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Effectiveness and Safety of Apatinib Plus Programmed Cell Death Protein 1 Blockades for Patients with Treatment-refractory Metastatic Colorectal Cancer: A Retrospective Exploratory Study

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This study aimed to investigate the efficacy and safety of apatinib plus programmed cell death protein 1 (PD-1) blockades for patients with metastatic colorectal cancer (CRC) who were refractory to the standard regimens. In this retrospective study, patients with metastatic CRC who received apatinib plus PD-1 blockades in clinical practice were included. The initial dosage of apatinib was 250 mg or 500 mg, and PD-1 blockades were comprised of camrelizumab, sintilimab and pembrolizumab. Efficacy and safety data were collected through the hospital's electronic medical record system. From October 2018 to March 2022, a total of 43 patients with metastatic CRC were evaluated for efficacy and safety. The results showed an objective response rate of 25.6% (95% CI, 13.5%-41.2%) and a disease control rate of 72.1% (95% CI, 56.3%-84.7%). The median progression-free survival (PFS) of the cohort was 5.8 months (95% CI, 3.81-7.79), and the median overall survival (OS) was 10.3 months (95% CI, 5.75-14.85). The most common adverse reactions were fatigue (76.7%), hypertension (72.1%), diarrhea (62.8%), and hand-foot syndrome (51.2%). Multivariate Cox regression analysis revealed that Eastern Cooperative Oncology Group (ECOG) performance status and location of CRC (left or right-side) were independent factors to predict PFS of patients with metastatic CRC treated with the combination regimen. Consequently, the combination of apatinib and PD-1 blockades demonstrated potential efficacy and acceptable safety for patients with treatment-refractory metastatic CRC. This conclusion should be confirmed in prospective clinical trials subsequently.

Key Words Metastatic colorectal cancer, Apatinib, Programmed cell death protein 1 blockades, Efficacy, Safety

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant tumors in digestive systms globally, ranking third in terms of incidence and second in mortality among all tumors [1]. According to the latest cancer epidemiological data, China was observed of approximately 555,000 new cases and 286,000 deaths annually [2]. Unfortunately, due to limitations in early diagnosis techniques, a large number of CRC patients in China were diagnosed with advanced or metastatic disease, missing the opportunity for surgical resection. In recent years, significant research breakthroughs in the treatment of metastatic CRC were scanty, except for Keynote177 trial, which demonstrated remarkable advancements in patients with mismatch repair-deficient (dMMR) tumors compared with chemotherapy [3]. However, for patients with other category of metastatic CRC, conventional chemotherapy remained a crucial therapeutic option.

Studies exhibited that combining oxaliplatin or irinotecan-based chemotherapy with bevacizumab, panitumumab or cetuximab significantly improved patient prognosis, resulting in a median overall survival (OS) of approximately 30 months [4-6]. Consequently, these regimens became the standard first-line therapeutic options for patients with metastatic CRC [7,8]. In the third-line treatment, the FRESCO study and CONCUR study demonstrated that the antiangiogenic small molecule tyrosine kinase inhibitors (TKIs: fruquintinib and regorafenib) provided further survival benefits for patients with

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CRC and were approved by guidelines as third-line treatment for patients with metastatic CRC [9,10].

Apatinib is also a small molecule TKI that selectively competes for the anti-angiogenesis of vascular endothelial growth factor receptor-2, and the preclinical and clinical studies suggest that it exhibits potential anti-tumor activity and acceptable tolerability for patients with advanced non-small cell lung cancer (NSCLC) and metastatic CRC [11,12]. In spite of the fact that TKIs monotherapy could significantly prolong the survival and bring clinical benefit for the patients, the objective response rate (ORR) was disappointing (< 10%) [13], suggesting that combination therapeutic strategy might be needed to improve the overall response clinically.

Additionally, immunotherapy that is represented by programmed cell death protein 1 (PD-1) blockades brings significant survival benefits to a small proportion of patients with metastatic CRC currently [14,15]. Unfortunately, it seems that less than 5% of patients with dMMR metastatic CRC may achieve significant survival benefit from immunotherapy administration currently [16]. Nonetheless, a substantial number of patients with metastatic CRC have not yet benefited from PD-1 monotherapy currently, which highlights the need for new combination strategies.

Interestingly, the synergistic action of the combination of anti-angiogenic drugs and PD-1 blockades was described in many cancer types recently [17]. Previous mechanistic studies had confirmed that apatinib could improve the anti-tumor efficacy of PD-1 blockades in a mouse model of colon cancer by up-regulating the expression of programmed cell death-ligand 1 and inhibiting angiogenesis [18]. Therefore, these studies provided a theoretical basis for the clinical application of apatinib combined with PD-1 blockades in metastatic CRC. Consequently, the aim of this study was to investigate the effectiveness and safety and prognostic factors of apatinib combined with PD-1 blockades in patients with metastatic CRC who were refractory to the previous standard regimens.

MATERIALS AND METHODS

Study design and eligibility criteria

Since both PD-1 blockades and apatinib had been used clinically over 3 years, some patients with metastatic CRC were treated with apatinib plus PD-1 blockades in clinical practice. Therefore, this trial was designed as a retrospective analysis and included patients with metastatic CRC who received apatinib plus PD-1 blockades at the Department of General Surgery of The Second Affiliated Hospital of Harbin Medical University from October 2018 to March 2022 retrospectively. The main inclusion criteria for this study included: (1) pathologically or cytologically confirmed colon or rectal adenocarcinoma; (2) age ≥ 18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0-2; (4) measurable target lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (5) underwent ≥ 2 prior lines of systemic standard therapy that included fluoropyrimidine, oxaliplatin, and irinotecan with or without anti–vascular endothelial growth factor or epidermal growth factor receptor monoclonal antibodies (6) treated with apatinib plus PD-1 blockades in clinical practice. The main exclusion criteria were: (1) a history of autoimmune diseases or receiving steroids or other immunosuppressive drugs; (2) concomitant with other tumors or serious diseases that might compromise the patient's survival; (3) response assessment data was not available, but those who were lost to follow-up during subsequent treatment could be included in this study. The study profile was illustrated in Figure 1. Eventually, a total of 43 patients with metastatic CRC were enrolled. The study was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University. Written informed consent was obtained by the subjects included according to the recommendations of the Declaration of Helsinki.

Administration of apatinib and PD-1 blockades and assessment of efficacy and safety

All patients included in this study were treated with apatinib

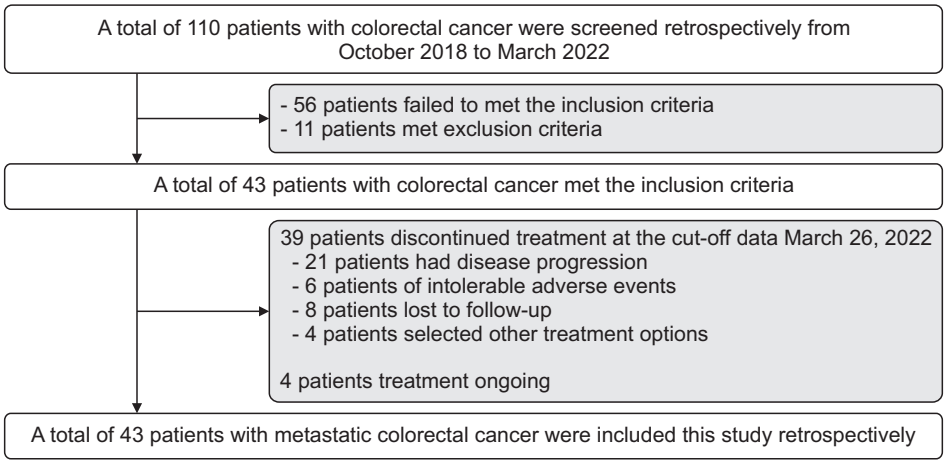

Figure 1. Flowchart of the retrospective study of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment. CRC, colorectal cancer; PD-1, programmed cell death protein 1.

plus a PD-1 blockade in clinical practice. The PD-1 blockades included camrelizumab, sintilimab and pembrolizumab, all of which had been licensed in China. The dosage of each PD-1 blockade was 200 mg, intravenously administered on day 1, every 21 days as one cycle. Apatinib was administered orally at an initial dosage of 250 mg or 500 mg per day until disease progression or intolerable toxicity. The dosage of apatinib was adjusted according to the safety profile during the combination administration.

Response of the combination therapy was evaluated based on RECIST version 1.1 criteria in the opinion of investigators [19]. The target lesions were assessed using computed tomography or magnetic resonance imaging scans every two cycles or depended on the actual situation. The primary endpoint of this study was progression free survival (PFS), and the secondary endpoints were OS, ORR, disease control rate (DCR), and safety.

Adverse reactions during the combination therapy of patients with apatinib plus PD-1 blockades were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [20], and the maximum grade of adverse reactions during the treatment was recorded and analyzed accordingly.

Statistical analysis

ORR was defined as the percentage of patients with complete response (CR) and partial response (PR) during treatment. DCR was defined as the proportion of patients with CR, PR and stable disease (SD). PFS was defined as the date of treatment with apatinib plus PD-1 blockade to the date of disease progression or death, whichever occurred first. OS was defined as the date of treatment with apatinib plus PD-1 blockade to the date of death from any cause. Statistical analysis was performed using SPSS version 25.0 (IBM Corp.). Kaplan-Meier survival curves for PFS and OS were generated using Stata version 14.0 (Stata Co.). The log-rank test was utilized to calculate survival differences based on baseline characteristics. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the 43 patients with metastatic CRC

The baseline characteristics of the 43 patients with metastatic CRC were shown in Table 1. The median age of the patients was 63 years (range: 21-79), with 24 patients (55.8%) older than 63 years. There were 23 and 20 patients with ECOG PS score of 0-1 and 2, respectively, and the majority of patients (62.8%) were male. Pathological stages IIIb and IV were found in 4 and 39 patients, respectively. Additionally, right-sided CRC was observed in 18 (41.9%) patients. Eleven patients received two lines of previous therapy, while 32 patients received three or more lines therapy. Most of the patients (62.8%) underwent surgical treatment. The MMR status of dMMR, proficient MMR, and unknown were noted in 4, 24, and 15 patients, respectively. A total of 23, 14, and 6 patients were treated with camrelizumab, sintilimab, and pembrolizumab, respectively. Initial dosage of apatinib with 250 mg was used in 26 (60.5%) patients.

Table 1. Baseline characteristics of the 43 patients with metastatic CRC

Characteristic	Total patients (n = 43)
Age (yr)	
Median (range)	63 (21-79)
≥ 63	24 (55.8)
< 63	19 (44.2)
ECOG PS score	
0-1	23 (53.5)
2	20 (46.5)
Sex	
Male	27 (62.8)
Female	16 (37.2)
Pathological stage	
IIIb	4 (9.3)
IV	39 (90.3)
Primary tumor site	
Right	18 (41.9)
Left or rectum	25 (58.1)
Previous systemic treatment	
Second line	11 (25.6)
Third line and above	32 (74,4)
Surgical treatment history	
Yes	27 (62.8)
No	16 (37.2)
MMR status	
dMMR	4 (9.3)
pMMR	24 (55.8)
Unknown	15 (34.9)
Number of metastases sites	
≤ 3	24 (55.8)
> 3	19 (44.2)
Liver metastases	
Yes	31 (72.1)
No	12 (27.9)
Initial dosage of apatinib (mg)	
250	26 (60.5)
500	17 (39.5)
PD-1 blockades	
Camrelizumab	23 (53.5)
Sintilimab	14 (32.6)
Pembrolizumab	6 (13.9)

Values are presented as number (%) or otherwise indicated. CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MMR, mismatch repair; dMMR, mismatch repair-deficient; pMMR, proficient mismatch repair; PD-1, programmed cell death protein 1.

Efficacy of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades

All the 43 patients with metastatic CRC were available for efficacy assessment. The best overall response of each patient during apatinib plus PD-1 blockades administration indicated that PR was observed in 11 patients, SD was noted in 20 patients, and PD was found in 12 patients. The waterfall plot for the best percentage change in target lesion among the 43 patients was shown in Figure 2. Most patients experienced significant reduction in target lesions after treatment with apatinib plus PD-1 blockades. As shown in Figure 3, ORR of the 43 patients was 25.6% (95% CI, 13.5%-41.2%), DCR was 72.1% (95% CI, 56.3%-84.7%).

Prognosis of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades

At the date of data cut-off (March 26, 2022), the median follow-up duration was 9.7 months (range: 0.9-25.5 months). A total of 29 progression or death events were observed at the date of data cut-off, which yielded a maturity for PFS data of 67.4%. As exhibited in Figure 4, the median PFS of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades was 5.8 months (95% CI, 3.81-7.79). And the 6-month PFS and 12-month PFS rate was 46.03% (95% CI, 30.68%-60.07%) and 34.69% (95% CI, 20.34%-49.46%), respectively.

Association between PFS and baseline characteristic subgroups was analyzed subsequently, and the univariate anal-

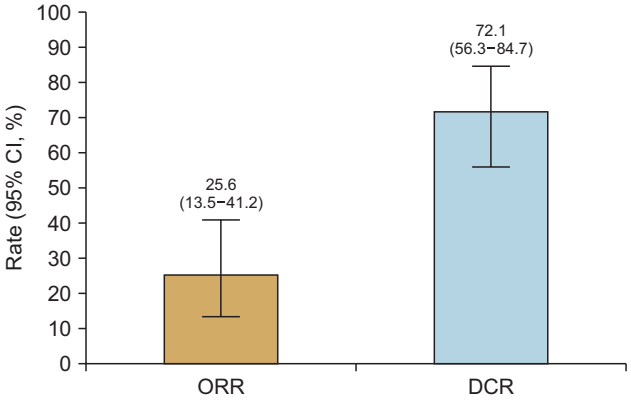

Figure 3. The ORR and DCR of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment. ORR, objective response rate; DCR, disease control rate; CRC, colorectal cancer; PD-1, programmed cell death protein 1.

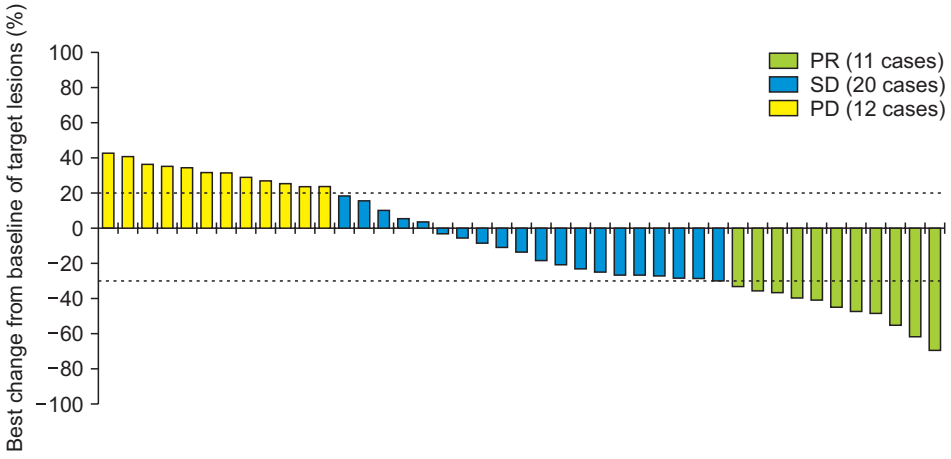

Figure 2. Waterfall plots of the best changes in target lesions of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment. CRC, colorectal cancer; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease; PD, progressive disease.

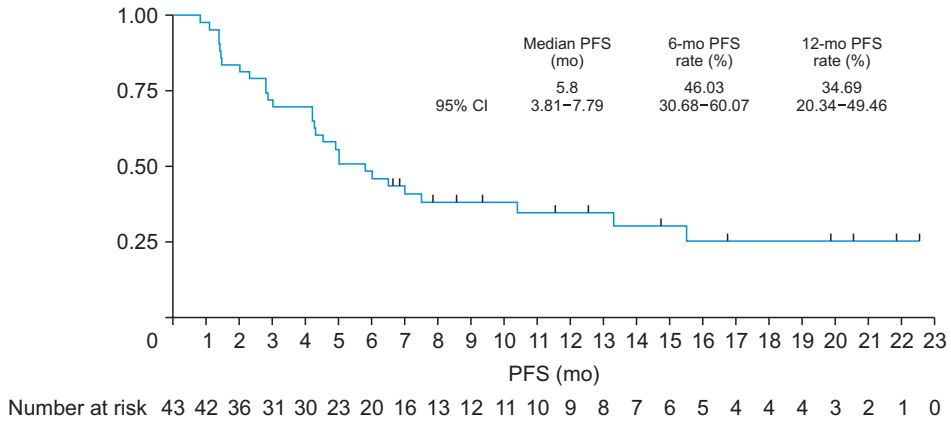

Figure 4. The progression-free survival of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment. CRC, colorectal cancer; PD-1, programmed cell death protein 1; PFS, progression free survival.

ysis results are shown in Table 2. The analysis revealed that ECOG PS score and tumor location were significantly associated with PFS. Patients with ECOG PS score of 0-1 had a longer PFS compared to those with 2 score (median PFS: 6.5 vs. 4.9 months, $P = 0.0011$). In addition, patients with left-side CRC conferred better PFS than those with right-side CRC (median PFS: 6.5 vs. 4.5 months, $P = 0.009$). Other baseline characteristics exhibited similar PFS, no significant statistical differences were observed ($P > 0.05$). Furthermore, multivariate Cox regression analysis was constructed for PFS including the baseline characteristics that were significant in the univariate analysis. The results indicated that ECOG PS score (hazard ratio [HR] = 0.75, $P = 0.029$) and tumor location (HR = 1.43, $P = 0.015$) remained statistically significant, suggesting that ECOG PS score and tumor location were independent factors to predict the PFS of patients who received apatinib plus PD-1 blockades.

Furthermore, a total of 27 death events were detected at the date of data cut-off. As shown in Figure 5, the median OS of 43 patients with metastatic CRC who received apatinib plus PD-1 blockades was 10.3 months (95% CI, 5.75-14.85), and the 12-month and 24-month OS rate was 46.58% (95% CI, 30.08%-61.51%) and 15.42% (95% CI, 3.48%-35.31%), respectively.

Table 2. Univariate and multivariate analyses of baseline characteristic subgroups and PFS in 43 patients with metastatic CRC

Characteristic	Median PFS (95% CI)	Univariate analyses (*P*-value)	Multivariate analyses	
			HR (95% CI)	*P*-value
Age (yr)		0.616		
≥ 63	6.0 (3.91-8.09)			
< 63	5.8 (4.03-7.57)			
ECOG PS score		0.011	0.75 (0.38-0.91)	0.029
0-1	6.5 (4.15-8.85)			
2	4.9 (3.82-5.98)			
Sex		0.413		
Male	5.0 (3.72-6.28)			
Female	6.0 (4.18-7.82)			
Pathological stage		0.318		
IIIb	6.5 (4.31-8.69)			
IV	5.8 (4.04-7.56)			
Primary tumor site		0.009	1.43 (1.09-1.93)	0.015
Right	4.5 (3.37-5.63)			
Left or rectum	6.5 (4.18-8.82)			
Previous systemic treatment		0.511		
Second line	6.0 (4.27-7.73)			
Third line and above	5.8 (4.02-7.58)			
Surgical treatment history		0.325		
Yes	6.0 (4.13-7.87)			
No	5.8 (3.94-7.66)			
MMR status				
dMMR	6.5 (4.82-8.18)	0.335		
pMMR	5.0 (3.85-6.15)			
Unknown	5.8 (4.11-7.49)			
Number of metastases sites		0.218		
≤ 3	6.0 (4.35-7.65)			
> 3	5.0 (3.82-6.18)			
Liver metastases		0.331		
Yes	5.8 (4.18-7.42)			
No	6.0 (4.09-7.91)			
Initial dosage of apatinib (mg)		0.235		
250	5.0 (3.89-6.11)			
500	5.8 (4.03-7.57)			
PD-1 blockades		0.418		
Camrelizumab	5.0 (3.78-6.22)			
Sintilimab	5.8 (4.06-7.54)			
Pembrolizumab	6.0 (4.36-7.64)			

PFS, progression free survival; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HR, hazard ratio; MMR, mismatch repair; dMMR, mismatch repair-deficient; pMMR, proficient mismatch repair; PD-1, programmed cell death protein 1.

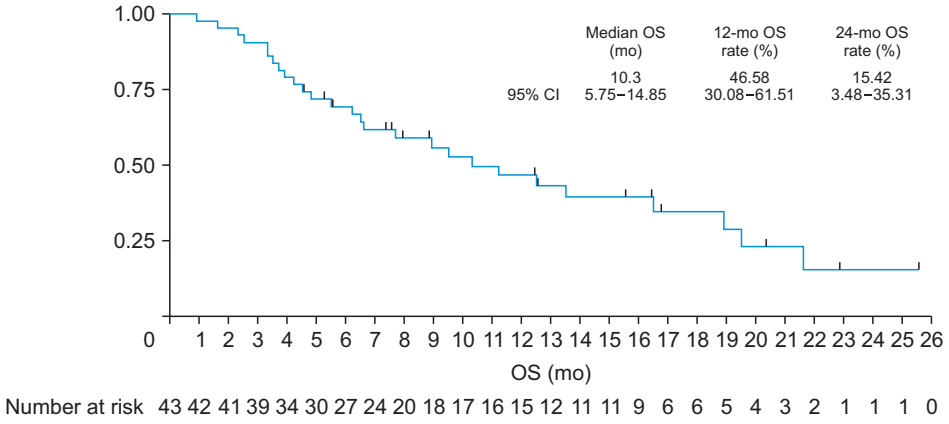

Figure 5. The overall survival of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment. CRC, colorectal cancer; PD-1, programmed cell death protein 1; OS, overall survival.

Table 3. The safety profile of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades treatment

Adverse reactions	Total	Grade 1-2	Grade 3-4
Fatigue	33 (76.7)	29 (67.4)	4 (9.3)
Hypertension	31 (72.1)	25 (58.1)	6 (14.0)
Diarrhea	27 (62.8)	24 (55.8)	3 (7.0)
Hand-foot syndrome	22 (51.2)	17 (39.5)	5 (11.6)
Nausea and vomiting	19 (44.2)	16 (37.2)	3 (7.0)
Rash	15 (34.9)	13 (30.2)	2 (4.7)
Hepatotoxicity	13 (30.2)	10 (23.3)	3 (7.0)
Pneumonia	11 (25.6)	10 (23.3)	1 (2.3)
Proteinuria	9 (20.9)	7 (16.3)	2 (4.7)
RCCEP	7 (16.3)	7 (16.3)	0 (0.0)
Hematologic toxicity	4 (9.3)	4 (9.3)	0 (0.0)

Values are presented as number (%). CRC, colorectal cancer; PD-1, programmed cell death protein 1; RCCEP, reactive cutaneous capillary endothelial proliferation.

Safety profile of the 43 patients with metastatic CRC who received apatinib plus PD-1 blockades

Adverse reactions of 43 patients who received apatinib plus PD-1 blockades were shown in Table 3. A total of 42 patients (97.7%) experienced adverse reactions irrespective of grades, including 29 patients (67.4%) with grade 3-4 adverse reactions. No grade 5 or unexpected adverse reactions were detected. Common adverse reactions included fatigue, hypertension, diarrhea, hand-foot syndrome, nausea and vomiting, rash, hepatotoxicity, pneumonia, proteinuria, reactive cutaneous capillary endothelial proliferation (RCCEP) and hematological toxicity. Among them, grade 3-4 adverse reactions included hypertension (14.0%), hand-foot syndrome (11.6%), fatigue (9.3%), diarrhea (7.0%), nausea and vomiting (7.0%), hepatotoxicity (7.0%), rash (4.7%), proteinuria (4.7%), and pneumonia (2.3%).

DISCUSSION

This retrospective study provided real-world evidence regarding the efficacy and safety of apatinib plus PD-1 blockades for patients with metastatic CRC who failed after the previous standard systemic therapy. Furthermore, univariate and multivariate analysis between baseline characteristic subgroups and PFS suggested that patients with ECOG PS score of 0-1 or left-side CRC were associated with superior PFS. The conclusion of this study was of potential significance in clinical practice for patients with metastatic CRC who received apatinib plus PD-1 blockades.

CRC was one heterogeneous malignant tumor in the digestive system and relatively limited breakthrough research progress was observed as the subsequent therapy for patients with metastatic CRC over the past decades [21]. Therefore, effective therapeutic options were urgently needed to prolong the survival of the patients [22]. At present, immunotherapy was gradually changing the therapeutic landscape for the treatment of multiple tumors. Although preliminary efficacy was reported in digestive tract tumors, only a small proportion of CRC patients benefited from immunotherapy currently [23]. Immunotherapy demonstrated a low response of tumor immune action in patients with microsatellite stable (MSS) metastatic CRC, known as “cold tumors” [24]. How to change the tumor immune microenvironment from “cold tumors” to “hot tumors” was a major challenge for immunotherapy of metastatic CRC. Previous study found that combination therapy had the possibility to break this bottleneck, especially the combination of anti-angiogenic drugs and PD-1 blockades might bring more survival benefits for patients with metastatic CRC [25]. Anti-angiogenic drugs might not only improve the tumor immune microenvironment, but also inhibit the generation of tumor neovascularization and achieve synergistic activity [26]. Previous study also confirmed the significant research progress regarding bevacizumab combined with atezolizumab in the treatment of advanced hepatocellular carcinoma and became the standard treatment option [27]. Apatinib increased the infiltration of immune cells and decreased tumor immune tolerance by acting on immature blood vessels and inducing vascular normalization [28]. Some retrospective studies also reported that apatinib

demonstrated preliminary efficacy for patients with metastatic CRC [29].

In this study, 43 patients with metastatic CRC who received apatinib plus PD-1 blockades yielded an ORR of 25.6%, a DCR of 72.1% and median PFS of 5.8 months. The ORR, DCR, and PFS in this study were superior to those in FRESCO and CONCUR trials without increasing the adverse reactions significantly [9,10]. Additionally, the efficacy results in this study were superior to those of PD-1 blockade monotherapy [30]. The result preliminarily indicated a synergistic activity of PD-1 blockades plus apatinib in metastatic CRC. Noteworthily, the previous REGONIVO trial included 25 patients with metastatic CRC of MSS status, which found that the ORR of regorafenib plus nivolumab (PD-1 blockade) was 33% and the median PFS was 7.9 months [31].

The majority of patients in our study were MSS metastatic CRC (over 55.8%), and the efficacy results were slightly worse than that in the REGONIVO trial numerically. This discrepancy might be due to the retrospective design of our study, patient management and compliance was inferior to prospective clinical trial. The synergistic activity of PD-1 blockades plus apatinib observed in this study highlighted that apatinib might improve the microenvironment of MSS tumor tissues and increase the immune response to PD-1 blockades. The potential underlying mechanism remains to be further investigate [32]. Previous studies also investigated the efficacy and safety of apatinib plus camrelizumab in patients with MSS metastatic CRC. However, their results exhibited that apatinib plus camrelizumab failed to improve the efficacy of patients and increased the occurrence of adverse reactions [33]. This explanation might be that their study included few CRC patients (only 10 patients), and the patients included in the study exhibited a high degree of heterogeneity. Collectively, whether apatinib plus PD-1 blockades might bring survival benefit for patients with metastatic CRC was still needs to be further confirmed in prospective clinical trials.

The median OS of 43 patients with metastatic CRC who received apatinib plus PD-1 blockades was 10.3 months, which was higher compared to those who received apatinib or PD-1 blockade monotherapy (7.9 months for apatinib and 8.5 months for PD-1 blockade, respectively) [12]. The reason might be that targeted drugs of different mechanisms of action (other anti-angiogenic TKIs and TAS102, etc.) had been licensed in China since 2018. Patients with metastatic CRC in this study might also receive other targeted drugs after the progression of apatinib plus PD-1 blockades, which might bring sustained survival benefits to patients consecutively.

The safety profile of the combination regimen indicated that the major adverse reactions of 43 patients with metastatic CRC who received apatinib plus PD-1 blockades included fatigue, hypertension, diarrhea, hand-foot syndrome, nausea and vomiting, rash, hepatotoxicity, pneumonia, proteinuria and RCCEP, which was basically consistent with the previous results of apatinib plus PD-1 blockade in the treatment of patients with advanced NSCLC [34]. However, it should be noted that the incidence of grade 3-4 adverse reactions in this study was 67.4%, which was slightly higher than that of apatinib or PD-1 blockade monotherapy, suggesting that the combination administration might augment the incidence of grade 3 or higher adverse reactions. Interestingly, RCCEP seemed to be the specific adverse reaction of camrelizumab that was administered among 23 patients in our study. Therefore, the actual incidence of RCCEP for camrelizumab administration was 30.4%, which might be slightly lower than that of the camrelizumab monotherapy in the other cancer (approximately 60%) [35]. It is likely that anti-angiogenic drugs might attenuate the occurrence of RCCEP caused by the treatment with camrelizumab to some extent. However, this conclusion needs to be further confirmed by large-sample clinical trials subsequently. Overall, the safety of apatinib plus PD-1 blockades in patients with metastatic CRC was tolerable and manageable.

Limitations existed exhist in this study objectively. Firstly, the sample size was small, the efficacy and safety of combination therapy regimens as the subsequent line treatment of patients with metastatic CRC needed to be further verified by large-sample trials. Additionally, our study was designed as a retrospective analysis with some biases that could not be avoided. Nevertheless, we thought apatinib plus PD-1 blockades might benefit patients with treatment-refractory metastatic CRC, providing promising guidance for patients with treatment-refractory metastatic CRC in clinical practice.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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