Original Article

Safety and effectiveness of apatinib in elderly patients with metastatic gastric cancer: a sub-analysis from the large-scale, prospective observational study of apatinib for gastric cancer treatment in a real-world clinical setting (AHEAD-G202)

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Background: Apatinib was shown to improve the survival of Chinese patients with refractory metastatic gastric cancer (mGC). As an orally administered drug, it has been widely used in elderly patients because the dosing schedule can be adjusted flexibly. However, data on the efficacy and safety of apatinib in elderly patients is scarce. The aim of this study was to evaluate the toxicity and effectiveness of apatinib for elderly patients with mGC in a real-world setting.

Methods: Data from the sub-population of patients who were ≥65 years enrolled in the AHEAD-G202 trial were analyzed. Patients with mGC were prospectively registered and initially received ≤850 mg oral apatinib daily combined or not combined with chemotherapy, at the investigator's discretion. The primary endpoint was safety. The secondary endpoints were overall survival (OS) and progression-free survival (PFS).

Results: A total of 117 patients were included. There were 51 (43.59%) patients in the low-dose (250 mg) group, 60 (51.28%) patients in the mid-dose (425 to 500 mg) group, and 6 (5.13%) patients in the high-dose (850 mg) group according to the initial daily doses. Hypertension (6.84%) was the only grade 3–4 adverse event (AE) with a prevalence of more than 5% and across the low-dose (11.76%), mid-dose (3.33%) and high-dose group (0%). The median OS and PFS were 7.13 months (95% CI: 5.04 to 9.22 months) and 4.27 months (95% CI: 3.24 to 5.29 months), respectively. The OS and PFS were similar among the 65–74 and ≥75 years groups (χ^2=1.406, P=0.306; χ^2=0.378, P=0.066, respectively). The OS and PFS were also comparable among the 3 dose groups.

Conclusions: Elderly patients with mGC can tolerate and benefit from apatinib therapy. A lower initial daily dosing strategy may be a suitable choice for elderly patients in clinical practice.

Keywords: Apatinib; elderly; metastatic gastric cancer (mGC); real world

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Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide. It is the fourth leading cause of cancer-related death, with close to 40% of new worldwide GC cases occurring in China annually (1,2). GC is typically a disease of the elderly. Most patients are diagnosed at a median age of ≥65 years. However, most guidance related to the management of GC is based on trials undertaken in the fit, younger patients at present because the subgroup of elderly patients is mostly underrepresented in clinical trials due to the poor organ functions and other underlying diseases. Hence, this subgroup, and data supporting treatment for elderly patients with metastatic gastric cancer (mGC) is scarce.

For patients with mGC, a comprehensive treatment strategy based on chemotherapy is adopted in clinical practice. The chemotherapeutic regimen generally involves a fluoropyrimidine, a platinum agent, and a taxane, however, the overall efficacy is limited. The results of the ToGA trial only showed a median survival of 13.8 months in HER2-positive mGC patients treated with chemotherapy plus trastuzumab (an anti-HER2 antibody) (3). According to the recently presented CheckMate 649 study (4), the combination of nivolumab and oxaliplatin-based doublet chemotherapy has become a new standard for mGC with combined positive score (CPS) ≥5 in the first-line setting (5). However, the median overall survival (OS) was only 14.4 months. Multiplatform molecular analysis of GC may help identify biomarkers to guide the selection of therapeutic agents (6). Thus, any potential novel therapies that will increase patient survival times are urgently needed.

Angiogenesis is important during tumor growth, development, and metastasis (7). Anti-angiogenic therapies, including anti-vascular endothelial growth factor (VEGF) antibodies and multi-receptor tyrosine kinase inhibitors (TKIs), have been shown to be attractive therapeutic strategies for GC (8-12). Among them, apatinib, which is an oral small molecule TKI that highly selectively binds to and strongly inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), has been approved by the National Medical Products Administration of China for the treatment of patients with mGC who fail second-line chemotherapy because of the pivotal phase III study (8). In a global multicenter phase III study (ANGEL study), which enrolled patients from Europe, America, Korea, and Japan, apatinib was administered as the third- or further-line treatment for GC and the primary study endpoint (OS) was not reached, while the secondary study endpoint [median progression-free survival (mPFS)] was 2.83 months (hazard ratio, 0.57; 95% CI: 0.46 to 0.79; P<0.0001) (13). In the ANGEL study, patients were from other regions except China. The baseline characteristics of the patients enrolled in these 2 phase III studies were different, which could also affect the OS. Therefore, the results of the ANGEL study could not dismiss the efficacy of apatinib in Chinese patients. In the pivotal phase III trial (8), apatinib with a dosage of 850 mg/day was shown to improve the OS of patients with mGC who experienced disease progression after 2 or more lines of systemic therapy compared with placebo (6.5; 95% CI: 4.8 to 7.6 *vs.* 4.7; 95% CI: 3.6 to 5.4 months, P=0.0149;

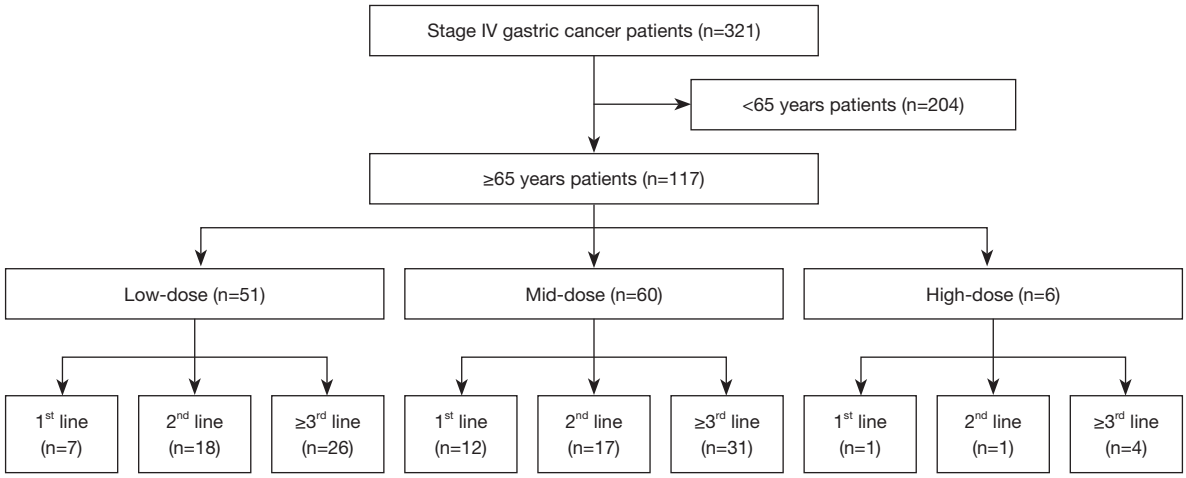

Figure 1 The study flowchart.

hazard ratio, 0.709; 95% CI: 0.537 to 0.937; P=0.0156). Although the subgroup analysis reported that patients ≥65 years achieved a survival benefit (hazard ratio, 0.55; 95% CI: 0.26 to 1.19), the number of patients aged between 65 and 70 years was limited (37 patients), and elderly patients (age >70 years) were excluded from the trial (8).

Additionally, toxicity in the pivotal phase III study was notably more severe with apatinib than with placebo, with a non-negligible rate of grade 3 to 4 hand-foot syndrome (8.5%), approximately 1 of 2 patients experiencing proteinuria (generally grade 1 to 2), and 5.7% of patients experiencing grade 3 to 4 neutropenia. Owing to the adverse events (AEs), dose reduction was observed in 21% of patients who finished apatinib treatment. Of the 40 patients that discontinued apatinib treatment, 22 patients (55.0%) stopped treatment as a result of toxicity. Moreover, it should be noted that there were just 21 elderly patients (>65 years) included in the apatinib group with a median age in the 2 arms (age 58 years) lower than that observed in routine practice, and AE dates specific to the elderly population were not reported (8). Therefore, evidence supporting the use of apatinib in elderly patients is currently weak. However, older adults with mGC who fail the guideline-recommended chemotherapy regimens or cannot undergo high-intensity chemotherapy and still have a good performance status are not rare and might benefit from an active antitumor treatment. In particular, the dosing schedule of apatinib can be adjusted more flexibly than other intravenous drugs. In this regard, apatinib could be a promising option in treating GC.

However, in clinic practice, patient populations are more heterogeneous compared with those treated in clinical trials. Therefore, the data from 21 elderly patients included in the pivotal phase III study may not fully represent the safety and efficacy profiles of apatinib in real-world settings. Consequently, large-scale, real-world studies may detect unexpected, clinically significant adverse drug reactions.

Therefore, we previously carried out a prospective, observational study [AHEAD-G202 (ClinicalTrial ID: NCT02668380)] to provide more clinical evidence of the treatment of apatinib in patients with advanced GC in the real world. The current study aimed to characterize the safety and effectiveness of apatinib in the subgroup of patients aged ≥65 years with mGC in the AHEAD-G202 trial. Those data will be applied to elderly mGC patients treated with apatinib in clinical practice. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-727/rc).

Methods

Study design and patients

Data from mGC patients who were 65 years or older enrolled in the AHEAD-G202 trial were analyzed (*Figure 1*). The AHEAD-G202 trial was a prospective, observational study (29 clinical sites in China). The study design and results from the overall population have been previously reported (14). Briefly, patients ≥65 years with histologically documented mGC and for whom apatinib administration was planned, were enrolled in this present

study. 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, New York Heart Association (NYHA) functional class III–IV cardiac insufficiency, or severe liver and kidney dysfunction were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Peking Union Medical College Hospital Ethics Committee (No. HS-806) and all participating centers were informed and agreed the study. All patients signed informed consent before enrollment.

Procedures

The recommended dose of apatinib (Jiangsu Hengrui Medicine, China) was 850 mg once daily for 4 weeks per cycle in the pivotal phase III trial (8). The dose of apatinib could be reduced, interrupted, or permanently discontinued to manage treatment-related AEs according to the product label and at the investigator's discretion. The dose could also be re-escalated to a maximum of 850 mg once toxic effects resolved. Patients received apatinib until disease progression, unacceptable toxicities, withdrawal of consent, or the investigator's decision to discontinue.

Outcomes

The main study objectives were to assess the safety, including the occurrence of unknown and clinically significant AEs, and the effectiveness of apatinib in real-world clinical practice. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. 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 and the Response Evaluation Criteria in Solid Tumors guidelines version 1.1 (15). The details have been described previously.

Statistical analysis

The primary endpoint of this study was safety. The secondary endpoints included OS, PFS, objective response rate (ORR) and disease control rate (DCR). The ORR was the proportion of patients with confirmed complete response (CR) and partial response (PR), and the DCR was the proportion of patients with confirmed CR, PR, and stable disease (SD). All time-to event variables were calculated from the date of apatinib initiation. OS was calculated to the date of death; PFS was defined as the time to first progression or death, whichever came first, PFS for patients without disease progression or death before or at the last visit was censored at the date of the last clinical or radiological assessment.

Treatment responses and AEs were both aggregated in the form of frequency counts and percentages. Kaplan-Meier curves were generated by GraphPad Prism 7.0 and compared by log rank testing to examine PFS and OS and their corresponding 95% confidence intervals (CIs). Cox proportional hazards modelling was used to evaluate predictors of OS and PFS. The covariates included in the multivariate analyzes were the baseline characteristics. Considering the correlation and hierarchy with respect to clinical importance among baseline variables, the variables were manually selected beforehand and finally picked using a stepwise method. Similar analyzes were performed for PFS. Toxicities were recorded as physicians stated or in the laboratory values obtained when patients received apatinib.

All analyses were conducted using SPSS version 21 (IBM, Armonk, New York, USA). 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

Baseline characteristics

Overall, of the 321 mGC patients in the AHEAD-G202 trial, 117 patients ≥65 years at 24 sites were enrolled in this study. The median age was 70 years (range, 65–88 years), and 73.5% of the patients were male. A total of 68 patients (58.12%) did not undergo gastrectomy. The most common sites of metastasis were lymph nodes (52.14%), liver (39.32%), lung (11.97%), and peritoneum (6.84%). A total of 97 patients had received prior chemotherapy. Among the patients who received combined regimens, 88% of them received oxaliplatin combined with fluorouracil, while 75% received fluorouracil among the patients who received a single regimen. A total of 21 patients had received previous radiotherapy. At baseline, 69.52% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and 28.21% had an ECOG performance status of 2 or 3. The baseline characteristics of the 117 patients are shown in *Table 1*.

Table 1 Patient demographic and baseline characteristics

Variables	≥65 years, n (%)		
	65–74 years (n=80)	≥75 years (n=37)	All (n=117)
Gender			
Female	21 (26.25)	10 (27.03)	31 (26.50)
Male	59 (73.75)	27 (72.97)	86 (73.50)
ECOG performance status			
0	4 (5.00)	4 (10.81)	8 (8.84)
1	53 (66.25)	18 (48.65)	71 (60.68)
≥2	19 (23.75)	14 (37.84)	33 (28.21)
Unknown	4 (5.00)	1 (2.70)	5(4.27)
No. of metastasis sites			
1–2	58 (72.50)	32 (86.49)	90 (76.92)
>2	22 (27.50)	5 (13.51)	27 (23.08)
Lauren classification			
Intestinal	14 (17.50)	7 (18.92)	21 (17.95)
Diffuse	10 (12.50)	9 (24.32)	19 (16.24)
Mixed	12 (15.00)	3 (8.11)	15 (12.82)
Unknown	44 (55.00)	18 (48.65)	62 (52.99)
Prior radiotherapy			
Yes	15 (18.75)	6 (16.22)	21 (17.95)
No	65 (81.25)	31 (83.78)	96 (82.05)
Prior gastrectomy			
Yes	25 (31.25)	11 (29.73)	36 (30.77)
No	46 (57.50)	22 (59.46)	68 (58.12)
Unknown	9 (11.25)	4 (10.81)	13 (11.11)
Line of apatinib therapy			
1	12 (15.00)	8 (21.62)	20 (17.09)
2	23 (28.75)	13 (35.14)	36 (30.77)
≥3	45 (56.25)	16 (43.24)	61 (52.14)
Initial dosage			
250 mg	35 (43.75)	16 (43.24)	51 (43.59)
425–500 mg	41 (51.25)	19 (51.35)	60 (51.28)
850 mg	4 (5.00)	2 (5.41)	6 (5.13)
Combination chemotherapy			
Mono-drug chemotherapy	19 (23.75)	8 (21.62)	27 (23.08)
Multi-drug chemotherapy	8 (10.00)	0 (0.00)	8 (6.84)
No chemotherapy	53 (66.25)	29 (78.38)	82 (70.09)

ECOG, Eastern Cooperative Oncology Group.

Apatinib treatment

Of the 117 patients, 20 (17.09%) patients were treated with apatinib as the first-line therapy, 36 (30.77%) as the second-line therapy, and 61 (52.14%) as the third- or higher-line therapy. A total of 35 patients received apatinib in combination with chemotherapy, 27 of whom received apatinib plus monotherapy (24 with fluorouracil) and the rest received apatinib plus doublet treatment (7 of whom received platinum combined with fluorouracil or paclitaxel combined with fluorouracil). The initial median dose of apatinib was 425±157 mg/day, and the average dose was 403 mg/day. Overall, 51 patients (43.59%) were in the low-dose group (250 mg/day), 60 patients (51.28%) were in the mid-dose group (425–500 mg/day), and 6 patients (5.13%) were in the high-dose group (850 mg/day).

Safety

Overall, 84.62% of patients reported apatinib treatment-emergent AEs. Hematologic AEs occurred in 10.26% of patients, while non-hematologic AEs occurred in 82.91%. In our patients, the most common AEs (≥10%) included hypertension (41.88%), fatigue (38.46%), hand-foot syndrome (21.37%), proteinuria (12.82%), and nausea (11.11%). Grade 3–4 AEs were infrequent, and the most common AEs were hypertension (6.84%), fatigue (3.42%), and dysphagia (2.56%) (*Table 2*).

Dose adjustments occurred in 13 (11.11%) patients, including 1 patient adjusted from 850 to 425 mg/day, 1 patient adjusted from 850 to 675 mg/day, and 11 patients with adjustments from 500 to 250 mg/day. The median dose was 250±150 mg/day, and the average dose was 375 mg/day. The reasons for the dose adjustments were hypertension, hand-foot syndrome, nausea, diarrhea, and thrombosis. Dose interruption occurred in 39 patients. Among them, 12 patients continued apatinib therapy after symptom control, while the other 27 patients discontinued due to AEs. The main causes of withdrawal were hypertension, hemorrhage, intestinal obstruction, and cerebral infarction. Thirteen cases withdrew due to gastrointestinal symptoms such as intestinal obstruction, abdominal pain, difficulty in swallowing, and vomiting, which were possibly caused by AEs of apatinib or by disease progression. Five patients withdrew due to gastrointestinal hemorrhage and 3 patients withdrew due to cerebral infarction.

There was no significant difference in the incidence of AEs and severe AEs among the low-dose, mid-dose, and high-dose groups (*Table 2*).

Apatinib was administered for more than 300 days (313–645 days) in 13 (11.11%) patients, and the AEs were well tolerated, including 250 mg/day in 3 patients, 425–500 mg/day in 9 patients, and 850 mg/day in 1 patient.

Effectiveness

At the time of data cutoff, the median PFS was 4.27 months (95% CI: 3.24 to 5.29 months) in the whole group (*Figure 2A*). The median PFS rates in the patients aged 65–74 years and patients aged ≥75 years were 3.53 months (95% CI: 2.38 to 4.69 months) and 4.80 months (95% CI: 3.54 to 6.06 months), respectively, and there was no significant difference in PFS between patients aged 65–74 years and those aged ≥75 years (χ^2=3.378, P=0.066) (*Figure 2B*). The median PFS rates were 4.87 months (95% CI: 3.64 to 6.10 months), 3.53 months (95% CI: 1.77 to 5.30 months), and 3.03 months (95% CI: 0.00 to 6.87 months) in the low-dose, mid-dose, and high-dose groups, respectively (*Figure 2C*). The median OS (mOS) was 7.13 months (95% CI: 5.04 to 9.22 months) in the whole patients (*Figure 3A*). The mOS rates in the patients aged 65–74 years and patients aged ≥75 years were 6.33 months (95% CI: 4.85 to 7.82 months) and 8.40 months (95% CI: 5.42 to 11.38 months), respectively, and there was also no significant difference in OS between patients aged 65–74 years and those aged ≥75 years (χ^2=1.406, P=0.306) (*Figure 3B*).The mOS rates were 7.93 months (95% CI: 4.98 to 10.88 months), 6.33 months (95% CI: 2.77 to 9.90 months), and 6.47 months (95% CI: 0.00 to 14.82 months) in the low-dose, mid-dose, and high-dose groups, respectively (*Figure 3C*). The PFS and OS in the low-dose group were longer than those in the mid-dose and high-dose groups, but there were no significant differences in PFS and OS among the 3 dose groups (χ^2=1.919, P=0.383; χ^2=0.426, P=0.808, respectively).

Tumor response to apatinib was evaluable for 84 patients among the ≥65 years old patients. CR was observed in 1 patient, PR was observed in 6 patients, and stabilization was achieved in 60 patients. Thus, the ORR was 8.33% and the DCR was 79.76%. The elderly patients were divided into 65–74 and ≥75 years groups, and the ORRs were 5.45% *vs.* 13.79%, respectively. The DCRs in the 65–74 and ≥75 years groups were 74.55% *vs.* 89.66%, respectively. There was no significant difference between the 2 groups (χ^2=4.023,

Table 2 Treatment-emergent adverse events in the study population

AE	Any grade, n (%)				Grade 3–4, n (%)			
	All (n=117)	250 mg (n=51)	425–500 mg (n=60)	850 mg (n=6)	All (n=117)	250 mg (n=51)	425–500 mg (n=60)	850 mg (n=6)
Hypertension	49 (41.88)	22 (43.13)	24 (40.00)	3 (50.00)	8 (6.84)	6 (11.76)	2 (3.33)	0
Fatigue	45 (38.46)	17 (33.33)	25 (41.67)	3 (50.00)	4 (3.42)	1 (1.96)	2 (3.33)	1 (16.67)
Hand-foot syndrome	25 (21.37)	5 (9.80)	19 (31.67)	1 (16.67)	2 (1.71)	0	2 (3.33)	0
Proteinuria	15 (12.82)	5 (9.80)	8 (13.33)	2 (33.33)	1 (0.85)	1 (1.96)	0	0
Nausea	13 (11.11)	4 (7.84)	8 (13.33)	1 (16.67)	0	0	0	0
Bleeding	11 (9.40)	2 (3.92)	8 (13.33)	1 (16.67)	2 (1.71)	2 (3.92)	0	0
Anorexia	10 (8.55)	7 (13.73)	3 (5.00)	0	2 (1.71)	1 (1.96)	1 (1.67)	0
Leukopenia	7 (5.98)	6 (11.76)	1 (1.67)	0	0	0	0	0
Diarrhea	6 (5.13)	2 (3.92)	4 (6.67)	0	1 (0.85)	0	1 (1.67)	0
Stomach ache	6 (5.13)	3 (5.88)	3 (5.00)	0	1 (0.85)	0	1 (1.67)	0
Vomiting	6 (5.13)	5 (9.80)	1 (1.67)	0	2 (1.71)	1 (1.96)	1 (1.67)	0
Thrombocytopenia	6 (5.13)	3 (5.88)	3 (5.00)	0	2 (1.71)	0	2 (3.33)	0
Dysphagia	6 (5.13)	1 (1.96)	5 (8.33)	0	3 (2.56)	1 (1.96)	2 (3.33)	0
Arrhythmia	5 (4.27)	4 (7.84)	1 (1.67)	0	1 (0.85)	0	1 (1.67)	0
Oral mucositis	4 (3.42)	3 (5.88)	1 (1.67)	0	1 (0.85)	1 (1.96)	0	0
Headache	4 (3.42)	2 (3.92)	2 (3.33)	0	0	0	0	0
Dizziness	4 (3.42)	2 (3.92)	2 (3.33)	0	0	0	0	0
Neutropenia	3 (2.56)	1 (1.96)	2 (3.33)	0	0	0	0	0
Anemia	3 (2.56)	1 (1.96)	2 (3.33)	0	1 (0.85)	0	1 (1.67)	0
Transaminase elevations	2 (1.71)	0	2 (3.33)	0	0	0	0	0
Hyperbilirubinemia	2 (1.71)	0	2 (3.33)	0	0	0	0	0
Intestinal obstruction	2 (1.71)	1 (1.96)	1 (1.67)	0	1 (0.85)	1 (1.96)	0	0
Hoarseness	1 (0.85)	0	1 (1.67)	0	0	0	0	0
Urinary tract infection	1 (0.85)	1 (1.96)	0	0	0	0	0	0
All	99 (84.62)	43 (84.31)	52 (86.67)	4 (66.67)	32 (27.35)	15 (29.41)	16 (26.67)	1 (16.67)

AE, adverse event.

P=0.674).

The ORRs were 5.71%, 10.81%, and 16.67% in the low-dose, mid-dose, and high-dose groups, respectively. The DCRs were 71.29% 81.08%, and 83.33% in the low-dose, mid-dose, and high-dose groups, respectively. There was no significant difference among the 3 dose groups (χ^2=1.870, P=0.760).

Discussion

The results of this multicenter, non-interventional, real-world study on 117 patients with mGC suggest that apatinib is feasible in real-life routine clinical practice for elderly patients with acceptable performance status and adequate organ function. To our knowledge, we present here the biggest large-scale, prospective, observational

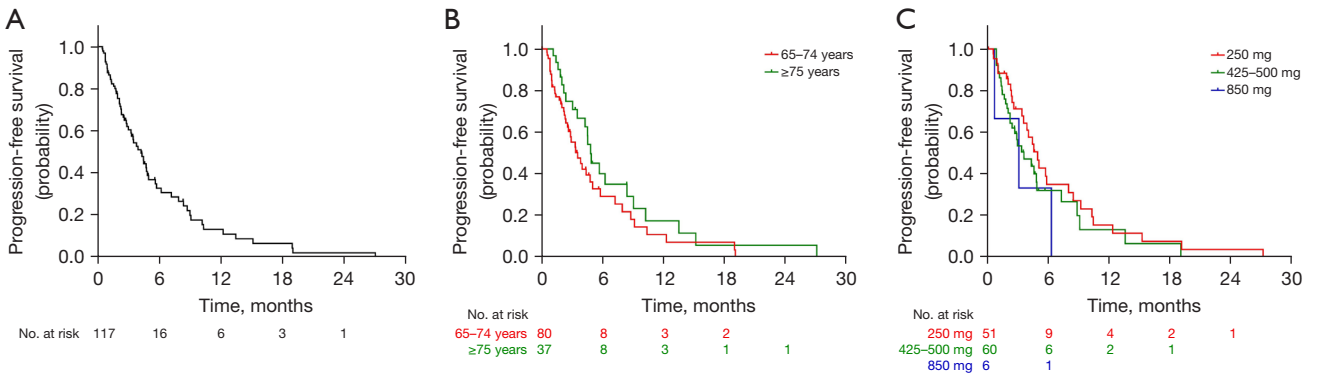

Figure 2 Kaplan-Meier estimates of PFS. (A) PFS for the ≥65 years population. (B) PFS stratified by age. (C) PFS stratified by dosing levels of apatinib. PFS, progression-free survival.

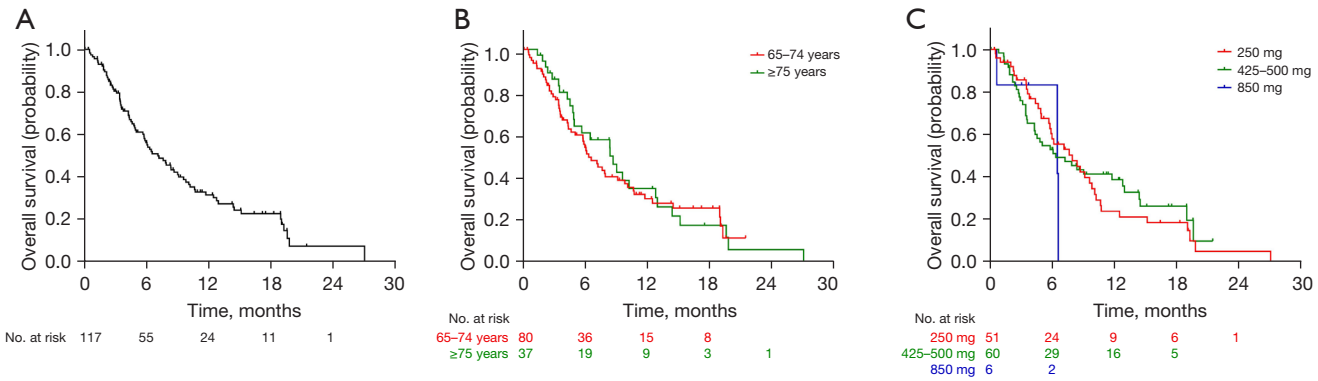

Figure 3 Kaplan-Meier estimates of OS. (A) OS for the ≥65 years population. (B) OS stratified by age. (C) OS stratified by dosing levels of apatinib. OS, overall survival.

study investigating the safety and effectiveness of apatinib in elderly patients with mGC in routine clinical practice.

The safety profile observed in the real-life setting was consistent with that reported in randomized phase II and phase III trials (8,16), with lower rates of most AEs, possibly because of the lower initial apatinib dosage and more effective management of AEs. Although many patients initiated apatinib at doses lower than the approved label dose, the mOS and PFS were in the range of what was reported in prior trials (8,16).

The incidence and severity of AEs in our study were generally consistent with the known safety profile of apatinib. The most common AEs were hypertension, fatigue, hand-foot syndrome, and nausea, which were also among the most frequently reported apatinib-related AEs in previous studies in GC, lung cancer, breast cancer, and ovarian cancer (8,16-24). No new safety signals were observed. No treatment-related death occurred. Except for a similar incidence of grade 3–4 hypertension, the rates of nearly all grade 3 AEs were lower than both phase II and phase III trials in GC (8,16). Additionally, some studies had shown that the early presence of anti-angiogenesis-related AEs including hypertension, proteinuria, or hand-foot syndrome during the first cycle of apatinib treatment was a viable biomarker of antitumor efficacy in patients with metastatic GC (21,25). The plan for further investigation of biomarkers with the biospecimens collected from our study is in progress.

Apatinib-related AEs led to dose modifications in 44.4% of patients and treatment discontinuation in 23.1% of patients, which was no more than the rates reported in the pivotal phase III trial (8). The lower rates of AEs and dose modifications could be due to almost 95% of patients starting treatment at doses lower than 850 mg, as the toxicity of apatinib is dose dependent (26), as well as better AE management. Consistent with this, in order to

avoid potential severe AEs, the dosage of apatinib in most of the ongoing clinical trials is 250 or 500 mg daily (http://clinicaltrials.gov/).

Despite the different dosing schedules reported in our study, apatinib effectiveness was consistent with a previous phase III trial (8). Higher than the latter, in our group of elderly patients, apatinib therapy led to a median PFS of 4.27 months (95% CI: 3.24 to 5.29 months), an mOS of 7.13 months (95% CI: 5.04 to 9.22 months), an ORR of 8.33%, and a DCR of 79.76% *vs.* 2.6 months (95% CI: 2.0 to 2.9 months), 6.5 months (95% CI: 4.8 to 7.6 months), 2.84% and 42.05% compared with the apatinib group in the pivotal phase III study. Thus, apatinib therapy in the elderly patients in our study seemed to be nearly as effective compared with the pivotal phase III trial (8). However, there are still some differences between our study and the phase III trials. On the one hand, patients' performance statuses in this study were much worse than those in clinical trials. Nearly 30% of patients had a baseline ECOG performance status of 2–3, while all patients in previous clinical trials scored 0 or 1. In our study, 27.50% of the patients had more than 2 metastatic lesions, while the corresponding rate in the phase III trial was 21%. Only 31.25% of patients in the present study had received gastrectomy, while the rate in the phase III trial was 69.3%. On the other hand, 47.86% of the patients included in the present study received apatinib as the first-line or second-line therapy. Meanwhile, combination with other therapy and dose up-regulation strategies were also allowed according to their actual performance status in our study. All of them weren't covered in the pivotal phase III trial, which might increase the response and survival of apatinib therapy. Several other studies have also demonstrated that the combination of apatinib with chemotherapy is more effective for GC treatment than apatinib alone (20,21,27-31). We believe it was these modifications in the treatment method that led us to obtain similar efficacy results with previous trials, even if patients performed worse and had a higher tumor burden. Moreover, these modifications, especially dose up-regulation and combination chemotherapy, did not increase the incidence of AEs, which means a lower initial apatinib dosing strategy represents an alternative approach for elderly patients. Meanwhile, in a phase II study which enrolled 48 patients aged ≥60 years with advanced GC who experienced progression on one or more lines of chemotherapy and received low-dose apatinib (500 or 250 mg per day), the mPFS was 3.00 months (95% CI: 2.17 to 3.84 months), the mOS was 8.10 months (95% CI: 4.35 to 11.85 months), the ORR was 16.7%, and the DCR was 72.9%. These data suggest that apatinib is effective and relatively tolerable for elderly patients with advanced GC. Several other studies have also shown that low-dose apatinib is an effective regimen for advanced GC (23,32-34). The PFS and OS in the low-dose group (250 mg/day) were better than those in the mid-dose (425–500 mg/day) group, but there was no statistical difference. There were only 6 cases in the high-dose group, and dose adjustments occurred in 2 cases due to AEs. Therefore, the initial dose of 250 mg/day might be an alternative strategy considering safety and effectiveness in clinical practice. Our also study showed that the mOS and PFS were similar between the 65–74 and ≥75 years groups. Apatinib was administered for more than 300 days in 13 (11.11%) elderly patients. These findings mean that elderly patients can benefit from apatinib therapy. However, while these results are consistent with the clinical impression, they should be confirmed in a randomized trial as the subgroup analysis may be biased.

Despite the encouraging results of our analysis, like any other observational study, there are several limitations including potential missing data, possible information bias, lack of a comparator arm, and an absence of independent monitoring and radiological centralized review that prevent us from drawing general conclusions. Clinical predictive markers were also not identified in our study.

In conclusion, the outcomes of the present study revealed that elderly patients can tolerate and benefit from apatinib therapy. Lower dose apatinib therapy might be an alternative approach with comparable activity and a lower incidence of AEs, and can be implemented in clinical practice for elderly mGC patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-727/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Peking Union Medical College Hospital Ethics Committee (No. HS-806) and all participating centers were informed and agreed the study. All patients signed informed consent before enrollment.

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