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Clinical efficacy and safety of apatinib in patients with advanced colorectal cancer as the late-line treatment

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Abstract

There is currently no standard therapeutic regimen available for patients with advanced colorectal cancer in whom the disease continues to progress after 2 or more lines of chemotherapy. The purpose of this study is to investigate the efficacy and safety of apatinib in patients with advanced colorectal cancer for whom at least two lines of prior chemotherapy had failed.

Twenty seven patients with advanced colorectal cancer who had failed at least 2 lines chemotherapy were treated with apatinib (500 mg/day). As a comparison control, 26 advanced colorectal cancer patients with comparable clinical baseline characteristics including age, sex, Eastern Cooperative Oncology Group (ECOG) score, pathological type, carcinoembryonic antigen (CEA) level, tumor location, number and location(s) of metastasis, and previous chemotherapies were subject to observation. Survival analyses were performed via the Kaplan–Meier method. The toxicity were evaluated in all patients this study according to the National Cancer Institute Common Toxicity Criteria 4 (NCI CTC version 4.0).

A total of 53 well-matched patients with advanced colorectal cancer were retrospectively analyzed. The median follow-up time was 6.0 months (2.0–16.0 months). The median PFS was significantly longer for apatinib group than for observation group (2.0 vs. 1.1 months; HR = 3.88; 95% confidence interval [CI], 1.91–7.88; $P < .001$). However, there was no significant difference between the 2 groups for median OS (5.0 vs. 4.0 months; HR = 1.03; 95% CI, 0.56–1.90; $P = .914$). The disease control rate of the apatinib group was significantly better than that of the observation group (70.4% vs 26.9%, $P = .002$). There was no significant difference in the overall remission rate between the 2 groups (3.7% vs 0%, $P = .322$). Advanced colorectal cancer patients with 2 or fewer metastatic sites experienced longer PFS than those with more than 2 sites. High ECOG scores, cancer localization to the right side of colon and lymph node metastasis were associated with increased risk of death and all remained independent factors affecting OS. The most common grade 3/4 treatment-related adverse events were hypertension and hand-foot skin syndrome.

Apatinib treatment for patients with advanced colorectal cancer who had failed chemotherapy achieved better disease control and prolonged PFS relative to untreated controls. The toxicity was manageable.

Abbreviations: CEA = carcinoembryonic antigen, DCR = disease control rate, ECOG = Eastern Cooperative Oncology Group, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, VEGFR-2 = vascular endothelial growth factor receptor 2.

Keywords: advanced colorectal cancer, apatinib, clinical efficacy

1. Introduction

Colorectal cancer is the 5th most common cause of cancer morbidity and mortality in China, with 37,630 new cases and 11,110 deaths associated with this disease each year.[1] The combination of oxaliplatin or irinotecan-based chemotherapy with bevacizumab, panitumumab, or cetuximab can significantly improve a patient's prognosis, and is the standard 1st-line treatment for advanced colorectal cancer.[2–4] However, at present, there is still no standard therapeutic regimen available for the patients who fail 2nd-line treatments of advanced colorectal cancer. As such, available treatment options are insufficient to meet with current medical needs.

Angiogenesis is a fundamental aspect of tumor growth and metastasis.[5,6] The specific binding of vascular endothelial growth factor (VEGF) to vascular endothelial growth factor receptor (VEGFR) promotes the proliferation and migration of vascular endothelial cells, increases vascular permeability, induces angiogenesis, and additionally drives tumor cell proliferation, infiltration, and metastasis.[7,8] Therefore, anti-angiogenic therapy has become a prior choice to conflict with cancers. Antiangiogenic drugs play anti-tumor effect by blocking the specific blinding of VEGF and VEGFR. Indeed, antiangiogenic agents enhanced innate immune cell infiltration and normalizes tumor vasculatures, which provide a perfect tumor microenvironment for the combined drugs activation.[9]

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Bevacizumab, one of the most successful anti-angiogenic drugs, has been demonstrated to delay tumor growth and metastasis through blocking the binding of VEGF-A (a VEGF subtype) and VEGFR-2, and it is 1st-line and 2nd-line therapy drug.[2,10,11]

Despite these therapeutic advances, after multiline treatment patients often experience treatment failure due to the development of drug resistance. Apatinib mesylate is a micromolecular VEGFR-2 inhibitor, that highly selectively binds to and strongly inhibits VEGFR-2, and thereby achieve anti-tumor effects.[12,13] Apatinib can also reverse multidrug resistance (MDR) in cancers mediated by MDR protein 1 (ABCB1), MDR-associated protein 1 (MARP1), and breast cancer resistance protein (BCRP).[14,15] In a number of previous phase I clinical trials, apatinib has exhibited desirable efficacy against multiple solid tumors (including gastric cancer and colorectal cancer). Phase II and III clinical trials of apatinib have established that it can significantly prolong progression-free survival (PFS) and overall survival (OS) in patients with advanced gastric cancer. Apatinib is a safe and effective micromolecular anti-angiogenic targeted drug.[16,17] Tian et al[15] have previously reported that, in colorectal cancer, apatinib mesylate showed good anti-tumor activity both in vitro and in vivo. At present, only a few retrospective studies on small-sample-size cases have similarly suggested apatinib might be effective for patients with advanced colorectal cancer.[18] Evidences that apatinib may offer a survival benefit in patients with advanced colorectal cancer who had failed multiple-line chemotherapies are extremely limited. Therefore, we carried out this study to give more clinical evidences of the treatment of apatinib in patients with advanced colorectal cancer.

2. Materials and methods

2.1. Ethics

This study was approved by the Medical Ethical Committee of the Affiliated Tumor Hospital of Guangxi Medical University. The written informed consent was obtained from all patients.

2.2. Patients and grouping

From January 2015 to January 2018, all patients with a confirmed diagnosis of advanced colorectal cancer at the Affiliated Tumor Hospital of Guangxi Medical University were enrolled in the present study. Inclusion criteria are as follows:

Colorectal cancer confirmed by histopathology,

Age from 18 to 75 years,

Patients with advanced or metastatic colorectal cancer who had failed 2nd-line or subsequent chemotherapy,

Treatment failure was defined as the occurrence of intolerable adverse reactions or disease progression during chemotherapy,

At least 1 measurable lesion according to response evaluation criteria in solid tumors (RECIST) Version 1.1,

ECOG score of 0–2,

No serious heart, liver or kidney insufficiency,

All patients signed informed consent documents before treatment.

Exclusion criteria are as follows:

Known apatinib allergy,

Blood pressure of drug-therapy-receiving patients that cannot be maintained below 140/90 mm Hg,

Hemorrhagic tendency,

Current or recent receipt of thrombolysis or anticoagulant therapy,

Patients who have recently undergone surgery and whose wounds have not healed.

2.3. Treatment regimen

All patients in the apatinib group were given apatinib, 500 mg qd, po half an hour after a meal, with 1 treatment cycle lasting 4 weeks. During each treatment cycle, not more than 2 drug withdrawals were allowed, with an accumulated total of not more than 14 days. During each treatment cycle, the dose of apatinib could be lowered by 250 mg qd due to any related side effects. The patients in the observation group did not receive any treatment or were only given symptomatic supportive treatment.

2.4. Efficacy and safety evaluation

After 4-week administration, an efficacy evaluation was performed according to RECIST version 1.1, with efficacy outcomes divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) groups. The overall response rate (ORR) = CR + PR, the disease control rate (DCR) = CR + PR + SD. Adverse events were evaluated according to the NCI CTC 4.0 in degrees ranging from 0 to 4.

2.5. Follow-up

Progression-free survival (PFS) is defined as the time interval from the start of apatinib treatment until tumor progression or death for any reason. Overall survival (OS) is defined as the time interval from the start of apatinib treatment to death from any cause. Follow-ups with all patients were conducted every 4 weeks. Serum CEA tests and abdominal contrast-enhanced CT/MRI were performed as appropriate according to standard procedures. Relevant information could be obtained through follow-up methods including telephone contact, as well as outpatient or inpatient medical records.

2.6. Statistical analysis

All data were analyzed using the SPSS 21.0 statistical software package. The categorical data were analyzed using the χ^2 test. The survival analysis and single factor analysis were performed using the Kaplan–Meier method and the log-rank test. During the risk ratio (HR) evaluation, the Cox risk regression model was employed. A $P < .05$ served as the threshold for statistical significance.

3. Results

3.1. Clinical characteristics

A total of 53 patients with advanced colorectal cancer who had failed 2nd-line or subsequent chemotherapy were enrolled in the study. Of these patients, 27 were randomly divided in the apatinib treatment group and 26 in the observation group. The patients in both groups had matched clinical baseline characteristics including age, sex, ECOG score, pathological type, CEA level, tumor location, number and location(s) of metastasis, and previous chemotherapies. The clinical characteristics and treatment factors of all patients are shown in Table 1.

3.2. Efficacy

The median follow-up time was 6.0 months (2.0–16.0 months). As of April 9, 2018, the cancer had progressed in 53 patients and

Table 1

Baseline demographic and clinical characteristics of patients.

Characteristic		N. (%) Apatinib (n = 27)	Observation (n = 26)	*P* Value
Age (years)				
Median age (range)		51.0 (28–89)	58.5 (34–78)	.697
Sex	Men	20 (74.1)	16 (61.5)	
	Women	7 (25.9)	10 (38.5)	.328
ECOG PS	0–1	14 (51.9)	12 (46.2)	
	2	13 (48.1)	14 (53.8)	.678
Smoking	No	13 (48.1)	19 (73.1)	
	Yes	14 (51.9)	7 (26.9)	.064
Drinking	No	12 (44.4)	18 (76.9)	
	Yes	15 (55.6)	8 (23.1)	.069
D-dimer	Normal	9 (33.3)	9 (34.6)	
	Rise	18 (66.7)	17 (65.4)	.922
LDH	Normal	11 (40.7)	9 (34.6)	
	Rise	16 (59.3)	17 (65.4)	.646
Serum ferritin	Normal	9 (33.3)	7 (26.9)	
	Rise	18 (66.7)	19 (73.1)	.611
CEA	Normal	7 (25.9)	6 (23.1)	
	Rise	20 (74.1)	20 (76.9)	.810
AFP	Normal	24 (88.9)	25 (96.2)	
	Rise	3 (11.1)	1 (3.8)	.317
Diagnosis	Colon cancer	16 (59.3)	11 (42.3)	
	Rectal cancer	11 (40.7)	15 (57.7)	.217
Tumor site	Left	19 (70.4)	19 (73.1)	
	Right	8 (29.6)	7 (26.9)	.827
No. of metastatic sites	≤2	14 (51.9)	12 (46.2)	
	>2	13 (48.1)	14 (53.8)	.678
Metastatic organ				
Liver	No	14 (51.9)	10 (38.5)	
	Yes	13 (48.1)	16 (61.5)	.328
Lymph nodes	No	12 (44.4)	12 (46.2)	
	Yes	15 (55.6)	14 (53.8)	.901
Differentiation	Medium-high	24 (88.9)	25 (96.2)	
	Low	3 (11.1)	1 (3.8)	.317
Surgical history	No	8 (29.6)	6 (23.1)	
	Yes	19 (70.4)	20 (76.9)	.589
No. of previous chemotherapy lines	2	17 (63.0)	10 (38.5)	
	≥3	10 (37.0)	16 (61.5)	.074

ECOG = Eastern Cooperative Oncology Group, LDH = Lactate dehydrogenase, CEA = carcinoembryonic antigen.

50 patients had died, including 25 patients in the apatinib group and 25 patients in the observation group, accounting for 94.3% of the total number of analysis events at the end of the total survival period. When compared with the observation group, the median PFS was significantly prolonged in the apatinib group (2.0 months; 95% CI, 1.78–2.22 vs 1.1 months; 95% CI, 0.88–1.32; $P < .001$; HR, 3.88; 95% CI, 1.91–7.88; $P < .001$) (Fig. 1A). However, there was no statistically significant difference in the median OS between the apatinib group and the observation group (5.0 months; 95% CI, 2.80–7.21 vs 4.0 months; 95% CI, 2.77–5.23; $P = .722$; HR, 1.03; 95% CI, 0.56–1.90; $P = .914$) (Fig. 1B).

The objective response rate was 3.7% in the apatin ib group and 0% in the observation group, and this difference between these 2 groups was not statistically significant ($P = .322$). The disease control rate of the apatinib group was significantly ($P = .002$) better than that of the observation group (70.4% VS 26.9%, Table 2).

Initially, the relationship between all clinical baseline variables and survival was investigated via single factor analysis. Those variables for which this analysis yielded a $P < .1$ were incorporated into the Cox risk regression model for multivariate analysis in order to predict the factors affecting survival outcomes. The variables incorporated into this multivariate analysis were ECOG score, number of previously received chemotherapies, number of metastatic sites, tumor site (left and right hemicolon localization), lymph node metastasis, and treatment methods. The results of this regression analysis revealed that advanced colorectal cancer patients with more than 2 sites had a poor PFS, and that apatinib could reduce the risk of disease progression in patients with advanced colorectal cancer. High ECOG scores, right-side colon cancer, and lymph node metastasis were associated with a poor OS (Table 3).

3.3. Safety

In 1 patient in the apatinib group, compound dose was reduced to 250 mg/d due to treatment-related toxicity. Three patients were dosed intermittently with apatinib due to intolerable toxicity; the number of drug withdrawals per cycle was not more than twice, and the total time of drug withdrawal was not more than 14 days. The main reasons for weight loss and intermittent use were

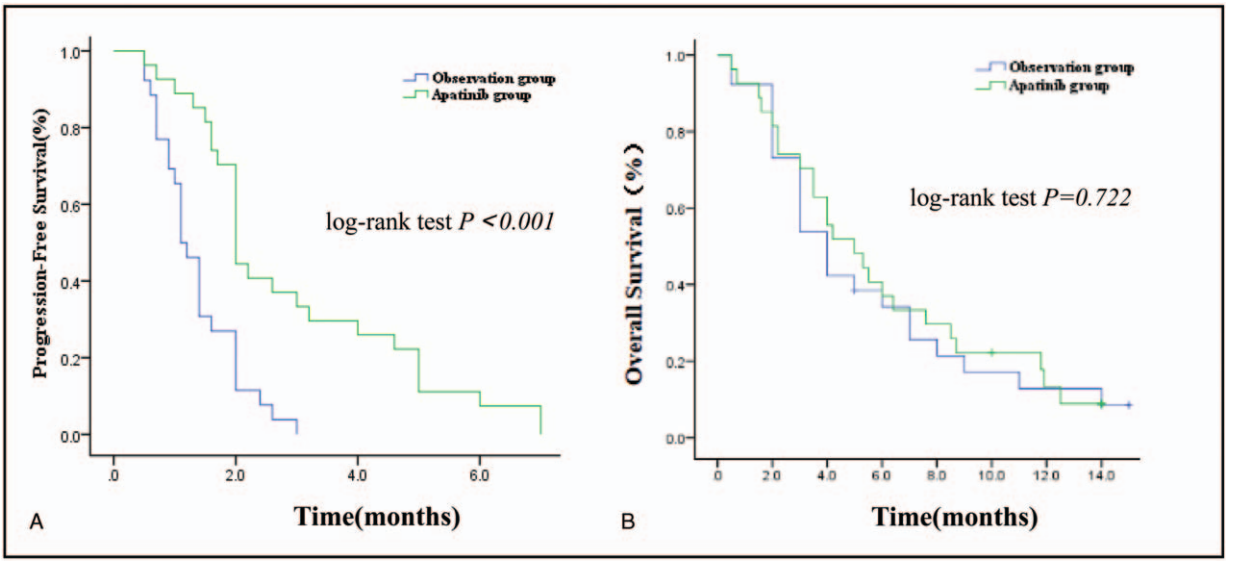

Figure 1. Kaplan–Meier estimates of progression-free survival (PFS) and overall survival (OS). (A)Median PFS was 2.0 months with apatinib compared with 1.1 months with observation (log-rank test $P < .001$). (B)Median OS was 5.0 months with apatinib compared with 4.0 months with observation (log-rank test $P = .722$). PFS = progression-free survival, OS = overall survival.

Table 2

Analysis of efficacy in full analysis set.

Variable	Apatinib (n = 27)	Observation (n = 26)	*P* value
Disease progression or death, No.	27	26	
Median PFS (95% CI), months	2.0 (1.78–2.22)	1.1 (0.88–1.32)	<.001
HR (95% CI)		3.88 (1.91–7.88)	<.001
Death, No.	24	23	
Median OS (95% CI), months	5.0 (2.80–7.21)	4.0 (2.77–5.23)	.722
HR (95% CI)		1.03 (0.56–1.90)	.914
Response (%)			
CR	0 (0%)	0 (0%)	
PR	1 (3.7%)	0 (0%)	
SD	18 (66.7%)	7 (26.9%)	
PD	8 (29.6%)	19 (73.1%)	
ORR (CR+PR)	1 (3.7%)	0 (0%)	.322
DCR (CR+PR+SD)	19 (70.4%)	7 (26.9%)	.002

CI = confidence interval, CR = complete response, DCR = disease control rate, HR = hazard ratio, ORR = overall response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease.

Table 3

Cox regression model of multivariable analysis for overall survival and progression-free survival.

Variables		HR (95% CI)	*P* Value
Progression-free survival			
ECOG PS	0–1 vs 2	0.66 (0.36–1.21)	.177
No. of previous chemotherapy lines	2 vs ≥3	0.54 (0.27–1.03)	.062
No.of metastatic sites	≤2 vs >2	0.18 (0.08–0.38)	.001
Lymph node metastasis	No vs yes	0.65 (0.35–1.21)	.177
Tumor site	Left vs right	0.93 (0.46–1.90)	.846
Treatment strategy	Observation vs apatinib	3.88 (1.91–7.88)	<.001
Overall survival			
ECOG PS	0–1 vs 2	0.43 (0.22–0.81)	.01
No. of previous chemotherapy lines	1–2 vs ≥3	0.70 (0.37–1.36)	0.295
Tumor site	Left vs right	0.38 (0.17–0.87)	.021
No.of metastatic sites	≤2 vs >2	0.97 (0.50–1.85)	.918
Lymph node metastasis	No vs yes	0.26 (0.13–0.52)	<.001
Treatment strategy	Observation vs apatinib	1.03 (0.56–1.90)	.914
		0.66 (0.36–1.21)	.177

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group.

Table 4

Adverse events related to treatment with apatinib.

Adverse events	Apatinib group (n = 27) No.(%)					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 1	Grade 3/4
Leukopenia	1 (3.7)	3 (11.1)	0 (0.0)	1 (3.7)	5 (18.5)	1 (3.7)
Neutropenia	1 (3.7)	4 (14.8)	0 (0.0)	1 (3.7)	5 (18.5)	1 (3.7)
Anemia	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)
Thrombocytopenia	1 (3.7)	0 (0.0)	1 (3.7)	0 (0.0)	2 (7.4)	1 (3.7)
Liver toxicity	2 (7.4)	2 (7.4)	1 (3.7)	0 (0.0)	5 (18.5)	1 (3.7)
Proteinuria	2 (7.4)	4 (14.8)	0 (0.0)	0 (0.0)	6 (22.2)	0 (0.0)
Hand-foot syndrome	1 (3.7)	1 (3.7)	3 (11.1)	0 (0.0)	5 (18.5)	3 (11.1)
Hypertension	0 (0.0)	3 (11.1)	4 (14.8)	0 (0.0)	7 (25.9)	4 (14.8)
Diarrhea	0 (0.0)	1 (3.7)	1 (3.7)	0 (0.0)	2 (7.4)	1 (3.7)
Nausea and vomiting	1 (3.7)	1 (3.7)	1 (3.7)	0 (0.0)	3 (11.1)	1 (3.7)
Bleeding	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)
Fatigue	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)

nausea, vomiting, and hand-foot skin syndrome. The adverse reaction with the highest incidence in this treatment group was hypertension (7/27, 25.9%), followed by proteinuria (6/27, 22.2%), hand-foot skin syndrome (5/27, 18.5%), decrease in neutropenia (5/27, 18.5%), abnormal liver function (5/27, 18.5%), and nausea and vomiting (3/27, 11.1%). The most common grade 3/4 toxicities were hypertension and hand-foot skin syndrome, with incidence rates of 14.8% (4/27) and 11.1% (3/27), respectively (see Table 4). These adverse reactions can be effectively treated via dose reduction or symptomatic treatment without affecting the subsequent dosing, improving patient apatinib tolerance.

4. Discussion

High vascular density in colorectal cancer patients is associated with disease recurrence and metastasis; indeed, given the low expression of vascular endothelial growth factor (VEGF) and its receptors in normal tissues and the high expression of these molecules in colorectal cancer, VEGF and its receptors are positively correlated with angiogenesis.[19,20] Therefore, inhibition of VEGF/VEGFR signal transduction is an intriguing therapeutic target for the treatment of colorectal cancer.

Apatinib mesylate is a new type of VEGFR-2 inhibitor, which was officially launched in China in 2014 owing to its good clinical efficacy and safety in the treatment of advanced gastric cancer. In addition, apatinib has also shown good clinical efficacy in solid tumors such as non-small cell lung cancer and breast cancer.[21–24] Apatinib mesylate has been verified to have good anti-tumor activity both in vitro and in vivo study.[15] Yet, evidence of good survival benefit and safety in patients with advanced colorectal cancer who had failed multiple-line chemotherapies still is extremely limited.

To the best of our knowledge, the present study is the 1st case-control study ever to compare the efficacy of using apatinib monotherapy for the treatment of patients with advanced colorectal cancer who had failed 2nd-line or subsequent chemotherapy. In our study, the median PFS of the apatinib monotherapy group was 0.9 months longer than that of the observation group ($P < .001$), and the disease control rate was significantly higher than that of the observation group (70.4% vs 26.9%, $P = .002$). In our OS analysis, we found that the OS in the apatinib group was longer than that in the observation group (5.0 months vs 4.0 months). Although the results of this study were not statistically significant ($P = .722$), they still suggested that aptatinib might increase OS and future studies with an expanded sample size should conducted to further explore this benefit. The prolonged survival in these patients with advanced colorectal cancer may be associated with improvement in PFS and DCR. Further multivariate analysis revealed that patients with more metastatic sites had a poorer PFS, likely because these patients were subject to enhanced tumor cell migration and invasiveness relative to those patients with fewer metastatic sites. In addition, in terms of OS, we found that advanced colorectal cancer patients with a poor physical status, primary tumor localization to the right colon, and lymph node metastases were subject to a significantly increased risk of death, which is consistent with previously results.[25] Furthermore, we also found that the PFS of patients with advanced colorectal cancer in the apatinib group was still better than that in the observation group (HR, 3.88; 95% CI, 1.91–7.88; $P < .001$), indicating that apatinib can significantly reduce the risk of disease progression in patients with advanced colorectal cancer.

In order to overcome the dilemma that no treatment options are available for patients with advanced colorectal cancer that progresses after all approved standard therapies, several studies have been conducted to explore the effectiveness of antiangiogenic agents in advanced colorectal cancer. Apatinib is one of most promising antiangiogenic target drugs. The CORRECT study,[26] an international, multicentre, randomised, placebo-controlled, phase III trial, showed that regorafenib, a novel oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumour angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF, and BRAFV600E), and the tumour microenvironment (PDGFR and FGFR), has survival benefits in patients with metastatic colorectal cancer after all standard therapies failed. Regorafenib brought a median OS benefit of 1.4 months compared with placebo (6.4months vs 5.0 months; hazard ratio 0·77; 95% CI, 0·64–0·94; $P = ·0052$). The FRESCO study[27] demonstrated that oral fruquintinib, a VEGFR inhibitor that blocks new blood vessel growth associated with tumor proliferation, resulted in a statistically significant increase in OS (9.3 months vs 6.6 months; hazard ratio 0.65; 95% CI, 0.51–0.83; $P < .001$) and PFS (3.7 months vs 1.8 months; hazard ratio 0.26; 95% CI, 0.21–0.34; $P < .001$) compared with placebo. These data, including those from apatinib, show that an antiangiogenesis strategy is active in treating colorectal cancer.

Patients generally tolerated apatinib well.[28] However, adverse reactions did occur and were considered to be manageable.

Strategies for the management of these toxicities may include dose reduction, discontinuation, symptomatic treatment, or termination. Phase I, II, and III clinical trials of apatinib have shown that hypertension, hand-foot skin syndrome, and proteinuria are the most common adverse events associated with such anti-angiogenic agents.[11,12,13] In the Phase III trial, the incidence of grade 3/4 hypertension, proteinuria, and hand-foot skin syndrome in the apatinib treatment group was 4.5%, 2.3%, and 8.5%, respectively. In our study, adverse events with an incidence rate greater than 10% included a decrease in white blood cell, neutropenia, liver toxicity, hypertension, hand-foot skin syndrome, proteinuria, nausea, and vomiting. The grade 3/4 adverse events with the highest incidence rates were hypertension and hand-foot skin syndrome, with rates of 14.8% and 11.1%, respectively, consistent with previous studies. In addition, the treatment-related adverse events of apatinib also similar to other antiangiogenic monoantibodies, like regorafenib, the 1st small-molecule multikinase inhibitor with survival benefits in metastatic colorectal cancer which has progressed after all standard therapies. In CORRECT trial,[26] the most common treatment-related Grade 3 or worse adverse events were hand-foot skin reaction (17%), hypertension (7%) and these adverse events are clinically controllable. Similar incidence rate was observed in apatinib from our study.

In summary, this study shows that apatinib alone can prolong the PFS of patients with advanced colorectal cancer who have failed 2nd-line or above chemotherapy. Although the intergroup comparison of OS did not reveal a statistically significant difference, these results still suggest that apatinib may increase OS and offer desirable clinical benefits. Apatinib also increased the incidence rate of adverse events such as hypertension and hand-foot skin syndrome, but these events were manageable. These data indicate that apatinib may be a new treatment option for patients with advanced progressive colorectal cancer after multiline chemotherapies. Because the price of apatinib is relatively cheaper than other targeted drugs and it can be reimbursed by medical insurance, so the cost of the drug is acceptable to most patients. However, this study has some limitations. First, the study is a single-center study with an inherent selection bias. All patients enrolled in this study were from China and the generalisability to other populations need to be discussed. Moreover, the planned ancillary analysis of clinical and biological predictive or prognostic factors should be reported in the future. Our research team is currently expanding the sample size and conducting clinical trials in multiple research centers to provide stronger evidence for the efficacy and safety of apatinib for last-line therapy in a wider population.

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