Effectiveness and safety of low-dose apatinib in advanced gastric cancer: A real-world study

Yingying Du | Qisheng Cao | Congqiao Jiang | Hui Liang | Zhongliang Ning | Chushu Ji | Jinguo Wang | Chaoping Zhou | Zonghui Jiang | Changjun Yu | Lei Li | Yong Zhao | Yuemei Xu | Tengyun Xu | Wenjun Hu | Daoqin Wang | Huaidong Cheng | Guihe Wang | Jinhua Zhou | Song Wang | Yanshun Zhang | Zhiqiang Hu | Xinzhong Li | Donghui Lu | Jun Zhang | Hua Xie | Guoping Sun

1Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, China
2Department of Interventional Oncology, People's Hospital of Ma'anshan, Ma'anshan, China
3Department of Gastrointestinal Surgery, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China
4Department of Tumor Radiotherapy, Lu'an Hospital of Traditional Chinese Medicine, Lu'an, China
5Department of Gastrointestinal Surgery, The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Cancer Hospital), Hefei, China
6Department of Oncology, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China
7Department of Gastrointestinal Surgery, Yijishan Hospital of WanNan Medical College, Wuhu, China
8Department of Surgical Oncology, Anqing Municipal Hospital, Anqing, China
9Department of Oncology, The First People's Hospital of Chuzhou City, Chuzhou, China
10Department of Gastrointestinal Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China
11Department of Surgical Oncology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China
12Department of Oncology, Lu'an Hospital of Traditional Chinese Medicine, Lu'an, China
13Department of Oncology, Jinzhai Country Hospital of Traditional Chinese Medicine, Lu'an, China
14Department of Oncology, People's Hospital of Fuyang City, Fuyang, China
15Department of Gastrointestinal Surgery, Wanbei Coal-Electricity Group General Hospital, Suzhou, China
16Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, China
17Department of Gastrointestinal Surgery, People's Hospital of Tongling City, Tongling, China
18Department of Oncology, The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China
19Department of Oncology, Huainan First People's Hospital, Huainan, China
20Department of Oncology, Huaibei Miners General Hospital, Huaibei, China
21Department of Oncology, The People's Hospital of Huaibei, Huaibei, China
22Department of Oncology, The 901 Hospital of the Joint Logistic Support Force of the People's Liberation Army of China, Hefei, China
23Department of Oncology, The Second People's Hospital of Wuhu, Wuhu, China
24Department of Oncology, The People's Hospital of Xuancheng City, Xuancheng, China

Yingying Du, Qisheng Cao, Congqiao Jiang, Hui Liang, and Zhongliang Ning, contributed equally.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. Cancer Medicine published by John Wiley & Sons Ltd.
Abstract
Apatinib has been demonstrated to be effective and safe among patients with gastric cancer failing after at least two lines chemotherapy. This study aimed to evaluate its effectiveness and safety of low-dose apatinib for the treatment of gastric cancer in real-world practice. We performed a prospective, multicenter observation study in a real-world setting. Patients with advanced gastric cancer more than 18 years old were eligible and received low-dose apatinib (500 mg or 250mg per day) therapy. The median progression-free survival (PFS), median overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety were assessed. Between September 2017 and April 2019, a total of 747 patients were enrolled. The mPFS was 5.56 months (95% CI 4.47-6.28), and mOS was 7.5 months (95% CI 6.74-8.88). Four patients achieved complete response, 47 achieved partial response, and 374 patients achieved stable disease. The ORR was 6.83% and DCR was 56.89%. In addition, multivariate Cox regression analysis indicated that hand-foot syndrome was one independent predictor for PFS and OS. The most common adverse events (AEs) at any grade were hypertension (36.55%), proteinuria (10.26%), hand-foot syndrome (33.53%), fatigue (24.9%), anemia (57.35%), leukopenia (44.49%), thrombocytopenia (34.21%), and neutropenia (53.33%). Grade 3-4 AEs with incidences of 5% or greater were anemia (13.97%), thrombocytopenia (7.14%), and neutropenia (6.67%). No treatment-related death was observed during the treatment of apatinib. The prospective study suggested that low-dose apatinib was an effective regimen for the treatment of advanced gastric cancer with tolerable or controlled toxicity in real world.

Trial registration: NCT03333967.

Keywords
advanced gastric cancer, apatinib, real-world

1 INTRODUCTION

Gastric cancer is one of the most common digestive system malignancy, with high morbidity and mortality worldwide, which is next only to lung cancer and liver cancer. For the early stage patients, surgery is the best treatment, however, approximately 80% of patients are initially diagnosed incurable due to locally advanced or metastatic gastric cancer. With the development of chemotherapeutic drugs, targeted drugs, and immunotherapy, the median survival of advanced gastric cancer has been extended to more than 12 months. However, the survival rate of 5 years remain poor with <10%. Thus, exploring novel therapy strategies are necessary.

Angiogenesis has been investigated widely and known as its contribution to initial and development of tumor. Vascular endothelial growth factor receptors (VEGFR), including VEGFR-1, VEGFR-2, VEGFR-3, and VEGFR-4, have been demonstrated to bind the vascular endothelial growth factor (VEGF) family to motivate angiogenesis signal pathway, and function important role as critical regulators of angiogenesis. Apatinib, as a specifically targeting VEGFR-2 and oral receptor tyrosine kinase inhibitor, has been shown that it could inhibit the angiogenesis of tumor through prohibiting VEGF-promoted tumor development. Also, Li et al have reported that apatinib expressively advanced overall survival (OS) and PFS with tolerable toxicities in chemotherapy-refractory advanced gastric cancer after failing at least two lines chemotherapy in the randomized, double-blind, placebo-controlled phase III trial and a randomized, placebo-controlled, parallel-arm, phase II trial, but the dose of 850 mg daily or 425 mg twice a day in the two trials resulted in many severe adverse events in clinical practice. Additionally, the dosage of 500 mg daily in clinical practice was commonly used mainly due to the concern of potential grade 3-4 adverse events such as hypertension, proteinuria, and hand-foot syndrome.

Preliminary data of this present have been released in ASCO 2019 (Abstract, 161) and ESMO 2018 Congress (683P). So, we further analyzed this prospective observation study in order to provide more clinical proof for the use of low-dose apatinib in patients with advanced gastric cancer.
2 | PATIENTS AND METHODS

2.1 | Patients

Patients receiving apatinib were included in this study from 23 centers in China. All men or women older than 18 years of age who pathologically or histologically confirmed advanced or metastatic adenocarcinoma of stomach were included. Patients with pregnancy or lactation, those with contraindications or allergy for apatinib, and those unsuitable to this study were excluded. All patients provided written informed consent before participating in the study. This study was approved by the local ethics committee of all hospitals.

2.2 | Study design and treatment

This was a prospective, multicenter observation study in a real-world setting. All patients received apatinib therapy by an oral administration once a day and the dose (500 mg or 250 mg) could be adjusted according to patient's performance status or adverse event.

2.3 | Efficacy and safety

Clinical responses were evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) until disease progression. The responses were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. The objective response rate (ORR) or disease control rate (DCR) was computed as the addition of CRs plus PRs or CRs plus PRs plus SDs, respectively. Survival status was followed up every 3 months to analyze the PFS and OS. The PFS or OS was defined as time from the start of apatinib administration until disease progression or death of any cause death according to RECIST 1.1, respectively. All treatment-related adverse events (AEs) were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

2.4 | Statistical analyses

The Kaplan-Meier method and log-rank test were used to analyze the PFS and OS. Multivariate analyses were performed with the Cox's proportional hazards regression model to explore the potential factors for PFS and OS. All the statistical analyses were performed using SAS 9.2 software (SAS Institute).

3 | RESULTS

3.1 | Patient characteristics

Between September 1, 2017 and April 15, 2019, 747 patients with advanced gastric cancer who received the treatment of apatinib were included in the FAS population. The patients' characteristics were shown in Table 1. All patients included 547 male and 200 female patients with the mean age of 62.33 years. In addition, 711 and 36 patients showed an ECOG performance status of 0/1 (95.18%) and ≥2 (4.82%), respectively. 58.63% of the included patients had metastases. The patients had experienced previous therapy such as...
gastrostomy (55.69%), chemotherapy (68.94%), and radiotherapy (2.41%). A total of 611 patients received the initial dose of 500 mg and 136 patients were treated with the initial dose of 250 mg.

3.2 | Effectiveness

A total of 516 patients were assessed by an imaging examination (CT or MRI). Among them, 4 patients showed CR, 47 patients (6.29%) achieved PR, 374 patients (50.06%) showed stable disease, and 91 patients (12.18%) were evaluated as progression disease after the treatment of apatinib. These data exhibited an ORR of 6.83% and a DCR of 56.89%. The specifics of the clinical responses were listed in Table 2.

For survival outcome, as shown in Table 3, the median PFS was 5.56 months (95% CI 4.74-6.28), and the 6-month and 12-month PFS rate were 47.04% (95% CI 42.93-51.05) and 22.85% (95% CI 18.40-27.60), respectively. The median OS was 7.5 months (95% CI 6.74-8.88), and the 6-month and 12-month OS rate were 58.54% (95% CI 54.34-62.49) and 32.25% (95% CI 27.47-37.64), respectively.

An exploratory univariate analysis was carried out by the Kaplan-Meier analysis and log-rank test. We found that there were significant association between the mPFS and combined therapy, apatinib suspension, number of metastases sites, and hand-foot syndrome (all \( P < .05 \)). Also, there were also significant association of mOS with combined therapy, dose adjustment, clinical stage, previous surgery history, hypertension, proteinuria, and hand-foot syndrome (all \( P < .05 \)). We also observed that apatinib treatment lines were not significantly associated with mPFS and mOS. Detailed results of univariate analysis were shown in Table 4.

In addition, as shown in Table 5, multivariate Cox regression analysis indicated that hand-foot syndrome was one independent predictor for PFS and OS. Also, combination regimen (apatinib plus taxol/docetaxel) was also one independent predictor for PFS.

### Table 2  Tumor responses

| Response | N (n = 747) | Percentage (%) |
|----------|-------------|----------------|
| CR       | 4           | <1             |
| PR       | 47          | 6.29           |
| SD       | 374         | 50.06          |
| PD       | 91          | 12.18          |
| Not evaluable | 231     | 30.92          |
| ORR      | 51          | 6.83           |
| DCR      | 425         | 56.89          |

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progression disease; PR, partial response; SD, stable disease.

### Table 3  Survival analysis of patients treated with apatinib

| Survival | Efficacy (n = 747) |
|----------|-------------------|
| mPFS (95% CI) | 5.56 (4.74-6.28)   |
| 6-mo (%) (95% CI) | 47.04 (42.93-51.05) |
| 12-mo (%) (95% CI) | 22.85 (18.40-27.60) |
| mOS (95% CI) | 7.5 (6.74-8.88) |
| 6-mo (%) (95% CI) | 58.54 (54.34-62.49) |
| 12-mo (%) (95% CI) | 32.25 (27.47-37.64) |

Abbreviations: mOS, median overall survival; mPFS, median progression-free survival.

3.3 | Safety

A total of 574 patients were enrolled for the assessment of safety. The occurring frequencies of all adverse events were 73.59%, and the occurring frequencies of grade \( \geq 3 \) AEs were 18.97%. No unexpected AEs and SAEs were observed. The most common AEs included hypertension (36.55%), proteinuria (10.26%), hand-foot syndrome (33.53%), fatigue (24.9%), anemia (57.35%), leukopenia (44.49%), thrombocytopenia (34.21%), and neutropenia (53.33%). Grade \( \geq 3 \) AEs with incidences of more than 5% were anemia (13.97%), thrombocytopenia (7.14%), and neutropenia (6.67%). The detailed AEs were shown in Table 6. In addition, 20 patients were reduced to the 250 mg dose from 500 mg dose and 44 patients were increased to 500 mg dose from 250 mg dose. A total of 178 patients suspended the administration (156 patients suspended one time, 17 suspended two times, and 5 suspended three times).

4 | DISCUSSION

Patients with advanced gastric cancer generally showed dismal prognoses. Two-drug regimens or three-drug regimens from fluoropyrimidine-based and platinum-based chemotherapies have been used as the standard therapy of first line.\(^9^-^1^1\) For HER2-positive advanced gastric or gastroesophageal junction (GEJ) cancer, trastuzumab in combination with chemotherapy dramatically extended the OS of the patients and might be a fresh standard therapy for this disease.\(^1^2\) For second-line therapy for gastric cancer, chemotherapeutic agents such as paclitaxel and irinotecan and antiangiogenic targeted agents such as ramucirumab have been recommended by NCCN guideline.\(^1^3\) The second-line chemotherapy achieved an mOS of 5.8-9.5 months and an mPFS of 2.2-3.6 months.\(^1^4\) Ramucirumab monotherapy or combination with paclitaxel benefits patients with the mOS of 5.2-9.6 months.\(^1^5\) Apatinib has been approved in patients with chemotherapy-refractory advanced or metastatic...
adenocarcinoma of the stomach or GEJ as third- or further-line treatment in China based on the results of a II and III trials, which showed the benefits of mPFS (2.6 months vs 1.8 months, \( P < .001 \)) and mOS (6.5 months vs 4.7 months, \( P = .0149 \)) compared with placebo control.5,6

In this real-world study, our results showed that the mPFS was 5.56 months (95% CI 4.47-6.28), and mOS was 7.5 months (95% CI 6.74-8.88), the DCR and ORR was 56.89% and 6.83%, respectively. These data were better than the previous studies. For example, Li et al observed that apatinib achieved an mPFS of 2.6-3.67 months and mOS of 4.27-6.5 months in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or GEJ in a phase II trial and III trial.5,6 In addition, in a real-world study, Zhang et al found that apatinib achieved an mPFS of 2.65 months, an mOS of 5.8 months, and ORR of 5.6% and DCR of 58.3% in 36 patients with advanced gastric adenocarcinoma or adenocarcinoma of GEJ after failing at least two lines of systemic therapy.16

| Variable                          | Number | mPFS (m) | \( P \) | mOS (m) | \( P \) |
|-----------------------------------|--------|----------|--------|---------|--------|
| Total patients                    | 747    | 5.56     |        | 7.5     |        |
| Apatinib treatment lines          |        |          |        |         |        |
| 1                                 | 325    | 5.72     | .61    | 7.63    | .80    |
| 2                                 | 209    | 5.52     |         | 7.50    |        |
| ≥3                                | 205    | 4.87     |         | 7.50    |        |
| Combined therapy*                 |        |          | .01    | .02     |        |
| Yes                               | 338    | 6.38     |         | 8.88    |        |
| No                                | 407    | 4.61     |         | 6.51    |        |
| Apatinib suspension               |        |          | .009   | .41     |        |
| No                                | 569    | 5.95     |         | 7.76    |        |
| Yes                               | 178    | 4.18     |         | 7.04    |        |
| Dose adjustment                   |        |          | .27    | .03     |        |
| Yes                               | 86     | 7.3      |         | 10.63   |        |
| No                                | 661    | 5.33     |         | 7.24    |        |
| Clinical stage                    |        |          | .15    | .04     |        |
| III                               | 101    | 6.74     |         | 10.43   |        |
| IV                                | 489    | 4.77     |         | 7.43    |        |
| Previous surgery history          |        |          | .09    | .01     |        |
| Yes                               | 416    | 5.69     |         | 8.68    |        |
| No                                | 331    | 5.33     |         | 7.24    |        |
| Number of metastases sites        |        |          | .01    | .98     |        |
| >2                                | 95     | 3.45     |         | 6.5     |        |
| ≤2                                | 331    | 5.69     |         | 7.5     |        |
| Hypertension                      |        |          | .664   | .03     |        |
| Yes                               | 198    | 5.26     |         | 9.67    |        |
| No                                | 322    | 4.14     |         | 7.27    |        |
| Proteinuria                       |        |          | .07    | .002    |        |
| Yes                               | 52     | 7.30     |         | 13.62   |        |
| No                                | 454    | 4.28     |         | 7.73    |        |
| Hand-foot syndrome                |        |          | <.001  | <.001   |        |
| Yes                               | 162    | 8.59     |         | 12.99   |        |
| No                                | 307    | 3.09     |         | 5.03    |        |

Note: \( P \) values by log-rank test are displayed.
Abbreviations: mOS, median overall survival; mPFS, median progression-free survival.

*Combined with XELOX, 5-FU, DCF, and EOX regimen.
In addition, univariate analysis found that mPFS and mOS were significantly associated with combined therapy and hand-foot syndrome. Combination with chemotherapy included apatinib plus taxol/docetaxel, XELOX, 5-FU, DCF, and EOX regimen, which would improve the survival of patients.

To exclude the effect of the confounders for survival outcome, we further performed the Cox regression analysis and found that apatinib plus taxol/docetaxel and hand-foot syndrome were independent significant factors to affect the PFS and hand-foot syndrome was only one independent significant factor to influence the OS. Li et al reported that apatinib treatment prolonged progression-free survival and lead to improved OS.17 Interestingly, we did not observe the apatinib plus taxol/docetaxel affect the OS by Cox regression analysis. Hand-foot syndrome has been recognized as a viable biomarker of antitumor efficacy and was associated with prolonged mOS and prolonged mPFS in previous study,18 consistently with our data.

In this study, apatinib was prescribed at a low dose of 500 mg or 250mg a day initially, which was lower than the previous reported dose in gastric cancer (850 mg daily or 425 mg twice a day)5,6; and a large number of studies have also demonstrated that the dose of apatinib 500 mg per day is effective in other solid tumors, such as thyroid cancer, breast cancer, sarcoma, lung cancer, hepatocellular carcinoma. Thus, this real-world study further provided the clinical implication for the use of low-dose apatinib in gastric cancer.

Hypertension, proteinuria, and hand-foot syndrome are the most common AEs in antiangiogenic therapy.19-21 The most common AEs in our study are almost similar to those reported in previous studies of apatinib.5,6 Besides, hematologic toxicities including anemia (57.35%), leukopenia (44.49%), thrombocytopenia (34.21%), neutropenia (53.33%) also occurred. Grade 3-4 AEs with incidences of more than 5% were anemia (13.97%), thrombocytopenia (7.14%), and neutropenia (6.67%).

TABLE 5 Multivariate Cox regression analyses for PFS and OS

|                | P      | HR    | 95% CI          | P      | HR    | 95% CI          |
|----------------|--------|-------|-----------------|--------|-------|-----------------|
| Gender         | .488   | 0.844 | 0.522-1.363     | .954   | 1.017687 | 0.561-1.850     |
| Age            | .453   | 0.860 | 0.580-1.275     | .137   | 0.6963783 | 0.432-1.122     |
| ECOG score     | .833   | 1.140 | 0.337-3.852     | .405   | 1.889048 | 0.4226-8.445    |
| Clinical stage | .864   | 1.051 | 0.595-1.855     | .558   | 0.8124894 | 0.405-1.629     |
| Surgery history| .989   | 0.997 | 0.661-1.505     | .218   | 0.7334019 | 0.448-1.201     |
| Chemotherapy history | .836 | 1.060 | 0.610-1.844 | .155   | 1.63683 | 0.830-3.227     |
| Treatment line  | .514   | 0.905 | 0.672-1.220     | .921   | 1.019407 | 0.696-1.493     |
| Combination regimen | .032* | 0.440 | 0.207-0.932     | .432   | 0.7238228 | 0.323-1.622     |
| Dose adjustment | .124   | 0.662 | 0.392-1.120     | .33    | 0.7285891 | 0.385-1.377     |
| Apatinib suspension | .889 | 1.030 | 0.681-1.556     | .209   | 0.727765 | 0.443-1.194     |
| Hypertension    | .677   | 0.920 | 0.619-1.365     | .114   | 0.6727261 | 0.411-1.100     |
| Proteinuria     | .204   | 0.662 | 0.351-1.250     | .108   | 0.4579196 | 0.176-1.188     |
| Hand-foot syndrome | 0**   | 0.230 | 0.139-0.376     | 0**    | 0.1876364 | 0.102-0.344     |
| Fatigue         | .629   | 0.892 | 0.562-1.416     | .454   | 0.8030185 | 0.452-1.427     |

*P < .05  
**P < .01

TABLE 6 Adverse events

| Adverse events | Any grade(%) | Grade ≥ 3 (%) |
|----------------|--------------|---------------|
| Hypertension   | 36.55        | 3.82          |
| Fatigue        | 24.9         | 2.01          |
| Hand-foot syndrome | 33.53    | 2.41          |
| Proteinuria    | 10.26        | 0.56          |
| Anemia         | 57.35        | 13.97         |
| Thrombocytopenia| 34.21        | 7.14          |
| Neutropenia    | 53.33        | 6.67          |
| Leukocytopenia | 44.49        | 1.84          |

In addition, univariate analysis found that mPFS and mOS were significantly associated with combined therapy and hand-foot syndrome. Combination with chemotherapy included apatinib plus taxol/docetaxel, XELOX, 5-FU, DCF, and EOX regimen, which would improve the survival of patients.

To exclude the effect of the confounders for survival outcome, we further performed the Cox regression analysis and found that apatinib plus taxol/docetaxel and hand-foot syndrome were independent significant factors to affect the PFS and hand-foot syndrome was only one independent significant factor to influence the OS. Li et al reported that apatinib treatment prolonged progression-free survival and lead to improved OS.17 Interestingly, we did not observe the apatinib plus taxol/docetaxel affect the OS by Cox regression analysis. Hand-foot syndrome has been recognized as a viable biomarker of antitumor efficacy and was associated with prolonged mOS and prolonged mPFS in previous study,18 consistently with our data.

In this study, apatinib was prescribed at a low dose of 500 mg or 250mg a day initially, which was lower than the previous reported dose in gastric cancer (850 mg daily or 425 mg twice a day)5,6; and a large number of studies have also demonstrated that the dose of apatinib 500 mg per day is effective in other solid tumors, such as thyroid cancer, breast cancer, sarcoma, lung cancer, hepatocellular carcinoma. Thus, this real-world study further provided the clinical implication for the use of low-dose apatinib in gastric cancer.

Hypertension, proteinuria, and hand-foot syndrome are the most common AEs in antiangiogenic therapy.19-21 The most common AEs in our study are almost similar to those reported in previous studies of apatinib.5,6 Besides, hematologic toxicities including anemia (57.35%), leukopenia (44.49%), thrombocytopenia (34.21%), neutropenia (53.33%) also occurred. Grade 3-4 AEs with incidences of more than 5% were anemia (13.97%), thrombocytopenia (7.14%), and neutropenia (6.67%).

5 CONCLUSION

Taken together, the prospective study suggested that low-dose apatinib was an effective regimen for advanced gastric cancer with manageable toxicity in the real-world study.
ACKNOWLEDGMENTS
Thank all the patients and their families volunteer to participate in the clinical study. We thank Cunnan Dong and Guoliang Chen for the writing and revision of this manuscript.

CONFLICT OF INTEREST
All authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS
All authors were in conception and design. All authors were involved in collection and assembly of data. All authors were involved in administrative support, data analysis, and interpretation. All authors approved the final manuscript and accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

ORCID
Yingying Du https://orcid.org/0000-0002-5149-4632
Guoping Sun https://orcid.org/0000-0002-4325-900X

REFERENCES
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
2. Karimi P, Islami F, Amandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev. 2014;23(5):700-713.
3. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30(13):1513-1518.
4. Nowak-Sliwinska P, Alitalo K, Allen E, et al. Consensus guidelines for the use and interpretation of angiogenesis assays. Angiogenesis. 2018;21(3):425-532.
5. Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J Clin Oncol. 2013;31(26):3219-3225.
6. Li J, Qin S, Xu J, et al. Randomized, double-blind, placebo-controlled, phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J Clin Oncol. 2016;34(13):1448-1454.
7. Sun G-P, Li D, Ning Z, et al. Exploration of patients with gastric cancer who benefit from apatinib: An updated real-world study. J Clin Oncol. 2019;37(4 Suppl):161.
8. Sun G, Li D, Ning Z, et al. A real world study of apatinib treatment in gastric cancer: current status and clinical benefit. Ann Oncol. 2018;29(Suppl 8):mdy282.067.
9. Kim GM, Jeung H-C, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer. Eur J Cancer. 2012;48(4):518-526.
10. Kang Y-K, Kang W-K, Shin D-B, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20(4):666-673.
11. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26(9):1435-1442.
12. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-697.
13. Qiu H, Zhou Z. Updates and interpretation on NCCN clinical practice guidelines for gastric cancer 2017 version 5. Zhonghua Wei Chang Wai Ke Za Zhi. 2018;21(2):160-164.
14. Sym SJ, Hong J, Park J, et al. A randomized phase II study of bi-weekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRO) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol. 2013;71(2):481-488.
15. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224-1235.
16. Zhang Y, Han C, Li J, et al. Efficacy and safety for apatinib treatment in advanced gastric cancer: a real world study. Sci Rep. 2017;7(1):13208.
17. Huang L, Wei Y, Shen S, et al. Therapeutic effect of apatinib on overall survival is mediated by prolonged progression-free survival in advanced gastric cancer patients. Oncotarget. 2017;8(17):29346-29354.
18. Liu X, Qin S, Wang Z, et al. Early presence of anti-angiogenesis-related adverse events as a potential biomarker of antitumor efficiency in metastatic gastric cancer patients treated with apatinib: a cohort study. J Hematol Oncol. 2017;10(1):153.
19. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma ( REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31-39.
20. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29(30):3968-3976.
21. Yoon HH, Bendell JC, Braith F, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter phase II trial. Ann Oncol. 2016;27(12):2196-2203.

How to cite this article: Du Y, Cao Q, Jiang C, et al. Effectiveness and safety of low-dose apatinib in advanced gastric cancer: A real-world study. Cancer Med. 2020;9:5008–5014. https://doi.org/10.1002/cam4.3105