Original Article

Apatinib in the treatment of gastric cancer in Henan Province: a multicenter prospective real-world observational study (Ahead-HAP01)

Yijie Ma[1#], Weijie Zhao[2#], Peichun Sun[3], Wenying Deng[1], Junli Deng[1], Hong Zong[4], Junsheng Wang[5], Yanzhen Guo[6], Huaimin Liu[7], Shundong Cang[8], Ke Shang[9], Xiaobing Chen[1], Jin Wang[10], Dezhi He[10], Gang Wu[11], Zhen Zhang[12], Liguo Zhang[13], Feng Xu[14], Chuntao Tian[15], Chaofeng Qiao[16], Gongbin Chen[17], Guifang Zhang[13], Tianjiang Ma[18], Liwei Gao[19], Guozheng Zhang[20], Jing Liu[20], Guy D. Eslick[21], Khaldoun Almhanna[22], Leonardo S. Lino-Silva[23], Giuseppe Aprile[24], Ning Li[1], Suxia Luo[1]

[1]Department of Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [2]Department of General Surgery, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [3]Department of Gastrointestinal Surgery, Henan Provincial People's Hospital, Zhengzhou, China; [4]Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [5]Department of Medical Oncology, Anyang Cancer Hospital, Anyang, China; [6]Department of Medical Oncology, The First Affiliated Hospital of Henan University of science and technology, Luoyang, China; [7]Integrated TCM & Western Medicine Department, The Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou, China; [8]Department of Medical Oncology, Henan Provincial People's Hospital, Zhengzhou, China; [9]Department of Medical Oncology, Xinyang Central Hospital, Xinyang, China; [10]Department of Gastroenterology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [11]Department of general surgury, Henan Provincial People's Hospital, Zhengzhou, China; [12]Department of Medical Oncology, Nanyang First People's Hospital, Nanyang, China; [13]Department of Medical Oncology, Xinxiang Central Hospital, Xinxiang, China; [14]Department of Internal Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [15]Department of Medical Oncology, Sanmenxia Central Hospital, Sanmenxia, China; [16]Department of general surgury, Jiaozuo Second People's Hospital, Jiaozuo, China; [17]Department of Medical Oncology, Shangqiu First People's Hospital, Shangqiu, China; [18]Department of Medical Oncology, Luohe Central Hospital, Luohe, China; [19]Department of Medical Oncology, Pingdingshan Coal General Hospital, Pinigdingshan, China; [20]Department of Medical Oncology, Hebi People's Hospital, Hebi, China; [21]The Centre for Research Excellence in Digestive Health, Hunter Medical Research Institute, The University of Newcastle, Newcastle, New South Wales, Australia; [22]Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University, Lifespan Cancer Institute, Rhode Island Hospital, Providence, RI, USA; [23]Department of Surgical Pathology, Oncology Center Tula's General Hospital, Tula de Allende, Hidalgo, Mexico; [24]Department of Oncology, San Bortolo General Hospital, AULSS8 Berica, Vicenza, Italy

Contributions: (I) Conception and design: N Li; (II) Administrative support: S Luo; (III) Provision of study materials or patients: P Sun, H Zong, Junsheng Wang, Y Guo, H Liu, S Cang, K Shang, X Chen, Jin Wang, D He, G Wu, Z Zhang, L Zhang, F Xu, C Tian, C Qiao, G Chen, G Zhang, Ma, L Gao, G Zhang, J Liu; (IV) Collection and assembly of data: Y Ma, W Zhao; (V) Data analysis and interpretation: W Deng, J Deng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Suxia Luo; Ning Li. The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, No. 127 Dongming Rd., Zhengzhou 450008, China. Email: zlyyluosuxia0361@zzu.edu.cn; lining97@126.com.

Background: Apatinib is approved in China for the treatment of advanced gastric adenocarcinoma that had progressed or relapsed after standard systemic chemotherapy treatments. However, the effectiveness of Apatinib under real-world condition has not been evaluated and the drug performance under ideal and controlled circumstances has not been validated. In fact, genetic factors, poor healthcare access, social economic status, comorbidities compliance and other factors play significant role in drug performance under "real-world" conditions. Real-world experience can help validate the safety and efficacy of apatinib.

Methods: In this observational, prospective study we evaluated the safety and efficacy of Apatinib in patient treated in China. Between March 2018 and March 2019, a total of 943 patients with gastric cancer treated with Apatinib were enrolled. Response Evaluation Criteria in Solid Tumors, version 1.1 and Common Terminology Criteria for Adverse Events, version 4.0 were used to evaluate efficacy and adverse effects.

Results: The median progression-free survival (PFS) was 5.65 months (5.22–6.05 months), and the median overall survival (OS) was 11.47 months (10.41–12.52 months). Apatinib in combination with more than two agents was superior to single agent apatinib in overall response rate (ORR) [18.18% *vs.* 9.43%, 95% confidence interval (CI): 1.03–5.90] and disease control rate (DCR) (82.82% *vs.* 77.87%, 95% CI: 1.21–2.59). Apatinib in combination with single agent chemotherapy was also superior to apatinib alone with DCR (86.29% *vs.* 77.87%, 95% CI: 1.47–2.99) irrespective of the dose (250 or 500 mg). In the patient cohort who received a starting dose of 250 mg, the DCRs of the combined treatment and monotherapy groups were 86.22% *vs.* 80.00% (95% CI: 1.18–3.09), respectively. The most common treatment-emergent adverse events were anemia, anorexia and thrombocytopenia (66.28%, 37.75%, 36.06%, respectively).

Conclusions: Efficacy of Apatinib in this observational study is promising and toxicities are manageable. Combination of Apatinib with chemotherapy agents has a higher response rate and better disease control at the expense of increased serious adverse events. Better OS can be achieved by receiving apatinib treatment earlier. As a supplement and further validation of explanatory randomized controlled trials, the real-world study reflects the real efficacy of apatinib in practical application.

Keywords: Apatinib; effectiveness; gastric cancer; real-world; safety

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Introduction

Gastric cancer is one of the most common malignant tumors of the digestive system in Asia. Unfortunately, most patients present with advanced incurable disease where the goals of treatment is palliative to control symptoms and improve survival (1). Gastric cancer incidence is unevenly geographically dispersed, with an unusually high incidence in East Asia, South America, and Eastern Europe (2). Henan is a populous province in China, and gastric cancer is the second most common malignancy with significant morbidity and mortality in the region.

Targeting angiogenesis has played a significant role in the treatment of several malignancies (3) . In gastric cancer, the role of Anti-angiogenic therapy has been limited until October 17, 2014, where the China Food and Drug Administration (CFDA) officially approved a small-molecule tyrosine kinase inhibitor (TKI) that selectively inhibits the vascular endothelial growth factor receptor-2 (VEGFR2), as a national class 1.1 new drug to treat advanced gastric cancer patients who failed second-line treatment (4,5). However, the effectiveness of Apatinib under real-world condition has not been evaluated and the drug performance under ideal and controlled circumstances has not been validated (6). In fact, genetic factors, diet, poor healthcare access, social economic status, comorbidities compliance and other factors play significant role in drug performance under "real-world" conditions.

Clinical trials usually have strict inclusion criteria, and the enrolled patients typically have, among other characteristics, better performance status than real-world patients. That is why efficacy can overestimate drug performance compared to clinical practice. Additionally, gastric cancer populations in different regions have distinct clinical characteristics. Consequently, therapeutic interventions' efficacy and adverse reactions may also vary. The efficacy and safety of apatinib in real-world scenarios remain unexplored (7,8). The population included in the phase III clinical study of apatinib is the population with more than second-line treatment. However, in the real world, due to the patient's constitution or personal will, some first-line and second-line treatment people also received apatinib treatment. In addition, apatinib was studied as a single drug for the treatment of advanced gastric cancer before it was marketed, but there are many patients in the real world who are treated with chemotherapy or immunotherapy. Therefore, clinical practice urgently needs to see the real world application, efficiency and safety data as a reference for the treatment of gastric cancer with apatinib.

We present results from a prospective study conducted in Henan province in china. A total of 943 gastric cancer patients treated with Apatinib between March 1, 2018, to March 1, 2019 were included. The aim of the study was

to better examine the efficacy and the toxicity of apatinib in an unselected population in order to optimize its future use. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5995/rc).

Methods

Patients

Patients with gastric cancer treated with apatinib from March 01, 2018, to March 01, 2019, who satisfied the following inclusion criteria were enrolled:

(I) Patients of both sexes aged ≥18 years;
(II) Patients with gastric adenocarcinoma diagnosed by pathology or histology;
(III) Patients who volunteered to join the study and signed the informed consent form;
(IV) Patients who were expected to benefit from the treatment according to the investigators.

The exclusion criteria were as follows:

(I) Patients confirmed to be allergic to apatinib mesylate tablets and/or its excipients;
(II) Pregnant or breastfeeding women;
(III) Patients with contraindications to apatinib;
(IV) Patients not deemed suitable for inclusion by their physician.

Patients who meet the criteria are observed non-interventionally after signing an informed consent form, and are followed up regularly according to the protocol design. All enrolled patients were from 14 sub-centers in Henan Province (see Appendix 1). This study was registered on https://clinicaltrials.gov/ (ID: NCT03478943). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by Ethics Committee of Henan Cancer Hospital (No. 2018012). All participating institutions were informed and agreed the study. All patients provided written informed consent before enrollment.

Trial design

In this multicenter, prospective observational study, gastric cancer patients treated with apatinib, first-, second-, third line or beyond were recruited. Apatinib monotherapy, apatinib combined with chemotherapy, and different doses of apatinib (dose range, 250–850 mg q.d.) were included in the statistical analysis. The efficacy and safety of apatinib in this patient population were reported.

Efficacy evaluation

Efficacy was evaluated according to version 1.1 of the efficacy evaluation standard for solid tumors.

Observation of adverse events

According to the National Cancer Institute (NCI) "Common Acute and Subacute Toxicity Classification Standard" adverse events (AEs) are classified into grades 1–5, as detailed in the NCI Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE 4.0). AEs not listed in the NCI toxicity classification standard were documented according to the following criteria:

(I) Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated;
(II) Grade 2 (moderate): minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living;
(III) Grade 3 (severe): hospitalization or prolongation of hospitalization; disabled; or limited to performing self-care activities of daily living;
(IV) Grade 4 (life-threatening): life-threatening consequences or urgent intervention indicated;
(V) Grade 5: (death): death related to an adverse event.

Follow-up

The follow-up period began after the last use of the study drug. The adverse reactions that have not been recovered will continue to be treated and followed up until they are recovered to grade 1 or completely recovered. The patients were followed up for a long time every 8 weeks (including telephone follow-up), and whether they used other anti-cancer treatments before the follow-up was collected. If other treatments are used, record the treatment plan, cycle number and outcome. Follow up until the patient dies and record the cause of death and specific time to obtain the overall survival (OS).

Statistical methods

The population included all available patients from the participating sites who received at least one dose of Apatinib. There was no formal sample size calculation. Quantitative data are presented as the number of cases, arithmetic mean, standard deviation, median, and range according to their

Table 1 Baseline characteristics of the included patients*

Items	Patients (N=943)
Age (years) (q1–q3)	61 [53–67]
Age, n (%)	
<65 years	591 (62.67)
≥65 years	352 (37.33)
Sex, n (%)	
Male	691 (73.28)
Female	252 (26.72)
Stage, n (%)	
II	48 (5.09)
III	415 (44.01)
IV	480 (50.90)
Line, n (%)	
First-line	227 (24.07)
Second-line	389 (41.25)
Third-line	280 (29.69)
> Third-line	47 (4.98)
Surgical history, n (%)	
Yes	476 (50.48)
No	467 (49.52)
Alpha-fetoprotein (AFP), n (%)	
<400 ng/mL	365 (38.71)
≥400 ng/mL	15 (1.59)
Unknown	563 (59.70)
Extragastric metastasis, n (%)	
Yes	431 (45.71)
No	512 (54.29)
Metastases involving organs, n (%)	
>2	60 (6.36)
≤2	371 (39.34)
Unknown	512 (54.29)
Hypertension, n (%)	
Yes	89 (9.44)
No	854 (90.56)
Hepatitis B, n (%)	
Yes	14 (1.48)
No	929 (98.52)

*, data deadline: 2020.4.1.

distribution. Qualitative data are presented as frequency, ratio, or percentage. Baseline data related to the efficacy evaluation were defined as the data obtained during the case screening period. The Cochran-Mantel-Haenszel (CMH) χ^2 test, Fisher's exact test, or Wilcoxon's rank-sum test of graded data were used to compare categorical variables among the groups. The *t*-test or Wilcoxon's rank-sum test was used for continuous variables. The χ^2 test was used to evaluate whether the baseline characteristics of the missing patients were similar to those of the statistical patients. The Kaplan-Meier method was used to estimate the progression-free survival (PFS) and OS curves and estimate the median PFS and median OS as well as their 95% confidence intervals. The objective response rates (ORRs) and disease control rates (DCRs) with their 95% confidence intervals were also calculated. All analyses were descriptive, performed in the overall population and in subgroups according to therapy setting. When $P<0.05$, it represents a statistically significant difference.

Results

Between March 2018 and March 2019, a total of 943 patients with gastric cancer treated with Apatinib were enrolled. The baseline characteristics are summarized in *Table 1*. There were 591 patients younger than 65 years of age (62.67%) with an age range of 19–93 years. There were 227 (24.07%) patients treated with apatinib in the first line, 389 (41.25%) in second-line, 280 (29.69%) in third-line, and 47 (4.98%) beyond third line. Of patients with measurable disease at baseline, 14 patients (1.48%) achieved complete response (CR), 75 (7.95%) achieved partial response (PR), 610 (64.69%) had stable disease (SD) as best response, and 149 (15.80%) had progressive disease (PD).A total of 95 patients (10.07%) could not be evaluated (imaging assessment was not available). The median PFS was 5.65 months (95% CI: 5.22–6.05 months), and the median OS was 11.47 months (95% CI: 10.41–12.52 months) (*Figure 1A,1B*).

Overall, the most common treatment-emergent adverse events (incidence ≥20%) were anemia; anorexia; thrombocytopenia, leukopenia, neurtopenia malaise and nausea. Aminotransferase increase, abdominal pain, abdominal distension, vomiting, and constipation were reported in 10–20% of patients. Proteinuria, positive fecal occult blood, diarrhea, hypertension, and palmar-plantar erythrodysesthesia syndrome were observed in less than 10% of patients. Adverse events are reported in *Table 2*.

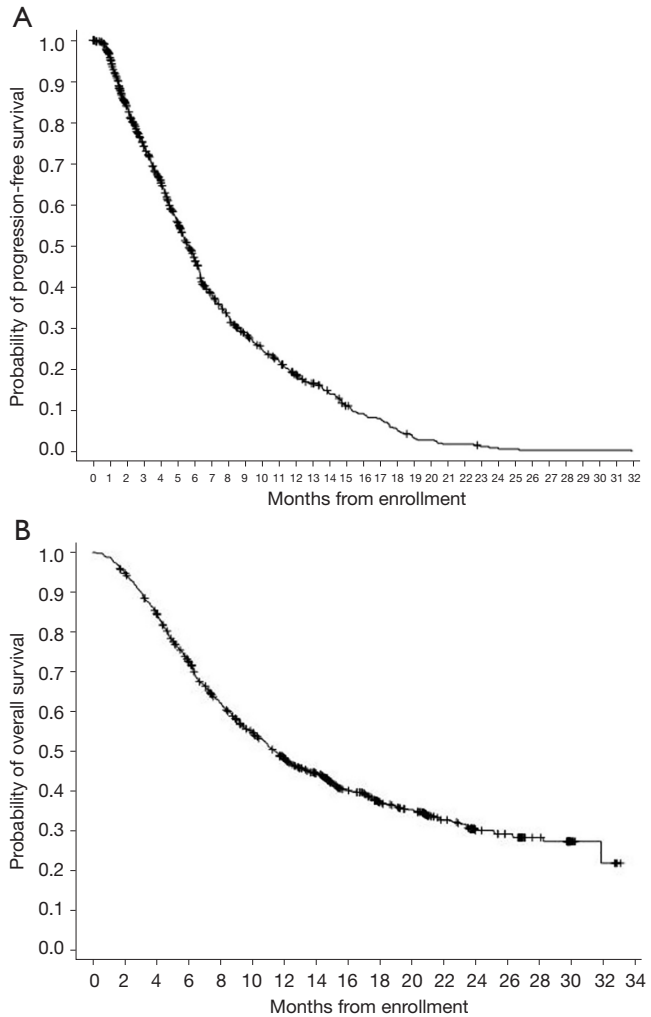

Figure 1 Progression-free survival (A) and overall survival (B) curves of the subjects.

The probability of adverse events in the different starting dose subgroups (250, 375, 425, 500, and 750 mg) was 93.71%, 85.71%, 100.00%, 86.49%, and 91.30%, respectively. Among these, the incidence of ≥ grade 3 adverse events was 23.37%, 14.29%, 50.00%, 23.65%, and 8.70%, respectively. The majority of patients were treated with either 250 or 500 mg dose and interestingly, both group reported similar adverse events. We analyzed the incidence of adverse events in the first-, second-, third-line and beyond. The probability of adverse events in these subgroups was 93.83%, 90.49%, 87.86%, and 87.23%, respectively, and serious adverse events (≥ grade 3) occurred in 33.04%, 22.88%, 18.93%, and 14.89% of the patients, respectively (*Table 3*).

Table 2 Distribution of adverse event

Toxicity	Patients (N=943) (%)
Anemia	625 (66.28)
Decreased platelet count	340 (36.06)
Decreased white blood cell	320 (33.93)
Decreased neutrophil count	318 (33.72)
Proteinuria	90 (9.54)
Fecal occult blood	79 (8.38)
Increased aminotransferase	171 (18.13)
Anorexia	356 (37.75)
Malaise	285 (30.22)
Abdominal pain	167 (17.71)
Hypertension	43 (4.56)
Palmar-plantar erythrodysesthesia syndrome	19 (2.01)

In the efficacy subgroup analysis, the ORRs of the first-, second-, third-line and beyond, were 14.85%, 10.08%, 8.50%, and 4.76%, respectively, and the differences were statistically significant. The DCRs was 80.20%, 83.19%, 81.38%, and 90.48% for first-, second-, third-line and beyond, respectively, and the differences were not statistically significant (*Table 4*). The median PFS of first-, second-, third-, and higher-line treatment was 7.00, 5.59, 4.90, and 5.68 months, respectively, and the difference was statistically significant. The median OS of first-, second-, third-, and higher-line treatment was 16.56, 11.50, 10.09, and 7.29 months, respectively, and the difference was statistically significant (*Table 5*).

Among all patients, 12 patients were treated with apatinib combined with programmed cell death protein 1 (PD-1) antibodies, and 349 patients were treated with apatinib combined with Teysuno (S-1) (33 patients could not be evaluated by imaging). There was no significant difference in PFS and OS between the two groups, which may be due to the small sample size of the PD-1 antibodies group. However, this requires further investigation with a larger sample size.

Discussion

This prospective study evaluated the efficacy and tolerability of rucaparib in patients with gastric cancer

Table 3 Incidence of adverse events by starting dose, treatment stage, and combined treatment

Items	Any grade AEs		Grade 1–2 AEs		Grade 3–5 AEs	
	N (%)	P value	N (%)	P value	N (%)	P value
Line						
First-line	213 (93.83)		210 (92.51)		75 (33.04)	
Second-line[a]	352 (90.49)	0.149	351 (90.23)	0.340	89 (22.88)	0.006
Third-line[b]	246 (87.86)	0.025	244 (87.14)	0.052	53 (18.93)	0.000
> Third-line[c]	41 (87.23)	0.121	41 (87.23)	0.241	7 (14.89)	0.017
Dose						
250 mg	417 (93.71)		415 (93.26)		104 (23.37)	
375 mg	6 (85.71)	0.408	6 (85.71)	0.446	1 (14.29)	0.578
425 mg[d]	24 (100.00)	0.978	21 (87.50)	0.291	12 (50.00)	0.005
500 mg[e]	384 (86.49)	0.000	383 (86.26)	0.001	105 (23.65)	0.922
750 mg	21 (91.30)	0.648	21 (91.30)	0.718	2 (8.70)	0.120
Monotherapy						
Monotherapy	243 (83.51)		241 (82.82)		43 (14.78)	
Combination therapy[f]	609 (93.40)	0.000	605 (92.79)	0.000	181 (27.76)	0.000

[a], compared to first-line therapy, second-line treatment is a protective factor for grade 3–5 AEs; [b], compared to first-line therapy, third-line treatment is a protective factor for any grade AEs and grade 3–5 AEs; [c], compared to first-line therapy, > third-line treatment is a protective factor for grade 3–5 AEs; [d], compared to 250 mg, 425 mg is a risk factor for grade 3–5 AEs; [e], compared to 250 mg, 500 mg is a protective factor for any grade AEs. Compared to 250 mg, 500 mg is a protective factor for grade 1–2 AEs; [f], compared to monotherapy, combination therapy is a risk factor for any grade AEs (grade 1–2 and grade 3–5 AEs). AEs, adverse events.

treated in a real-world setting. The use of Apatinib in real-life, either in the first, second, third and beyond treatment showed a favourable benefit-risk profile outside clinical trials in Henan China. The concept of a real-world study (RWS) originates from practical clinical research trials. It represented an early stage of pharmacoepidemiology and was first proposed by Williamson and Barrett in 1966 (9). The first published RWS was conducted by Kaplan *et al.* in 1993 on the efficacy evaluation of ramipril (10). The Cures Act of 2016 uses real-world evidence to approve new indications that meet post-marketing research requirements. Moreover, the US Food and Drug Administration (FDA) published an article in the *New England Journal of Medicine* titled "*Real World Evidence - What is it and What does it tell us?*" (11). Therefore, real-world evidence is critical for decision-making in clinical practice (12,13).

In this real-world study of apatinib in the treatment of gastric cancer, 943 patients were included in this analysis. The median PFS of the included patients was 5.65 months (5.22–6.05 months) compared to 2.8 months in previous phase III trial. Median overall survival in our analysis was 11.47 months (10.41–12.52 months) compared to 7.6 months in previous phase III trial. In addition, the clinical study of apatinib combined with docetaxel in advanced gastric cancer carried out by Yang's team showed a median PFS of 4.5 months (14). In contrast, Wang *et al.* reported a median PFS of 4.2 months and a median OS of 7.13 months (15). Therefore, compared with previous clinical studies (14,15), apatinib seems to have better efficacy and consistent safety results. However, interpretation from our study may be challenging due to the heterogeneity of the patient population, for that any comparison or conclusion drawn from these data should be interpreted with caution especially that in china, medical workers have greater flexibility in adjusting doses and frequency of administration as well as using different combination treatments in comparison to randomized clinical trials.

In addition, the data showed that the combination of apatinib and other therapies had higher ORRs and DCRs as well as longer median PFS and median OS than apatinib

Table 4 ORR and DCR endpoint subgroup analysis

Subgroup analysis	n	ORR				DCR			
		Rate (%)	P	OR	95% CI	Rate (%)	P	OR	95% CI
All	848	10.50				82.43			
Age (years)									
0–45	85	9.41				80.00			
45–65	449	10.47	0.911	1.05	0.48–2.30	83.52	0.733	0.91	0.54–1.55
Above 65	314	10.83	0.847	1.08	0.48–2.43	81.21	0.451	0.81	0.47–1.40
Line	848	10.50							
First-line	202	14.85				80.20			
Second-line	357	10.08	0.127	0.67	0.40–1.12	83.19	0.171	1.30	0.89–1.88
Third-line[a]	247	8.50	0.036	0.53	0.30–0.96	81.38	0.917	1.02	0.69–1.50
> Third-line	42	4.76	0.100	0.29	0.07–1.27	90.48	0.186	1.69	0.78–3.70
Dose									
250 mg	407	10.32				84.77			
375 mg	7	14.29	0.667	1.60	0.19–13.6	85.71	0.610	1.74	0.21–14.6
425 mg	23	13.04	0.621	1.37	0.39–4.79	82.61	0.851	1.10	0.40–3.02
500 mg[b]	389	10.80	0.991	1.00	0.64–1.57	80.72	0.021	0.70	0.52–0.95
750 mg	22	4.55	0.423	0.44	0.06–3.32	63.64	0.072	0.45	0.19–1.07
Startup dose 250 mg									
Monotherapy	95	12.63				80.00			
Combination therapy[c]	312	9.62	0.569	0.81	0.40–1.65	86.22	0.009	1.91	1.18–3.09
Startup dose 500 mg									
Monotherapy	131	7.63				77.10			
Combination therapy[d]	258	12.40	0.077	1.95	0.93–4.07	82.56	0.003	1.86	1.23–2.83
Treatment plan									
Apatinib only	244	9.43				77.87			
Apatinib combined with one agent[e]	321	11.84	0.193	1.43	0.83–2.47	86.29	0.000	2.09	1.47–2.99
Apatinib combined with two agents[f]	227	8.81	0.903	1.04	0.56–1.94	82.82	0.003	1.77	1.21–2.59
Apatinib combined with more than two agents[g]	44	18.18	0.043	2.46	1.03–5.90	75.00	0.376	1.36	0.69–2.70
Apatinib combined with PD-1 agents	12		0.984	0.00	0.00–1.00	83.33	0.208	2.68	0.58–12.5
Startup dose method 1									
250–375 mg	414	10.39				84.78			
425–500 mg[h]	412	10.92	0.958	1.01	0.65–1.57	80.83	0.024	0.71	0.53–0.96
750 mg	22	4.55	0.418	0.43	0.06–3.29	63.64	0.069	0.45	0.19–1.06

[a], compared to first-line therapy, third-line treatment is a risk factor for ORR; [b], compared to 250 mg, 500 mg is a risk factor for DCR; [c], compared to monotherapy, combination therapy is a protective factor for DCR; [d], compared to monotherapy, combination therapy is a protective factor for DCR; [e], compared to apatinib only, apatinib combined with one agent is a protective factor for ORR; [f], compared to apatinib only, apatinib combined with two agents is a protective factor for DCR; [g], compared to apatinib only, apatinib combined with two agents is a protective factor for DCR; [h], compared to 250–375 mg, 425–500 mg is a risk factor for DCR. ORR, overall response rate; DCR, disease control rate; OR, odds ratio; CI, confidence interval.

Table 5 PFS and OS endpoint subgroup analysis

Subgroup analysis	n	Median PFS				Median OS			
		Month	P	OR	95% CI	Month	P	OR	95% CI
All	943	5.65				11.47			
Age (years)									
0–45	89	4.04				9.20			
45–65[a]	502	5.59	0.043	0.77	0.60–0.99	12.06	0.039	0.75	0.57–0.99
Above 65[b]	352	6.18	0.047	0.77	0.59–1.00	11.56	0.050	0.75	0.57–1.00
Line									
First-line	227	7.00				16.56			
Second-line[c]	389	5.59	0.091	1.20	0.97–1.47	11.50	0.002	1.42	1.14–1.77
Third-line[d]	280	4.90	0.001	1.44	1.16–1.79	10.09	0.001	1.49	1.18–1.88
> Third-line[e]	47	5.68	0.197	1.27	0.88–1.83	7.29	0.000	2.29	1.60–3.30
Startup dose									
250 mg	445	5.36				11.93			
375 mg	7	8.61	0.381	0.64	0.24–1.73		0.247	0.44	0.11–1.77
425 mg	24	6.05	0.475	0.84	0.53–1.34	20.93	0.230	0.70	0.39–1.25
500 mg	444	5.82	0.098	0.87	0.74–1.03	10.61	0.088	1.16	0.98–1.36
750 mg[f]	23	4.02	0.017	1.72	1.10–2.68	12.02	0.981	0.99	0.59–1.67
Startup dose 250 mg									
Monotherapy	111	4.70				10.18			
Combination therapy	334	5.42	0.773	0.96	0.74–1.25	12.12	0.243	0.85	0.65–1.12
Startup dose 500 mg									
Monotherapy	162	4.90				10.09			
Combination therapy	282	6.31	0.287	0.88	0.69–1.11	10.81	0.749	0.96	0.76–1.22
Treatment plan									
Apatinib only	292	4.96				10.09			
Apatinib combined with one agent	348	5.42	0.915	1.01	0.84–1.22	10.71	0.739	1.03	0.85–1.25
Apatinib combined with two agents[g]	245	6.18	0.047	0.81	0.65–1.00	15.24	0.005	0.72	0.58–0.91
Apatinib combined with more than two agents	46	7.10	0.362	0.84	0.59–1.22	11.19	0.958	0.99	0.68–1.44
Apatinib combined with PD-1 agents	12	5.32	0.759	0.90	0.46–1.76	14.97	0.519	0.78	0.37–1.66
Startup dose method 1									
250–375 mg	452	5.42				12.06			
425–500 mg	468	5.88	0.105	0.88	0.75–1.03	10.81	0.123	1.14	0.97–1.34
750 mg[h]	23	4.02	0.015	1.73	1.11–2.70	12.02	0.991	1.00	0.60–1.69

[a], compared to 0–45 years of age, 45–65 is a protective factor for PFS and OS; [b], compared to 0–45 years, >65 years of age is a protective factor for PFS; [c], compared to first-line therapy, second-line treatment is a risk factor for OS; [d], compared to first-line therapy, third-line treatment is a risk factor for PFS and OS; [e], compared to first-line therapy, > third-line treatment is a risk factor for OS; [f], compared to 250 mg, 750 mg is a risk factor for PFS; [g], compared to apatinib only, apatinib combined with two agents is a protective factor for PFS and OS; [h], compared to 250–375 mg, 750 mg is a risk factor for PFS. PFS, progression-free survival; OS, overall survival; OR, odds ratio; CI, confidence interval.

alone, and the differences were statistically significant. This suggests combining apatinib and other therapies may be more beneficial than apatinib monotherapy and possibly should be used at an earlier stage of the disease. However, as mentioned before, caution should be exercised when interpreting this data given the different variable and the retrospective nature of the data collected.

The overall safety profile of Apatinib in this real-life setting was acceptable and consistent with previously reported data. No new safety signals were identified (16-18). Interestingly, we observed a decrease in the incidence of adverse reactions in second and higher-line treatments compared with first-line treatment. This may be related to more aggressive symptoms control and the use of apatinib as a single agent in later-line therapy. However, this still needs in-depth observation and analysis in the follow-up study. Althought radiological images were not centrally reviewed and this may have influenced the response rate and PFS, in our study the median OS of patient treated with apatinib alone or in combination compared favourably with the median OS of those treated within the registrative TAGS trial, in which less than 15% of oriental patient were enrolled (19).

Conclusions

This study represents real-world evidence of patients treated with apatinib outside clinical trials in Henan, china. Efficacy results of apatinib, even in heavily pre-treated patients, are similar and in some cases better to those from pivotal clinical trials. The safety profile of apatinib in a real-life setting is manageable and predictable. In addition, our results suggested that, in the real world, the combination of apatinib with other therapies could provide more significant benefits. In addition, a lower initial dose was found to provide benefits. These results need to be confirmed in randomized trials. Even with more aggressive management of side effects in the real world, adverse events remain relatively high, which may be related to the poor performance status in patients in the real world. With the rapid development of immunotherapy, a combination of targeted therapy and immune check point inhibitors more common. At the time of this study, immune checkpoint inhibitors were not commonly used in the treatment of gastric cancer for the lack of data and the cost. The number of patients in this study with immune check point inhibitors was small, which could not reflect the real-world situation. Our team will focus on the effectiveness and safety of apatinib combined with immunotherapy in the real world in the follow-up study.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5995/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5995/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5995/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). The study was approved by Ethics Committee of Henan Cancer Hospital (No. 2018012). All participating institutions were informed and agreed the study. All patients provided written informed consent before enrollment.

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