Original Article

Efficacy and safety of low-dose apatinib plus S-1 versus regorafenib and fruquintinib for refractory metastatic colorectal cancer: a retrospective cohort study

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Background: At present, regorafenib and fruquintinib are the standard regimens for refractory metastatic colorectal cancer patients in China, but both options have limited efficacy. The aim of this study was to investigate the efficacy and safety of low-dose apatinib plus S-1 compared with regorafenib and fruquintinib in patients with metastatic colorectal cancer (mCRC) refractory to standard therapies.

Methods: The records of 114 patients with refractory mCRC in our center from April 2016 to September 2020 were retrospectively reviewed. Among these patients, 43 received apatinib 250 mg/day combined with S-1, 36 received regorafenib starting at 80 mg/day with weekly escalation, and 35 received fruquintinib 5 mg/day orally. Patients received radiographic examination every 1.5–2 months during the treatment period, progression-free survival time and overall survival time were analyzed and recorded.

Results: The baseline clinical characteristics of the patients were broadly similar among the three groups. The median progression-free survival (mPFS) was 3.9 months [95% confidence interval (CI): 2.5–5.3] in the apatinib plus S-1 group, 3.1 months (95% CI: 1.9–4.2) in the fruquintinib group, and 2.4 months (95% CI: 2.1–2.7) in the regorafenib group, the mPFS of apatinib plus S-1 was significantly longer than that of regorafenib (HR =0.49, P=0.003) and fruquintinib (HR =0.60, P=0.048). The median overall survival (OS) was 8.2 months (95% CI: 5.4–11.0) in the apatinib plus S-1 group, 7.8 months (95% CI: 5.3–10.3) in the fruquintinib group, and 7.5 months (95% CI: 4.2–10.7) in the regorafenib group, which was comparable among the 3 groups. There was no statistical difference in disease control rate (DCR) among the three groups. Patients in the apatinib plus S-1 group had a higher incidence of hematological toxicity including anemia (62.8%), neutropenia (30.2%), and thrombocytopenia (39.5%), and the hand-foot skin reaction (58.3%) was more prevalent in the regorafenib group, while the adverse reaction of hypertension (45.7%) in the fruquintinib group was very significant.

Conclusions: Low-dose apatinib plus S-1 prolonged PFS compared with regorafenib and fruquintinib, and is a potential alternative regimen for the treatment of refractory mCRC with tolerable and controlled toxicity.

Keywords: Apatinib; S-1; regorafenib; fruquintinib; metastatic colorectal cancer (mCRC)

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Introduction

Colorectal cancer (CRC) is the fifth most common cancer and one of the leading causes of cancer-related death in China (1). The 5-year survival rate for patients with CRC ranges from 90% for patients in the localized stages to 14% in the advanced stages (2). The most common cause of death in CRC patients is distant metastasis. In China, about 40% of patients present with stage IV at the time of initial diagnosis (3).

The first- and second-line therapy for metastatic colorectal cancer (mCRC) comprise a combination of cytotoxic drugs including oxaliplatin, fluorouracil, and irinotecan, and molecular targeted drugs such as bevacizumab, cetuximab, aflibercept, and panitumumab. The median survival time for advanced CRC has now reached 30 months by rational drug distribution (4). Currently, the drugs approved for third-line treatment of mCRC in China include regorafenib, fruquintinib, and TAS-102 (5-8). In China, regorafenib and fruquintinib are commonly used as third-line treatments, but these two regimens have limited efficacy.

Apatinib is a small molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2 (VEGFR2) that selectively binds to and inhibits VEGFR2, blocking downstream signaling pathways and inhibiting tumor growth (9). Previous studies have demonstrated that apatinib has good antitumor activities and controllable toxicity in several kinds of malignant tumors, including gastric, breast, and non-small cell lung cancer (10-13). As a derivative of fluorouracil (5-FU), S-1 comprises tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (OXO) (14). Due to its broad-spectrum anti-tumor effect, S-1 has been approved for the treatment of gastric cancer and pancreatic cancer, and has been widely used in the treatment of several solid tumors, including lung cancer, nasopharyngeal cancer, cervical cancer, and CRC (15-19).

The combined therapy of fluorouracil and anti-vascular therapy has demonstrated synergistic efficacy and improved antitumor activities in metastatic colorectal cancer, while the toxicity of the combination regimen were considered to be tolerated in the treatment of other cancer types (20-22). Although apatinib and S-1, respectively, are used in the treatment of advanced CRC, the efficacy and safety of their combination remain unclear. The aim of the study was to investigate the efficacy and safety of apatinib plus S-1 compared with regorafenib and fruquintinib in patients with refractory advanced CRC. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-285/rc).

Methods

Study design and patients

We retrospectively collected the clinical data of patients with mCRC who received apatinib plus S-1, regorafenib, or fruquintinib at Department of Digestive System Oncology, Tongji Hospital of Huazhong University of Science and Technology, from April 2016 to September 2020 and whose clinical data were complete. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20201221), and the requirement of informed consent was waived by the Ethics Committee due to the observational retrospective design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The inclusion criteria were as follows: histologically confirmed colorectal adenocarcinoma; refractory or intolerant to at least 2 lines of chemotherapy, including fluoropyrimidine, oxaliplatin, and irinotecan, regardless of bevacizumab or cetuximab; treatment with apatinib plus S-1, regorafenib, or fruquintinib from April 2016 to September 2020; efficacy evaluation after medication conducted at least once.

Study procedures

Apatinib plus S-1 regimen consisted of apatinib 250 mg orally per day and S-1 40 mg/m^2 of body surface area, administered orally twice a day on days 1–14 in a 21-day cycle. Patients were treated with regorafenib in a dose-escalation manner, starting with 80 mg/day orally with weekly escalation, increasing by 40 mg/week to the standard dose of 160 mg/day for 21 days over a 28-day treatment cycle, if no significant drug-related adverse events (AEs) occurred. Patients in the fruquintinib group were administered fruquintinib 5 mg/day orally for 21 days over a 28-day treatment cycle. All cases received the best supportive care. Imaging examinations were performed every 1.5–2 months to assess tumor response, and patients after disease progression were followed up by telephone every 2 months until death.

Data collected included demographics, treatment details,

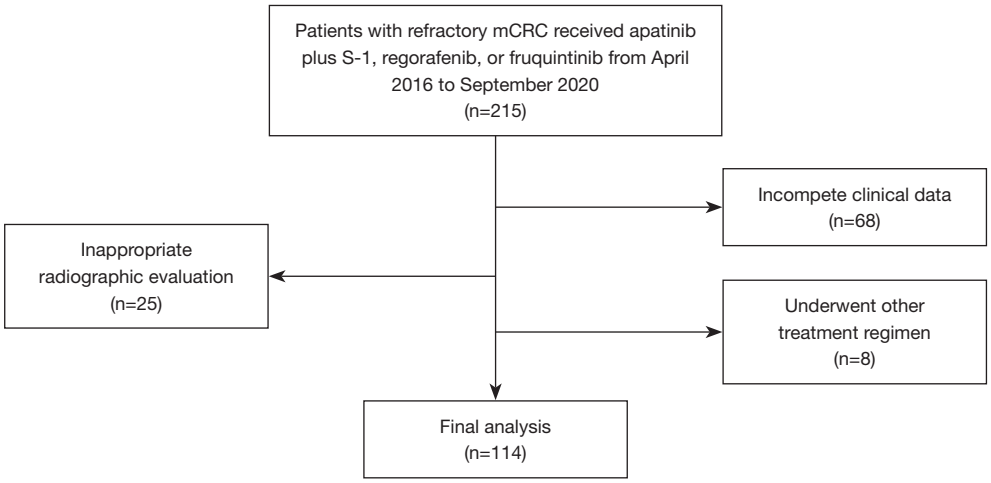

Figure 1 Patient enrollment and exclusion process.

clinical outcomes, and treatment-related toxicities.

Clinical outcomes

Efficacy endpoints included progression-free survival (PFS; defined as the time from study treatment initiation to disease progression), overall survival (OS; defined as the time from treatment initiation until death), objective response rate (ORR; defined as the proportion of patients with complete or partial response), disease control rate (DCR; defined as the proportion of patients with complete or partial response, or stable disease (SD) recorded ≥8 weeks after study treatment initiation). Tumor response was assessed by investigators using Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST; version 1.1). The AEs were evaluated using the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE; version 4.03).

Statistical methods

Kaplan-Meier curves were used to estimate the PFS and OS. Log-rank test was used to compare PFS and OS among the treatment groups. Hazard ratio (HR) and corresponding 95% confidence interval (CI) was determined by Cox proportional hazards model. The chi-square test was used to compare the constituent ratio among the three groups. Multivariate analysis was performed to control for confounding factors. The lost follow-ups were treated as censored cases. If the missing data was unavailable, we analyzed the existing data and supposed the missing data as random missing. Statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA), and 2-sided $P<0.05$ was considered statistically significant. Kaplan-Meier survival curves were generated using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

Patients

Of the 215 cases screened, a total of 114 cases (71 males and 43 females) were included in the final analysis, while the rest cases were excluded due to incomplete clinical data, inappropriate radiographic evaluation, or other treatment regimens were performed. Patient enrollment and exclusion process was shown in *Figure 1*. The median age of all cases was 54 years (range, 25–89 years). A total of 43 cases received apatinib plus S-1, 36 cases received regorafenib, and 35 cases received fruquintinib. Patients' demographics and baseline characteristics are depicted in *Table 1*. All cases had been previously treated with oxaliplatin, fluoropyrimidine, and irinotecan. More than half of the cases had liver metastasis before administration, including 60.5% in the apatinib plus S-1 group, 72.2% in the regorafenib group, and 71.4% in the fruquintinib group. Approximately 30% of cases had not been tested for RAS/BRAF status, and the proportion in the apatinib plus S-1 group was 46.5%. The proportion of cases who had previously received VEGF inhibitors or epidermal growth-factor receptor (EGFR) inhibitors was similar in the fruquintinib and the regorafenib groups, but the proportion was lower in

Table 1 Clinical characteristics of 114 patients with refractory mCRC

Characteristics	Apatinib + S1 (n=43)	Regorafenib (n=36)	Fruquintinib (n=35)	P value
Age (years)				0.567
Median [range]	52 [25–76]	58.5 [27–80]	55 [34–89]	
>70 years, n (%)	3 (7.0)	4 (11.1)	5 (14.3)	
≤70 years, n (%)	40 (93.0)	32 (88.9)	30 (85.7)	
Gender (male), n (%)	30 (69.8)	21 (58.3)	20 (57.1)	0.436
ECOG PS, n (%)				0.779
0–1	38 (88.4)	31 (86.1)	32 (91.4)	
2	5 (11.6)	5 (13.9)	3 (8.6)	
Primary location, n (%)				0.240
Right	16 (37.2)	12 (33.3)	7 (20.0)	
Left	27 (62.8)	24 (66.7)	28 (80.0)	
With liver metastasis, n (%)	26 (60.5)	26 (72.2)	25 (71.4)	0.453
No. of metastatic organs >2, n (%)	26 (60.5)	24 (66.7)	25 (71.4)	0.592
CEA >200, n (%)	9 (20.9)	11 (30.6)	7 (20.0)	0.501
RAS/BRAF status, n (%)				0.014
Wild-type	8 (18.6)	11 (30.6)	10 (28.6)	
RAS mutant	13 (30.2)	18 (50.0)	18 (51.4)	
BRAF mutant	2 (4.7)	3 (8.3)	1 (2.9)	
Unknow	20 (46.5)	4 (11.1)	6 (17.1)	
MMR status, n (%)				0.194
pMMR	16 (37.2)	21 (58.3)	21 (60.0)	
dMMR	1 (2.3)	0	1 (2.9)	
Unknow	26 (60.5)	15 (41.7)	13 (37.1)	
Prior targeted agents, n (%)				0.000
Cetuximab	4 (9.3)	3 (8.3)	2 (5.7)	
Bevacizumab	10 (23.3)	21 (58.3)	21 (60.0)	
Both	0 ()	1 (2.8)	3 (8.6)	
Without	29 (67.4)	11 (30.6)	9 (25.7)	
Time of prior antitumor therapy ≥18 months, n (%)	13 (30.2)	13 (36.1)	14 (40.0)	0.660
Therapeutic line				0.590
3rd	37 (86.0)	29 (80.6)	27 (77.1)	
4th and above	6 (14.0)	7 (19.4)	8 (22.9)	

mCRC, metastatic colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; RAS, RAS gene; BRAF, BRAF gene; pMMR, proficient mismatch repair; dMMR, mismatch repair deficient.

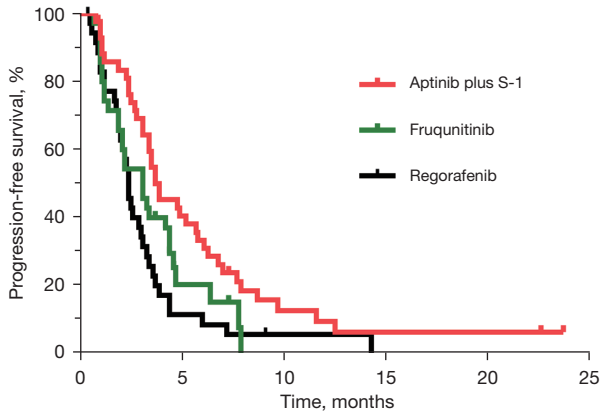

Figure 2 Kaplan-Meier estimates for progression-free survival in patients with metastatic colorectal cancer receiving apatinib plus S-1, fruquintinib and regorafenib.

the apatinib plus S-1 group. Cases with left hemicolon and rectum cancer sites were dominant in all 3 groups, especially 80.0% in the fruquintinib group. Only 2 cases had mismatch repair deficient (dMMR) tumor, 1 in the apatinib plus S-1 group and the other in the regorafenib group. Only 30.2% of cases in the apatinib plus S-1 group had received prior antitumor therapy for more than 18 months, compared with 40.0% in the fruquintinib group. In general, baseline comparisons among the three groups showed differences only in RAS/BRAF status and prior use of targeted agents (*Table 1*).

Efficacy

During the median follow-up time of 12.5 months (95% CI: 8.7–16.2), 88.6% of cases developed disease progression and 64.0% of cases died. Patients in the apatinib plus S-1 group had significantly longer PFS compared with those in the regorafenib group (HR =0.49, 95% CI: 0.31–0.79, P=0.003), and the fruquintinib group (HR =0.60, 95% CI: 0.36–0.99, P=0.048). Median PFS was 3.9 months (95% CI: 2.5–5.3) in the apatinib plus S-1 group, 3.1 months (95% CI: 1.9–4.2) in the fruquintinib group, and 2.4 months (95% CI: 2.1-2.7) in the regorafenib group. The Kaplan-Meier survival curve of PFS is shown in *Figure 2*. The PFS at 16 weeks was 48.8% in the apatinib plus S-1 group, 37.1% in the fruquintinib group, and 19.4% in the regorafenib group. Multivariate analysis revealed that age <70 years (HR =2.4, 95%CI: 1.2-4.8, P=0.015), treatment with regorafenib (HR =2.1, 95% CI: 1.3–3.6, P=0.005), fourth-line and above treatment (HR =2.3, 95% CI: 1.3–3.9, P=0.000), and Eastern Cooperative Oncology Group performance status 2 (ECOG PS2; HR =2.1, 95% CI: 1.1–4.0, P=0.037) were independent predictors of decreased PFS (*Table 2*).

Median OS was 8.2 months (95% CI: 5.4–11.0) in the apatinib plus S-1 group, 7.8 months (95% CI: 5.3–10.3) in the fruquintinib group, and 7.5 months (95% CI: 4.2–10.7) in the regorafenib group, which was comparable among the 3 groups. The Kaplan-Meier survival curve of OS is shown in *Figure 3*. Multivariate analysis revealed that age <70 years (HR =2.6, 95%CI: 1.1-6.5, P=0.046), ECOG PS2 (HR =10.9, 95% CI: 4.8–24.5, P=0.000), fourth-line and above treatment (HR =2.7, 95% CI: 1.4–5.2, P=0.002), and more than two organs of metastasis (HR =2.1, 95% CI: 1.2–3.7, P=0.011) were independent predictors of decreased OS (*Table 2*).

Partial response (PR) was achieved by 1 case in the apatinib plus S-1 group, resulting in a 2.3% ORR, and no cases had PR in the regorafenib and the fruquintinib group. The DCR was 36 of 43 (83.7%) cases in the apatinib plus S-1 group, 25 of 35 (71.4%) cases in the fruquintinib group and 24 of 36 (66.7%) cases in the regorafenib group, and no significant difference was shown among the 3 groups. Additionally, 14 cases (32.6%) in the apatinib plus S-1 group experienced disease control for more than 6 months, compared with 4 cases (11.4%) in the fruquintinib group and 3 cases (8.3%) in the regorafenib group.

Safety

All patients in the apatinib plus S-1 group received the full-dose of apatinib and S-1, and there were no drug-related adverse effects necessitating drug discontinuation or dose reduction. Overall, the incidence of hematological toxicities was higher in the apatinib plus S-1 group. There was 1 case grade 3 neutropenia which developed after treatment; the patient continued on to complete the treatment after granulocyte colony-stimulating factor (G-CSF) support; more than 60% of cases experienced anemia during the course of treatment, but all had grade 1–2. Only 16 cases (44.4%) reached the standard dose of 160 mg in the regorafenib group, while 2 cases were unable to escalate the dose due to adverse effects and remained at 80 mg. The major dose-limiting toxicity in the regorafenib group was hand-foot-skin reaction (HFSR), with more than half of cases reporting various grades of HFSR, and 13.9% of patients with grade 3–4. The predominant adverse reaction in the fruquintinib was hypertension, which occurred in nearly half of the patients and 14.3% of cases developed grade 3 or above hypertension. The HFSR in the

Table 2 Multivariate Cox regression analyses for PFS and OS

Variables	PFS		OS	
	AHR (95% CI)	P value	AHR (95% CI)	P value
Age				
≥70 years	1		1	
<70 years	2.374 (1.182–4.767)	0.015	2.573 (1.017–6.509)	0.046
ECOG PS				
0–1	1		1	
2	2.051 (1.044–4.027)	0.037	10.858 (4.802–24.548)	0.000
Primary location				
Left	1		1	
Right	1.086 (0.688–1.715)	0.723	1.151 (0.667–2.020)	0.598
Liver metastasis				
With	1		1	
Without	0.858 (0.535–1.377)	0.525	0.570 (0.318–1.022)	0.059
CEA >200 ng/mL				
With	1		1	
Without	0.721 (0.416–1.250)	0.244	1.141 (0.613–2.123)	0.678
Number of metastasis organs				
≤2	1		1	
>2	1.433 (0.911–2.256)	0.120	2.094 (1.186–3.700)	0.011
RAS/BRAF status				
Wild-type	1		1	
RAS mutant	1.361 (0.718–2.579)	0.345	1.594 (0.727–3.496)	0.245
BRAF mutant	1.447 (0.708–2.958)	0.311	2.024 (0.806–5.082)	0.133
Unknow	1.197 (0.430–3.339)	0.730	1.326 (0.377–4.663)	0.660
Prior targeted agents				
With	1		1	
Without	0.992 (0.375–2.628)	0.987	2.288 (0.606–8.644)	0.222
Prior antiangiogenic therapy				
With	1		1	
Without	1.133 (0.462–2.776)	0.785	0.853 (0.260–2.800)	0.793
Time of prior anti-tumor therapy				
≥18 months	1		1	
<18 months	1.378 (0.861–2.204)	0.181	1.865 (1.053–3.304)	0.033
Therapeutic line				
3rd	1		1	
4th or above	2.294 (1.336–3.936)	0.000	2.741 (1.448–5.190)	0.002

Table 2 (*continued*)

Table 2 (*continued*)

Variables	PFS		OS	
	AHR (95% CI)	P value	AHR (95% CI)	P value
Therapeutic regiment				
Apatinib plus S-1	1		1	
Regorafenib	2.121 (1.250–3.599)	0.005	0.873 (0.437–1.743)	0.700
Fruquintinib	1.437 (0.813–2.540)	0.212	0.645 (0.331–1.254)	0.196

AHR, adjusted hazard ratio; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen.

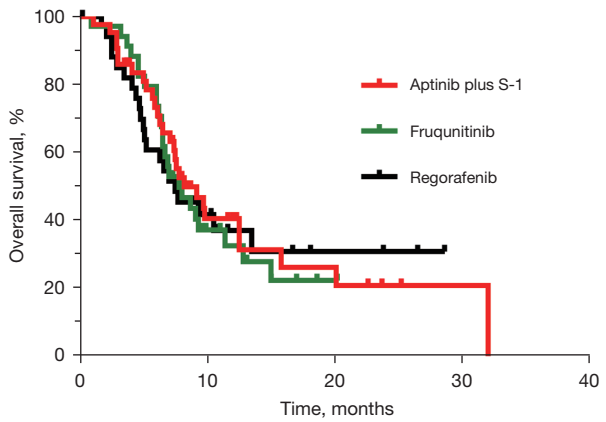

Figure 3 Kaplan-Meier estimates for overall survival in patients with metastatic colorectal cancer receiving apatinib plus S-1, fruquintinib and regorafenib.

fruquintinib group was prominent, 40% of the patients had HFSR, of which about 8.6% reached grade 3 or above. In total, 18 cases (51.4%) in the fruquintinib group underwent dose reduction due to adverse reactions. The AEs are summarized in *Table 3*.

Discussion

In this study, it was shown that the combination of apatinib and S-1 significantly improved PFS compared to the combination of apatinib with either regorafenib and fruquintinib in patients with chemo-refractory mCRC, and there was a trend towards longer OS, but it did not reach statistical significance. In this study, mPFS of patients in the regorafenib and the fruquintinib groups were 2.4 and 3.1 months, respectively, which was consistent with 1.9 months in the CORRECT trial and 3.7 months in the FRESCO trial (5,6). Considering the short absolute PFS benefit of third-line treatments in previous clinical trials, we interpreted that, compared with the regorafenib group, the absolute 1.5-month PFS improvement observed in the apatinib plus S-1 group was clinically meaningful in the salvage treatment of advanced CRC.

In a prospective open-label, single-arm, phase II study, patients with mCRC who had received at least 2 prior regimens of standard therapies were treated with apatinib in a daily dose of 500 mg, the median PFS was 3.9 months and median OS was 7.9 months (23). The study concluded promising efficiency for patients with refractory CRC, especially in patients with PS 0–1 and without liver metastasis. As a novel oral 5-FU derivative, S-1 has been widely used in the treatment of gastrointestinal malignancies; S-1 has been confirmed to be as effective as 5-FU and capecitabine for patients with advanced CRC (24). Apatinib is a highly selective tyrosine kinase inhibitor of VEGF signaling inhibitor that potently suppresses the kinase activities of VEGFR-2, c-kit, c-src, and PDGRFb, effectively inhibits tumor proliferation and migration, reduces vascular density, and exerts potent antitumor activity. Combined with chemotherapy, targeting anti-angiogenic drugs play a synergistic anti-tumor role via inhibiting neovascularization, inducing vascular normalization, increasing tumor oxygenation, and enhancing the delivery of cytotoxic drugs (25). An *in vitro* study showed that the combined use of apatinib and 5-FU displayed a synergistic inhibition effect on the growth of Ls174t CRC xenograft tumors (9). Besides, low-dose apatinib combined with S-1 has been shown to be effective in the salvage treatment of gastric cancer, lung cancer, and nasopharyngeal cancer (20,26,27).

In a randomized, phase 2 trial named C-TASK FORCE, TAS1-2 combined with bevacizumab showed significant improvement in PFS and tolerable toxicity in patients with refractory CRC (21). Similarly, in a phase II single-

Table 3 Adverse events

Variables	Apatinib plus S-1 (n=43)		Regorafenib (n=36)		Fruquintinib (n=35)	
	All grades	Grade 3–4	All Grades	Grade 3–4	All Grades	Grade 3–4
Clinical adverse event, n (%)						
Fatigue	13 (30.2)	1 (2.3)	17 (47.2)	5 (13.9)	6 (17.1)	1 (2.9)
Hypertension	11 (25.6)	4 (9.3)	8 (22.2)	3 (8.3)	16 (45.7)	5 (14.3)
Loss of appetite	14 (32.6)	0	10 (27.8)	2 (5.6)	7 (20.0)	0
Oral mucositis	4 (9.3)	0	2 (5.6)	0	1 (2.9)	0
HFSR	12 (27.9)	3 (7.0)	21 (58.3)	5 (13.9)	14 (40.0)	3 (8.6)
Bleeding	1 (2.3)	0	2 (5.6)	0	1 (2.9)	0
Laboratory abnormalities, n (%)						
Thrombocytopenia	17 (39.5)	0	10 (27.8)	1 (2.8)	7 (20.0)	0
Anemia	27 (62.8)	0	20 (55.6)	2 (5.6)	11 (31.4)	0
Neutropenia	13 (30.2)	1 (2.3)	3 (8.3)	0	2 (5.7)	1 (2.9)
ALT elevation	10 (23.3)	0	8 (22.2)	0	5 (14.3)	0
Proteinuria	12 (27.9)	0	12 (33.3)	0	11 (31.4)	0

HFSR, hand-foot-skin reaction; ALT, alanine transaminase.

arm study using low-dose apatinib combined with S-1 in refractory mCRC, the mPFS and mOS were 7.9 and 12.9 months, respectively (28). These studies suggested that the combination of single-drug chemotherapy with anti-angiogenesis therapy can bring survival benefits to patients in the salvage treatment of mCRC.

Before 2018, regorafenib and fruquintinib had not been covered by medical insurance in mainland China and their costs were prohibitive to financially disadvantaged patients, while the regimen of apatinib plus S-1 was readily accepted by those patients who could afford them. As a result, fewer patients in the apatinib plus S-1 group underwent RAS/BRAF testing, as these patients could not afford the expensive cost of targeted drugs, including bevacizumab and cetuximab. Similarly, more than two-thirds of patients in this group did not receive anti-VEGF or anti-EGFR drugs in first- or second-line treatment and the proportion was significantly higher than that of the fruquintinib and the regorafenib group. Targeted therapy has been confirmed to reduce the risk of progression in patients with advanced CRC (8), therefore, the time of prior antitumor therapy in the apatinib plus S-1 group was the shortest among the 3 groups. Subgroup analysis in the CONCUR trial showed that patients who were not exposed to a targeted treatment before seemed to gain a greater benefit than those who had received at least 1 previous targeted therapy (8), so the PFS benefit of apatinib plus S-1 in this study may partly contribute to simple prior-line treatment. The result of multivariate regression analysis revealed that patients having received more than 3 lines of previous treatments was an independent predictor for PFS shortening, and more than half of the patients were treated with fruquintinib as fourth-line or later therapy, so after controlling for confounding variables, there was no significant difference in PFS between the fruquintinib and the apatinib plus S-1 group. However, the PFS benefit of the apatinib plus S-1 group was not affected by the number of previous anticancer therapies compared to the regorafenib group.

In a phase III trial of apatinib in patients with chemo-refractory metastatic gastric cancer, the administration of apatinib 850 mg/day orally was associated with a high incidence of hematological and non-hematological adverse reactions, especially 19.9% of patients had bleeding, and 3.4% patients experienced a grade 3–4 AE of bleeding (10). In general, high-dose apatinib has been poorly tolerated; some clinical studies have revealed that low-dose apatinib is better tolerated (22,29). The dose of apatinib administrated in this study was 250 mg/day, which was much lower than the previous reports. Due to the combination with cytotoxic drugs after multi-line chemotherapy, hematological

toxicities such as anemia, neutropenia, and thrombocytosis were more frequent, but severe adverse reactions were rare. The combinations of apatinib and S-1 was superior to regorafenib and fruquintinib in non-hematological toxicities such as hypertension, proteinuria and HFSR. Only 1 case in the apatinib plus S-1 group developed grade 1 AE of bleeding, which was comparable to the regorafenib and the fruquintinib groups. The results of this study demonstrated that low doses of apatinib combined with S-1 provided potential clinical benefits and the side effects were tolerable.

The study had some limitations. First, this was a retrospective study with a small number of patients from a single-center; second, although all cases were from the same center and had received at least 2 lines of chemotherapy, the baseline characteristics of patients in the 3 groups were not completely comparable; third, some patients who were not evaluated for efficacy after medication were excluded from the final analysis, which may have led to overestimation of efficacy and underestimation of AEs.

In summary, low-dose apatinib combined with S-1 could bring potential clinical benefit to patients with refractory mCRC, and adverse effects were generally tolerated. Therefore, large-scale prospective multicenter randomized clinical trials are expected to validate the results of this study in the future.

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Footnote

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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-22-285/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 approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20201221), and the requirement of informed consent was waived by the Ethics Committee due to the observational retrospective design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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