = 13	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic toxicities								
Leukopenia	7 (3.0)	0	5 (6.0)	0	2 (1.5)	0	0	0
Neutropenia	5 (2.2)	0	3 (3.6)	0	2 (1.5)	0	0	0
Anemia	2 (0.9)	0	0	0	2 (1.5)	0	0	0
Thrombocytopenia	8 (3.5)	3 (1.3)	5 (6.0)	1 (1.21)	3 (2.2)	2 (1.5)	0	0
Nonhematologic toxicities								
Proteinuria	32 (13.9)	8 (3.5)	9 (10.8)	2 (2.4)	20 (14.8)	6 (4.4)	3 (23.1)	0
Hypertension	104 (45.0)	8 (3.5)	43 (51.8)	3 (3.6)	55 (40.7)	4 (3.0)	6 (46.2)	1 (7.7)
Hand–foot syndrome	37 (16.0)	7 (3.0)	10 (12.1)	1 (1.2)	26 (19.3)	6 (4.4)	1 (7.7)	0
Transaminase elevations	4 (1.7)	1 (0.4)	0	0	4 (3.0)	1 (0.7)	0	0
Hyperbilirubinemia	2 (0.9)	0	1 (1.2)	0	1 (0.7)	0	0	0
Bleeding	14 (6.0)	2 (0.9)	4 (4.8)	1 (1.2)	9 (6.7)	1 (0.7)	1 (7.7)	0
Fatigue	76 (32.9)	7 (3.0)	28 (33.7)	1 (1.2)	43 (31.9)	5 (3.7)	5 (38.5)	1 (7.7)
Alkaline phosphatase elevations	1 (0.4)	0	1 (1.2)	0	0	0	0	0
Abdominal pain	3 (1.3)	0	3 (3.6)	0	0	0	0	0
Loss of appetite	9 (3.9)	1 (0.4)	6 (7.2)	1 (1.2)	3 (2.2)	0	0	0
Hypoalbuminemia	0	0	0	0	0	0	0	0
Diarrhea	13 (5.6)	3 (1.3)	5 (6.0)	0	8 (5.9)	3 (2.2)	0	0
Arrhythmia	3 (1.3)	0	2 (2.4)	0	1 (0.7)	0	0	0
Nausea	40 (17.3)	3 (1.3)	16 (19.3)	2 (2.4)	20 (14.8)	1 (0.7)	4 (30.8)	0
Vomiting	11 (4.8)	2 (0.9)	8 (9.6)	1 (1.2)	3 (2.2)	1 (0.7)	0	0
Intestinal obstruction	5 (2.2)	1 (0.4)	2 (2.4)	0	3 (2.2)	1 (0.7)	0	0
Oral mucositis	5 (2.2)	0	2 (2.4)	0	3 (2.2)	0	0	0
Urinary tract infection	1 (0.4)	0	0	0	1 (0.7)	0	0	0
Headache	3 (1.3)	0	2 (2.4)	0	1 (0.7)	0	0	0
Dizziness	3 (1.3)	0	2 (2.4)	0	1 (0.7)	0	0	0
Lumbar pain	1 (0.4)	0	1 (1.2)	0	0	0	0	0
Difficulty in swallowing	9 (3.9)	5 (2.17)	2 (2.4)	2 (2.4)	7 (5.2)	3 (2.2)	0	0
Hoarse voice	0	0	0	0	0	0	0	0
Stomach pain	1 (0.4)	0	0	0	1 (0.7)	0	0	0

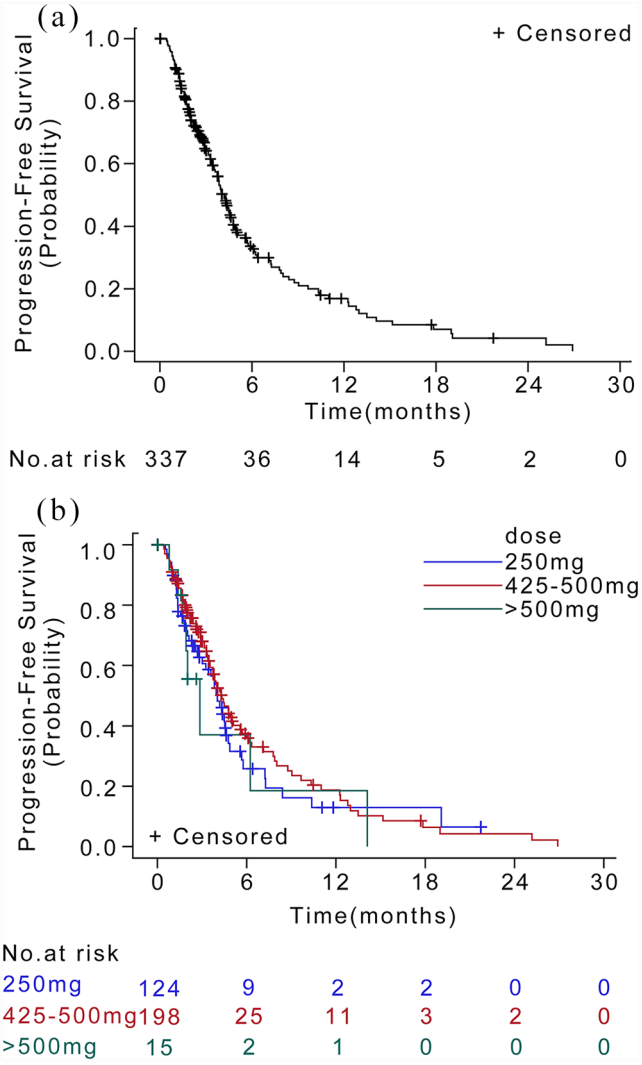

Figure 2. Kaplan–Meier estimates of progression-free survival (PFS). (a) PFS for the overall population. The median PFS was 4.20 months (95% CI, 4.60–4.77). (b) PFS stratified by dosing levels of apatinib. The median PFS was 4.03 months (95% CI, 2.83–4.63), 4.33 months (95% CI, 3.53–5.10), and 2.87months (95% CI, 1.40–14.10) for the low-, mid-, and high-dose groups, respectively ($\chi^2 = 1.3839$, $p = 0.5006$).

In the mid-dose group, the most common grade 3/4 AEs were hand–foot syndrome (4.4%) and proteinuria (4.4%), followed by fatigue (3.7%), and hypertension (3.0%). Grade 3/4 hypertension and fatigue occurred each in 1/13 (7.7%) patient in the high-dose group.

PFS and OS

At the study cutoff time, 31.7% (107/337) patients had died. The primary cause of death was tumor metastasis (73/107, 68.2%). The median PFS was 4.20 months (95% CI, 4.60–4.77) for the overall population (Figure 2(a) and Supplementary Table 4). The median PFS was 4.03 months (95% CI, 2.83–4.63), 4.33 months (95% CI, 3.53–5.10), and 2.87 months (95% CI, 1.40–14.10) for the low-, mid-, and high-dose groups, respectively ($\chi^2 = 1.3839$, $p = 0.5006$) (Figure 2(b)). The median OS was 7.13 months (95% CI, 6.17–7.93) for the overall population (Figure 3(a)). Furthermore, the median OS was 6.27 months (95% CI, 5.50–7.77), 7.43 months (95% CI, 6.17–8.90), and 7.87 months (95% CI, 3.43–14.03) for the low-, mid-, and high-dose groups, respectively ($\chi^2 = 1.7672$, $p = 0.4133$) (Figure 3b). Our multivariate Cox regression analysis showed no significant difference in PFS and OS among the three dose groups (Supplementary Tables 5 and 6).

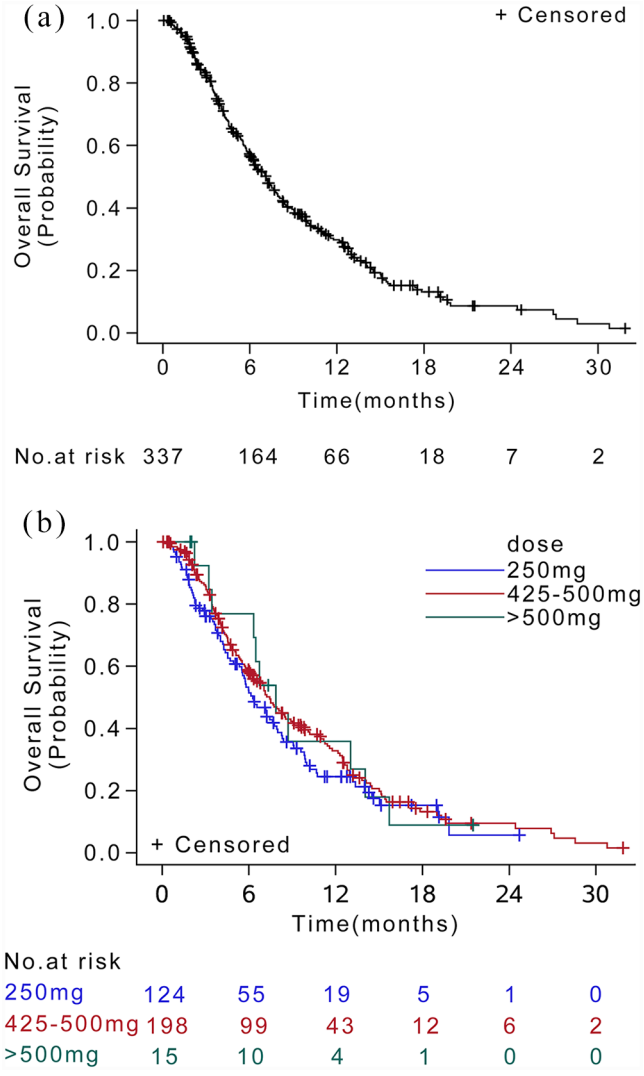

Figure 3. Kaplan–Meier estimates of overall survival (OS). (a) OS for the overall population. The median OS was 7.13 months (95% CI, 6.17–7.93). (b) OS stratified by dosing levels of apatinib. The median OS was 6.27 (95% CI, 5.50–7.77), 7.43 (95% CI, 6.17–8.90), and 7.87 months (95% CI, 3.43–14.03) for the low-, mid-, and high-dose groups, respectively ($\chi^2 = 1.7672$, $p = 0.4133$).

Tumor response to apatinib was evaluable for 249 patients. CR/PR was achieved in 14.0% and SD in 62.6% of the patients. The ORR was 14.0% and the DCR was 76.6% (Supplementary Table 4).

Discussion

To the best of the authors' knowledge, this is hitherto the largest real-world study concerning the safety and effectiveness of apatinib in advanced gastric adenocarcinoma. It included data from 337 advanced gastric cancer patients from 29 institutions across 4 provinces of northern China and yielded real-world results for apatinib. As for first-line advanced gastric cancer therapy, apart from extending survival of advanced gastric cancer patients, safety is an important aim for second and subsequent lines of advanced gastric cancer therapy. The current study demonstrated that though treatment-emergent toxicities of any grade were common among advanced gastric cancer patients in our study cohort, they were generally well tolerated, and hypertension remained the only grade 3/4 AEs that occurred in more than 5% of the patients and across the three dosing groups. Furthermore, grade 3/4 apatinib alone-emergent AEs were infrequent (<5%), with hypertension and proteinuria being the most commonly reported grade 3/4 AEs.

Hypertension, fatigue, nausea, and hand–foot syndrome were among the most common apatinib alone-emergent AEs of any grade in our study and there were no new unreported AEs *versus* previous studies.[15–17,24,29] This is consistent with other studies on antiangiogenic agents[15,16,29] for advanced gastric cancer and also with a phase III clinical trial in advanced gastric cancer patients who were refractory to chemotherapy.[17] Noticeably, compared with the phase III trial, our population had a lower incidence of apatinib alone-emergent grade 3–4 hypertension (3.5% *versus* 4.5%), hand–foot syndrome (3.0% *versus* 8.5%), while proteinuria (3.5% *versus* 2.3%) increased slightly. In addition, the incidence of grade 3/4 hematologic toxicities was lower in our cohort compared with the phase III clinical trial: anemia (0% *versus* 6.3%) and neutropenia (0% *versus*5.7%) and thrombocytopenia (1.3% *versus* 2.8%). The difference of apatinib dosage in the two studies may partially explain the overall more benign profile of our study patients. Almost all of our patients (95.5%) were treated with apatinib at a dose lower than 850 mg once daily, which was used in the phase III study.[30] Both the low- (250 mg) and mid-dose (425–500 mg) groups in our study had lower incidences of grade 3–4 hematologic toxicities, and a lower rate of grade 3–4 hand–foot syndrome and proteinuria compared with the phase III trial. The number of patients in the high-dose group is too small to make any meaningful comparison.

Approximately half of our patients (49.3%) required at least one dose interruption and a quarter of the patients (24.3%) had at least one dose adjustment. Our higher rate of dose modifications resulting from toxicity compared with the phase III study (21.0%) may be due to the more liberal policy of dose modifications in our study, which allowed both dose reductions and escalations, while the phase III study allowed dose reductions up to three times to a dose level not lower than 375 mg once daily and did not allow dose re-escalation. Furthermore, our study population also had lower incidences of grade 3–4 hand–foot syndrome, hypertension, and proteinuria compared with patients who received apatinib 425 mg twice daily in a phase II study.[24]

Though the phase III trial concluded that apatinib at a dose of 850 mg once daily had a favorable safety profile, more than half (55%) of the patients discontinued apatinib therapy because of toxicity.[17] The higher rate of hand–foot syndrome (8.5%) and grade 3/4 neutropenia (5.7%) in the patients receiving apatinib monotherapy in the phase III trial should be considered in the context that advanced gastric cancer patients receive apatinib along with chemotherapy in the real-world setting, and that the combination therapy could have higher rates of hand–foot syndrome and grade 3/4 neutropenia. In a phase II study of Chinese metastatic triple-negative breast cancer patients, the initial daily dose of 750 mg in apatinib monotherapy was lowered to 500 mg daily because of toxicities.[31] In a separate phase II study of Chinese nontriple-negative breast cancer patients, apatinib at 500 mg/day was also associated with noticeable grade 3/4 AEs [hypertension (20.5%), hand–foot syndrome (10.3%), and proteinuria (5.1%)].[32] These studies suggest that among Chinese cancer patients, lower doses of apatinib may be more preferable owing to safety concerns. A real-world study also demonstrated that lower doses of apatinib could benefit patients with less toxicity in advanced gastric cancer patients.[27]

Only a small proportion of our patients followed the initial dosing regimen of 850 mg once daily specified in the study protocol owing to AEs. Lower doses of apatinib were given following feedback from oncologists and recommendation by the drug manufacturer and an expert consensus.[28] Furthermore, approximately half of our patients were treated by first- or second-line chemotherapy. Given the dismal prognosis of advanced gastric cancer patients despite chemotherapy, combination regimens such as ramucirumab and paclitaxel have been used as first- or second-line treatment.[33,34] Therefore, in our study, advanced gastric cancer patients who were treated by first- or second-line chemotherapy were also offered apatinib therapy. In an ongoing real-world study of 954 gastric cancer patients in China, 679 patients with metastatic gastric cancer including first-line apatinib in 287 (42.2%) patients, second-line apatinib in 207 (30.5%) patients, and third-line apatinib in 185 (27.3%) patients were enrolled. Among all of 954 patients, 375 patients were evaluated for effectiveness.[35] The interim results of the study showed that patients receiving the combination regimen of apatinib and chemotherapy had significantly longer median PFS *versus* those receiving apatinib monotherapy (apatinib plus chemotherapy: 5.03 months, 95% CI, 3.70–7.30 *versus* apatinib monotherapy: 3.33 months, 95% CI, 2.37–4.33; $p = 0.003$).

Effectiveness analysis of the current multicenter study showed that the median PFS was 4.20 months (95% CI, 4.60–4.77) for our overall population, which is numerically higher than that reported in the phase III trial [2.6 months (95% CI, 2.0–2.9)]. The median PFS is also numerically higher in our low-dose group [4.03 months (95% CI, 2.83–4.63)], and the mid-dose group [4.33 months (95% CI, 3.53–5.10)], while the high-dose group [2.87 months (95% CI, 1.40–14.10)] had a similar PFS to that of the phase III trial. Meanwhile, our overall population had a median OS [7.13 months (95% CI, 6.17–7.93)] that is largely comparable with that of the phase III trial [6.5 months (95% CI, 4.8–7.6)], which is numerically lower than our mid-dose group [7.43 (95% CI, 6.17–8.90)] and the high-dose group [7.87 months (95% CI, 3.43–14.03)]. Moreover, our patients also had a higher ORR than that of the phase III trial (14.0% *versus* 2.84%) as well as a higher DCR (76.6% *versus* 42.05%). Our effectiveness data should be interpreted with the consideration that the patients had received different lines of apatinib therapy, which was given at different doses and with or without concurrent chemotherapy.

Our data suggest that lower doses of apatinib (250–500 mg) may yield comparable survival outcomes with those achieved with a higher dose (850 mg) with fewer side effects. Apatinib has recently emerged as a promising antiangiogenesis agent for advanced gastric cancer and has been approved by CFDA in China for the treatment of patients with advanced gastric cancer refractory to two or more lines of prior chemotherapy.[36,37] Our study showed that slightly less than half of our patients used apatinib as first- or second-line therapy. Importantly, our data also demonstrated that advanced gastric cancer patients received apatinib therapy at much lower doses than that used in clinical trials. We found that lower doses of apatinib, particularly 425–500 mg, yielded clinical outcomes comparable with those from higher dose of the drug and with lower incidences of grade 3–4 AEs *versus* 850 mg apatinib as used in the clinical trials. In the current report, we did not analyze line-specific outcomes. It would be of interest to analyze the safety and outcome of apatinib as third or higher line therapy for advanced gastric cancer in this real-world setting and delineate the safety and effectiveness of moderate doses of apatinib *versus* high doses of apatinib. Apart from efficacy, safety is a very important consideration in apatinib as second or higher lines of treatment in advanced gastric cancer.[13,22]

One limitation of the current study is a lack of stringent inclusion and exclusion criteria, leading to a heterogeneous patient population. Though the study was carried out in a real-world setting, all the patients received apatinib therapy at tertiary care institutions. Therefore, our findings may not be applicable to primary and secondary care settings. Furthermore, this study did not have a control arm and effectiveness and safety data were compared mainly with the phase III trial on apatinib. In addition, this study has a noninterventional design and is observational. There were no standardized assessments at the beginning dose as in the clinical trials. While clinical trials provide invaluable information, observational noninterventional studies are important sources of information about the use of agents in the real-world clinical setting. This current trial, to the best of the authors' knowledge, is the first real-world study of advanced gastric cancer patients investigating apatinib utilization in routine clinical practice. The study offers the first-hand effectiveness and safety data of apatinib in the real world, which are informative for physicians and patients. This study includes patients in first- and second-line treatment, which can provide evidence for the application of apatinib in the first- and second-line treatment for gastric cancer. Finally, safety analysis of this study helps gain better knowledge of and familiarization with possible side effects and how to deal with them.

Conclusion

This real-world data demonstrated that patients given apatinib at the dose level of 425–500 mg once daily showed similar effectiveness to phase II/III clinical trial with a favorable safety profile. The incidence of AEs is consistent with that of phase II/III clinical data, and no new AEs were reported in the present study.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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