Original Article



# Apatinib plus 5-fluorouracil as a third or subsequent-line treatment option for metastatic colorectal cancer: a phase-II, single-arm, prospective study

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**Background:** For metastatic colorectal cancer (mCRC) patients for whom at least 2 lines of previous standard therapies have failed, the prognosis is often unfavorable due to very limited subsequent treatment options. We sought to explore the efficacy of apatinib, an oral small-molecule vascular endothelial growth factor receptor-2 inhibitor, plus 5-fluorouracil (5-FU) as a third- or subsequent-line treatment for mCRC.

**Methods:** In this phase-II, single-arm, prospective study, the eligible patients had been histologically confirmed to have adenocarcinoma of the colon or rectum for which at least 2 previous regimens of standard therapies had failed. All the patients were treated with a daily dose of 250 mg of apatinib, in combination with capecitabine, Tegafur Gimeracil Oteracil Potassium Capsule (S-1), or 5-FU, until disease progression, unacceptable toxicity, or consent withdrawal.

**Results:** From June 2017 to April 2018, 16 patients were enrolled in this study. Among them, 4 achieved partial response, 7 had stable disease, and 5 had progression disease, resulting in an objective response rate of 25.00% [95% confidence interval (CI): 7.27–52.38%], and a disease control rate of 68.75% (95% CI: 41.34–88.98%). The median progression-free survival (PFS) was 4.83 months (95% CI: 2.17–8.90 months), and the median overall survival (OS) was 9.10 months (95% CI: 5.59–15.18 months). The common treatment-related adverse events (AEs) were hand-foot syndrome (56.25%), hypertension (37.50%), proteinuria (37.50%), gingival bleeding (18.75%) and abdominal pain (18.75%). Grade 3 AEs, including hand-foot syndrome (18.75%), hypertension (12.50%), and proteinuria (12.50%), were observed in 7 patients.

**Conclusions:** The combination regimen of apatinib plus 5-FU had encouraging anti-tumor efficacy, and is a feasible third- or subsequent-line treatment option for mCRC.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT03210064.

**Keywords:** Cancer; apatinib; 5-fluorouracil (5-FU); third-line treatment

Submitted Dec 22, 2021. Accepted for publication Jan 20, 2022.
doi: 10.21037/atm-22-77
**View this article at:** https://dx.doi.org/10.21037/atm-22-77

## Introduction

Due to its high morbidity and mortality, cancer is a major public health problem worldwide, and colorectal cancer has become a predominant cancer type in recent years (1,2). According to the 2018 Global Cancer Surveillance Data, there were about 4.3 million new cancer cases in China, of which colorectal cancer ranked the second, accounting for 12.2% new cancer cases (1). Approximately 25% of colorectal cancer patients have metastatic disease at the time of diagnosis (3). Treatment recommendations for metastatic colorectal cancer (mCRC) include single or combination chemotherapy [5-fluorouracil (5-FU), capecitabine, oxaliplatin, and irinotecan] with or without targeted therapy (bevacizumab, and cetuximab) (4). These regimens are generally used for first- and second-line treatments. Third-line treatment options for patients for whom first- and second-line standard therapies fail are very limited.

Apatinib is a small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor-2 (VEGFR2). It inhibits angiogenesis, and in 2014, was approved for the third-line treatment of advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction in China (5). The anti-tumor activity of apatinib has also been shown in studies of other cancer types (6-8). Bevacizumab is a monoclonal antibody that also targets VEGFR2. Previous studies have demonstrated that fluorouracil-based chemotherapy in combination with bevacizumab significantly improves progression-free survival (PFS) and overall survival (OS) in the first- and second-line treatment of mCRC (4,9). Given that both apatinib and bevacizumab are antiangiogenic drugs targeting VEGFR2, we conducted a single-arm, phase-II clinical study to evaluate the safety and efficacy of a low-dose apatinib combined with fluoropyrimidine in the treatment of mCRC patients for whom previous chemotherapy treatments had failed. We present the following article in accordance with the TREND reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-77/rc).

## Methods

### *Study design and patients*

This was a single-arm, prospective, phase-II study. To be eligible for inclusion in the study, patients had to meet the following criteria: (I) be aged 18–70 years; (II) have a histological diagnosis of mCRC; (III) have had progressed through or were intolerant to at least 2 previous regimens of standard therapy, including fluoropyrimidine plus either oxaliplatin or irinotecan, with or without bevacizumab or cetuximab treatment; (IV) have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1; (V) have at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST); (VI) have a life expectancy of at least 3 months; and (VII) have adequate blood, renal, and hepatic functions. Patients were excluded if they had uncontrolled hypertension, grade or above heart disease, clear gastrointestinal bleeding tendency, blood coagulation disorder, central nervous system metastasis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided written informed consent before entry to the study. This study was approved by the institutional ethics committee of Hubei Cancer Hospital (No. LLHBCH2017KY-005).

### *Treatment schedule*

All the patients received apatinib and 5-FU [capecitabine, Tegafur Gimeracil Oteracil Potassium Capsule (S-1), or 5-FU]. Apatinib (250 mg) was orally administered once daily for 28 consecutive days (28 days/cycle). For capecitabine, a dose of 1,000 mg/m$^2$ was orally administered twice daily for the first 14 consecutive days on a 21-day cycle. For S-1, an oral dose of 40 mg [body surface area (BSA) <1.25 m$^2$], 50 mg (1.25< BSA <1.5 m$^2$), or 60 mg (BSA >1.5 m$^2$) was administered twice daily for 14 consecutive days, followed by 7 days off in a 21-day cycle. For 5-FU, a dose of 400 mg/m$^2$ was first intravenously injected, followed by a 46-hour continuous infusion of 2,400–3,000 mg/m$^2$ in a 14-day cycle. This combination regimen was continued until disease progression, unacceptable toxicity, or consent withdrawal. After 6 weeks of administration, a validity assessment was performed according to RECIST version 1.1.

### *Efficacy and safety assessments*

The primary endpoint was the objective response rate (ORR). The secondary endpoints were PFS, OS, and the disease control rate (DCR). ORR was defined as the proportion of patients who acquired a complete response (CR) or partial response (PR). DCR was defined as the proportion of patients who acquired a CR or PR or stable disease (SD). PFS was defined as the time from enrollment to disease progression, and OS was defined as the time from

**Table 1** Baseline characteristics of all enrolled patients

| Characteristic | Patients (N=16) |
|---|---|
| Median age [interquartile range] | 55 [51–63] |
| Age, no. (%) | |
| <55 years | 8 (50.00) |
| ≥55 years | 8 (50.00) |
| Gender, no. (%) | |
| Male | 6 (37.50) |
| Female | 10 (62.50) |
| Site, no. (%) | |
| Rectum | 7 (43.75) |
| Colon | 9 (56.25) |
| Pathological differentiation, no. (%) | |
| Median | 13 (81.25) |
| Low | 3 (18.75) |
| Liver metastasis, no. (%) | |
| Yes | 8 (50.00) |
| No | 8 (50.00) |
| Surgery, no. (%) | |
| Yes | 14 (87.50) |
| No | 2 (12.50) |
| Treatment line, no. (%) | |
| Third-line | 10 (62.50) |
| > Third-line | 6 (37.50) |
| Previous therapy, no. (%) | |
| Non-targeted drugs | 9 (56.25) |
| Targeted drugs | 7 (43.75) |

enrollment to death from any cause. Treatment response was evaluated at the baseline, every 2 cycles during the treatment period, and every 3 months during follow-up period by computed tomography or magnetic resonance imaging. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

### *Statistical analysis*

In this study, the statistical analysis was conducted using R software (version 4.0.1). The ORR refers to the proportion of participants who achieved CR or PR. The DCR refers to the proportion of participants who achieved CR, PR, or SD. Ninety-five percent confidence intervals (CIs) were calculated using the Clopper-Pearson method. Median OS, and median PFS were estimated with the Kaplan-Meier method, and 95% CIs were calculated using the Brookmeyer-Crowley method. The incidence rates of different AEs were analyzed using descriptive statistics.

## Results

### *Baseline characteristics*

From June 2017 to April 2018, 16 patients met the eligibility criteria for the study. Patients' baseline characteristics are summarized in *Table 1*. Patients had a median age of 55 years (range, 51–63 years), and 6 were male and 10 were female. Half of the patients had liver metastasis. Most of the patients (n=14) had undergone previous surgery treatment. Seven patients had received previous targeted therapy, and 9 had not.

### *Efficacy*

Among the 16 patients, 1 received a regimen of apatinib plus 5-FU, 8 received a regimen of apatinib plus capecitabine, and 7 received a regimen of apatinib plus S-1. Efficacy assessments were conducted for all patients. No patients achieved CR. PR was achieved by 4 patients, and SD was exhibited in 7 patients. Five patients had progressive disease (PD). Thus, the ORR was 25.00% (95% CI: 7.27–52.38%), and the DCR was 68.75% (95% CI: 41.34–88.98%) (see *Table 2*). The survival outcomes are illustrated in *Figures 1*,*2*. The median PFS was 4.83 months (95% CI: 2.17–8.90 months), and the median OS was 9.10 months (95% CI: 5.59–15.18 months).

### *Safety*

Treatment-related AEs were observed in all the patients. The most common AE was hand-foot syndrome (9, 56.25%). Other common AEs included hypertension (6, 37.50%), proteinuria (6, 37.50%), hemorrhage (3, 18.75%), abdominal pain (3, 18.75%), vomiting (1, 6.25%), and nausea (2, 12.50%). Grade 3 AEs, including hand-foot syndrome (18.75%), proteinuria (12.50%), and hypertension (12.50%), were observed in 7 patients (43.75%). There was no grade 4 or above AE (see *Table 3*). All the AEs were controllable.

**Table 2** Tumor response

| Best response | Patients (N=16) |
|---|---|
| CR, no. (%) | 0 (0) |
| PR, no. (%) | 4 (25.00) |
| SD, no. (%) | 7 (43.75) |
| PD, no. (%) | 5 (31.25) |
| Missing, no. (%) | 0 |
| Overall, no. | 16 |
| ORR, % (95% CI) | 25.00 (7.27–52.38) |
| DCR, % (95% CI) | 68.75 (41.34–88.98) |

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

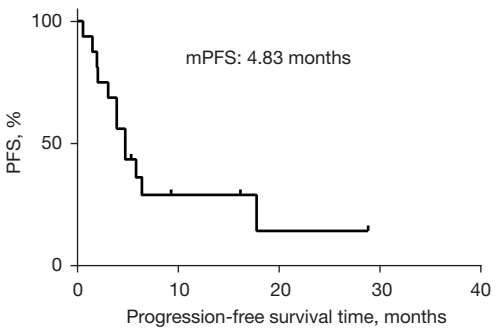


**Figure 1** Kaplan-Meier analysis of progression-free survival. mPFS, median progression-free survival.

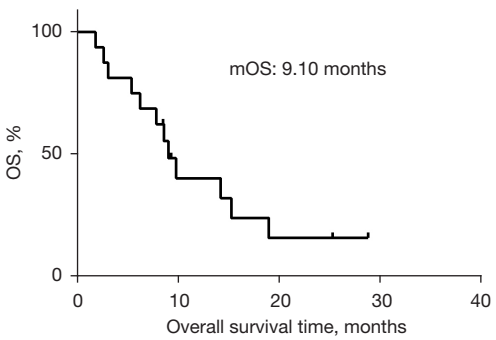


**Figure 2** Kaplan-Meier analysis of overall survival. mOS, median overall survival.

## Discussion

In this single-arm phase-II study, we evaluated the efficacy and safety of low-dose apatinib combined with 5-FU (capecitabine, S-1, or 5-FU) in the treatment of mCRC. The ORR was 25%, and the DCR was 68.75%. The median PFS and median OS were 4.83 and 9.10 months, respectively. The total incidence of grade 3 AEs was 43.75%, and no grade 4 or above AE occurred. To the best of our knowledge, this is the first study to examine the efficacy of apatinib in combination with 5-FU in mCRC treatment.

Due to the complex mechanisms of tumor formation and development, tumor treatment is a challenge. As early as 1971, Folkman proposed that the growth of solid neoplasms always depends on the formation of new blood vessels (10). At the beginning of the 21st century, the advent of angiogenesis inhibitors provided a new approach for combating advanced cancers that are refractory to conventional surgery and chemotherapy. A promising angiogenesis inhibitor, apatinib, was approved as a third-line treatment for gastric cancer in 2014. Since then, multiple clinical studies have been conducted to explore the anti-tumor efficacy of apatinib in other solid tumors.

In the field of colorectal cancer treatment, several previous clinical studies have explored the anti-tumor efficacy of apatinib monotherapy. In a phase-II study, 26 patients with colon or rectum adenocarcinoma were treated with apatinib at a daily dose of 500 mg, in a third-line or higher setting, and the median PFS was 3.9 months (95% CI: 2.1–5.9 months), and the median OS was 7.9 months (95% CI: 4.6–10.1+ months). The incidence rates of grade 3 to 4 hypertension, hand-foot syndrome, proteinuria, and diarrhea were 76.92%, 11.54%, 73.08%, and 23.08%, respectively (11). In another study investigating the efficacy of apatinib monotherapy as a third- or subsequent-line treatment for colorectal cancer, 500 mg of apatinib was administered once daily, and the ORR was 8.3% (4/48), the DCR reached 68.8% (33/48), and the median PFS and OS were 4.8 months (95% CI: 3.653–5.887 months) and 9.1 months (95% CI: 5.155–13.045 months), respectively. The most prevalent grade 3–4 AEs were hypertension (12.5%), hand-foot syndrome (10.4%), thrombocytopenia (10.4%), and proteinuria (8.3%) (12). Given the treatment-related side effects, we used a low dose (250 mg) of apatinib in our study. By comparing the results of our study with those of the above 2 studies, we found that the overall efficacy of a combination regimen of low-dose apatinib and 5-FU was superior to apatinib monotherapy for mCRC treatment. Additionally, the incidence of grade 3–4 AEs was lower in our study than the other 2 studies.

Previous studies have shown that apatinib in combination

**Table 3** Overview of adverse events

| Event | Patients (N=16) | | | |
|---|---|---|---|---|
| | Any grade | Grade 1 | Grade 2 | Grade 3 |
| Hand-foot syndrome, no. (%) | 9 (56.25) | 2 (12.50) | 4 (25.00) | 3 (18.75) |
| Proteinuria, no. (%) | 6 (37.50) | 2 (12.50) | 2 (12.50) | 2 (12.50) |
| Hypertension, no. (%) | 6 (37.50) | 2 (12.50) | 2 (12.50) | 2 (12.50) |
| Hemorrhage, no. (%) | 3 (18.75) | 3 (18.75) | 0 | 0 |
| Abdominal pain, no. (%) | 3 (18.75) | 1 (6.25) | 2 (12.50) | 0 |
| Vomiting, no. (%) | 1 (6.25) | 1 (6.25) | 0 | 0 |
| Nausea, no. (%) | 2 (12.50) | 0 | 2 (12.50) | 0 |

with chemotherapeutics exhibits a better anti-cancer effect than chemotherapy alone; for example, Li *et al.* found that an apatinib plus capecitabine group had longer PFS and a higher ORR and DCR in treating advanced triple-negative breast cancer than a capecitabine alone group (13). Further, a meta-analysis study showed that compared to S-1 alone, the combination of apatinib with S-1 significantly improved patients' PR rate, ORR, and DCR. In the studies included in the meta-analysis, at least 500 mg of apatinib was administered daily. However, the group receiving the combined therapy had higher rates of hand-foot syndrome, hypertension, albuminuria, and hemoglobin reduction (14). Based on the information presented above, it is reasonable to conclude that apatinib in combination with chemotherapy is superior to apatinib or chemotherapy alone in treating advanced cancers. Additionally, the dose of apatinib should be controlled to minimize the incidence of severe AEs.

The excellent anti-tumor efficacy of the combination regimen in our study may be associated with multiple anti-tumor mechanisms of apatinib and the cytotoxicity of 5-FU. First, apatinib was shown to inhibit the Raf/MEK/ERK, p38-MAPK, and PI3K/AKT/mTOR signaling pathways by suppressing VEGFR2 to prevent endothelial cell growth and migration, thereby block the tumor angiogenesis (15-17). Second, various studies have shown that apatinib possesses the properties of inhibiting proliferation and inducing the apoptosis of tumor cells (18,19). Additionally, apatinib has been shown to have inhibitory effects on cell migration and invasion (20). Thus, apatinib acts on tumor cells directly in addition to the anti-angiogenic mechanism. Third, apatinib enhances the sensitivity of chemotherapeutics; for example, Wei *et al.* demonstrated that apatinib sensitized esophageal cancer to cisplatin via the Akt/β-catenin pathway (21).

Despite the encouraging results of our study, its limitations should not be ignored. The small sample size and the lack of a control group inevitably led to a statistical bias. Thus, randomized controlled trials with a larger sample size need to be conducted to validate our findings in the future.

## Conclusions

The present study suggested that apatinib in combination with 5-FU is an efficient and safe third- or subsequent-line treatment option for patients with mCRC, but further studies with larger sample sizes and control groups are required to confirm our results. The therapeutic mechanism of this combination regimen may be associated with the synergistic anti-tumor action in addition to the respective anti-tumor effects of apatinib and chemotherapy drugs. However, the exact mechanisms related to the efficacy of apatinib combined with 5-FU in the treatment of mCRC need to be further explored.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the TREND reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-77/rc

*Data Sharing Statement:* Available at https://atm.amegroups.com/article/view/10.21037/atm-22-77/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-77/coif). All authors report that the study protocol was supported by the Jiangsu Hengrui Pharmaceutical Group Co., Ltd. The authors have no other 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). All patients provided written informed consent before entry to the study. This study was approved by the institutional ethics committee of Hubei Cancer Hospital (No. LLHBCH2017KY-005).



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**Cite this article as:** Chen R, Yang L, Hu S, Yin Z, Nie Y, Xu H, Zhong Y, Zhu Y, Liang X, Xu H. Apatinib plus 5-fluorouracil as a third or subsequent-line treatment option for metastatic colorectal cancer: a phase-II, single-arm, prospective study. Ann Transl Med 2022;10(2):100. doi: 10.21037/atm-22-77

 