Original Article

Fruquintinib in combination with sintilimab or TAS-102 as third-line or above treatment in patients with metastatic colorectal cancer: a real-world study

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Background: For metastatic colorectal cancer (mCRC), the efficacy of third-line or above treatments is not ideal. Combining targeted vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR) biological agents with chemotherapy or anti-programmed death receptor 1 (PD-1) treatment can bring longer survival benefits to patients with mCRC compared with the application of a single drug. In this study, fruquintinib was used as the research drug, and the main purpose was to compare the efficacy and safety of fruquintinib in combination with sintilimab (FS) or trifluridine and tipiracil (TAS-102) (FT) in the third-line or above treatment in mCRC patients.

Methods: Based on real-world clinical practice, mCRC patients who progressed after second-line or higher-line chemotherapy regimens and received FS or FT as third-line or above treatment from December 2020 to November 2022 were analyzed. Progression-free survival (PFS) was the primary endpoint. Safety, disease control rate (DCR) and objective response rate (ORR) were secondary end points.

Results: In the FS group, 47 patients received FS, and in the FT group, 45 patients received FT. The DCR values in the FS and FT groups were 80.9% (38/47) and 55.6% (25/45), respectively (P<0.05). The median PFS (mPFS) in the FS group was 6.0 months, and the mPFS in the FT group was 3.5 months (P<0.05). Most adverse events (AEs) were grade 1–2 in severity.

Conclusions: As a third-line or above regimen in mCRC patients, compared to FT, treatment with FS provides a higher DCR and longer mPFS and is better tolerated. The combination of fruquintinib and sintilimab may become a new treatment option for mCRC patients.

Keywords: Metastatic colorectal cancer (mCRC); fruquintinib; sintilimab; trifluridine and tipiracil (TAS-102); progression-free survival (PFS)

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in China. Approximately 80% of CRC patients lose the chance of surgery due to advanced disease or metastasis at the time of initial diagnosis. Systemic therapy for patients with advanced or metastatic colorectal cancer (mCRC) remains a cytotoxic-based chemotherapy regimen, including fluorouracil, irinotecan, and oxaliplatin. Compared with other malignant tumors, many patients with CRC can obtain a relatively long survival time after

standardized first- and second-line treatments and have the opportunity to apply third-line and subsequent drug treatments. However, in general, the efficacy of third-line and subsequent treatments is unsatisfactory.

Immune checkpoint inhibitors typified by anti-programmed death receptor 1 (PD-1) have been shown to be remarkably successful in treating various solid malignancies (1-4). However, the role of anti-PD-1 in mCRC has generally been limited to mCRC patients with microsatellite instability high (MSI-H) or mismatch repair-deficient (dMMR), who account for only 4.6% of mCRC patients (5). Most mCRC patients are microsatellite-stable (MSS) or proficient mismatch repair (pMMR) and may not benefit from immune checkpoint inhibitor monotherapy. At present, biological agents targeting vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR), including bevacizumab and regorafenib, are used to treat mCRC (6,7). Fruquintinib, a VEGFR blocker, normalizes tumor blood vessels and produces synergistic antitumor effects in combination with cytotoxic drugs and anti-PD-1 drugs (8,9). Fruquintinib has been approved by the China Food and Drug Administration for mCRC patients who have received at least two previous standard antitumor therapies (10).

Although fruquintinib improves the prognosis of mCRC, the objective effective rate of fruquintinib monotherapy was only 4.7% in the FRESCO study. At present, many prospective single-arm studies, including REGONIVO, REGOTORI, REGOMUNE and others, have investigated the efficacy of multitargeted antiangiogenic tyrosine kinase inhibitors (TKIs) plus anti-PD-1 in the third-line therapy of MSS mCRC (11-13). Multitargeted antiangiogenic TKIs (regorafenib or fruquintinib) combined with anti-PD-1 have become a new strategy for the treatment of MSS mCRC (14).

TAS-102, which consists of a thymidine analog and a thymidine phosphorylase inhibitor, is also known as trifluridine-tipiracil, an oral chemotherapeutic agent (15). TAS-102 treatment significantly prolonged overall survival (OS) compared with placebo in mCRC patients refractory to standard therapy (16,17). In the RECOURSE trial, survival benefits were observed in patients using TAS-102 in different subgroups (18). TAS-102 is recommended as the third-line therapy for mCRC (Class 1A) by the Guidelines of the Chinese Society of Clinical Oncology (CSCO) 2022. TAS-102 is well tolerated and can be used in combination with other agents in the later-line treatment of mCRC. In a phase 1–2 clinical study, 25 mCRC patients who were ineffective or intolerant to standard treatment received TAS-102 combined with anti-VEGF therapy, with a median OS (mOS) of 11.4 months and a median progression-free survival (mFPS) of 5.6 months, showing favorable antitumor effects (19).

Although clinical studies have confirmed that targeted VEGF or VEGFR biological agents combined with chemotherapy or anti-PD-1 treatment can bring longer survival benefits to patients compared with the application of a single drug, the efficacy and side effects of the two combined treatment modalities still need to be comprehensively considered. This study compared the efficacy and safety of fruquintinib combined with sintilimab (FS) or TAS-102 (FT) as third-line and beyond treatment for MSS mCRC. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-867/rc).

Highlight box

Key findings

- As a third-line or above regimen in metastatic colorectal cancer (mCRC) patients, treatment with fruquintinib plus sintilimab (FS) provides a higher disease control rate and longer compared with fruquintinib plus trifluridine and tipiracil (TAS-102) (FT).

What is known and what is new?

- Fruquintinib improves the prognosis of mCRC.
- Treatment with FS provides a longer median progression-free survival and is well tolerated in patients with microsatellite-stable (MSS) mCRC who progress after receiving second-line or higher chemotherapy regimens.

What is the implication, and what should change now?

- Large-scale clinical trials are needed to further verify the effectiveness and safety of FS or FT as third-line or above treatment for MSS mCRC.

Methods

Patients

In this study, we included mCRC patients who progressed after second-line or above chemotherapy regimens admitted to Chongqing University, Cancer Hospital from December 2020 to November 2022. The following were the main inclusion criteria: (I) age ≥18 and ≤75 years; (II) expected survival time of more than 3 months; (III) Eastern Cooperative Oncology Group performance status

(ECOG PS) score ≤2 points; (IV) mCRC confirmed by histology or cytology; (V) progression after receiving at least ≥2 regimens containing fluorouracil, oxaliplatin or irinotecan; and (VI) microsatellite instability (MSI) detected as MSS or pMMR. SAS statistical analysis system was used to generate random numbers and formed a random coding table. Patients were strictly enrolled according to the corresponding random coding table and assigned to FS group and FT group.

Study treatment

In this study, our patients were treated with FS or FT until unacceptable toxicity, disease progression or death occurred. In the FS group, fruquintinib was given orally at a dose of 4 mg once a day on week 1 to week 3 every 4 weeks with a dose reduction from 4 to 3 mg if intolerable side effects or toxicity occurred; sintilimab was administered at a dose of 200 mg intravenously every 21 days. In the FT group, the same dose of fruquintinib was given; TAS-102 was given orally at a dose of 35 mg/m^2 twice a day on days 1–5 and days 8–12 every 4 weeks. If intolerable toxicity occurred during treatment, the dose of TAS-102 was reduced by 5 mg/m^2.

Efficacy and safety assessments

To assess clinical efficacy, all patients in this study underwent computed tomography (CT) scans every 8 weeks after the start of treatment. The efficacy includes progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR) according to the Response Criteria in Solid Tumors (RECIST 1.1). The disease control rate (DCR) was SD + PR + CR, and the objective response rate (ORR) was PR + CR. Adverse events (AEs) were evaluated according to the Common Criteria for Adverse Events version 5.0.

Statistical analysis

The Kaplan-Meier method was used to calculate progression-free survival (PFS). The differences between the FS and FT groups were compared using the log-rank test. P<0.05 was considered statistically significant. PFS was defined as the time from starting FS or FT to death or disease progression. The rank sum test and Chi-square test were used to analyze the clinical data. The hazard ratios were calculated by a Cox regression model. All statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, Illinois, USA).

Ethics

The study was approved by the Ethics Committee of the Chongqing University, Cancer Hospital and conducted in accordance with the World Medical Association Declaration of Helsinki (as revised in 2013). All the patients included in the study provided written informed consent.

Results

Patient and treatment characteristics

In this study, 92 mCRC patients who progressed after treatment with second-line or above chemotherapy regimens were included. Forty-seven mCRC patients received FS (FS group), and 45 mCRC patients received FT (FT group). There were 44 females and 48 males. All of the included patients aged from 35 to 74 years old, and the majority of patients had an ECOG score of 0–1 (87.0%). Sixty-one patients (66.3%) had the primary tumor in the left colon, 28 patients (30.4%) in the right colon, and 3 patients (3.3%) in the rectum. The number of colonic metastatic sites ranged from one to two in 48 patients (52.2%), while the number of metastatic sites ranged from three or more in the other 44 patients (47.8%). FS or FT was given as third-line therapy in 43 (46.7%) patients, and as fourth-line or above therapy in the other 49 (53.3%) patients. All patients enrolled in this study were confirmed to pMMR status or MSS. In addition, the gene states of *KRAS*, *BRAF* and *NRAS* were also determined. The *KRAS* gene was mutated in 35 patients (38.0%), and in most patients, the *BRAF* and *NRAS* genes were wild-type (93.5% and 91.3%, respectively). All patients received chemotherapy and targeted therapy in the past, and the chemotherapy regimen included FOLFOX, CAPEOX and FOLFIRI. Targeted therapy included anti-VEGF therapy (bevacizumab, 58 patients, 63.0%) and anti-EGFR therapy (cetuximab, 26 patients, 28.3%). The six patients with *BRAF* gene mutations (two in FS group and four in FT group) included in this study had not received *BRAF* inhibitor treatment. As shown in *Table 1*, baseline characteristics were similar in the two groups.

Efficacy

By November 2022, 87 patients (94.6%) had met the

Table 1 Characteristics of all patients

Characteristic	Total (n=92)	FS group (n=47)	FT group (n=45)	P
Age (years)				0.301
Median [range]	60 [35–74]	59 [39–72]	61 [35–74]	
≥65	18 (19.6)	12 (25.5)	6 (13.3)	
Sex				0.537
Female	44 (47.8)	21 (44.7)	23 (51.1)	
Male	48 (52.2)	26 (55.3)	22 (48.9)	
ECOG PS				0.936
0–1	80 (87.0)	41 (87.2)	39 (86.7)	
2	12 (13.0)	6 (12.8)	6 (13.3)	
Primary tumor site				0.748
Left colon	61 (66.3)	32 (68.1)	29 (64.5)	
Right colon	28 (30.4)	13 (27.7)	15 (33.3)	
Rectum	3 (3.3)	2 (4.2)	1 (2.2)	
With liver metastasis	53 (57.6)	26 (55.3)	27 (60.0)	0.65
Number of metastatic sites				0.537
≤2	48 (52.2)	26 (55.3)	22 (48.9)	
≥3	44 (47.8)	21 (44.7)	23 (51.1)	
Treatment line				0.686
3	43 (46.7)	21 (44.7)	22 (48.9)	
≥4	49 (53.3)	26 (55.3)	23 (51.1)	
KRAS mutation status				0.631
Wild type	57 (62.0)	28 (59.6)	29 (64.4)	
Mutant	35 (38.0)	19 (40.4)	16 (35.6)	
NRAS mutation status				0.499
Wild type	84 (91.3)	42 (89.4)	42 (93.3)	
Mutant	8 (8.7)	5 (10.6)	3 (6.7)	
BRAF mutation status				0.368
Wild type	86 (93.5)	45 (95.7)	41 (91.1)	
Mutant	6 (6.5)	2 (4.3)	4 (8.9)	
Whether previously treated with bevacizumab or cetuximab[#]				
Bevacizumab	58 (63.0)	28 (59.6)	30 (66.7)	0.076
Cetuximab	26 (28.3)	16 (34.0)	10 (22.2)	0.208

Data are presented as n (%) if not otherwise specified. [#], in the previous treatment, some patients in this study received bevacizumab, some patients received cetuximab, some patients received the above two targeted therapies, and some patients did not receive the two targeted therapies. FS, fruquintinib plus sintilimab; FT, fruquintinib plus TAS-102; TAS-102, trifluridine and tipiracil; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Efficacy of FS or FT in mCRC

Best response	FS (n=47)	FT (n=45)	P
CR	0	0	–
PR	8	6	–
SD	30	19	–
PD	9	20	–
ORR	17.0%	13.3%	0.623
DCR	80.9%	55.6%	0.009

FS, fruquintinib plus sintilimab; FT, fruquintinib plus TAS-102; TAS-102, trifluridine and tipiracil; mCRC, metastatic colorectal cancer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

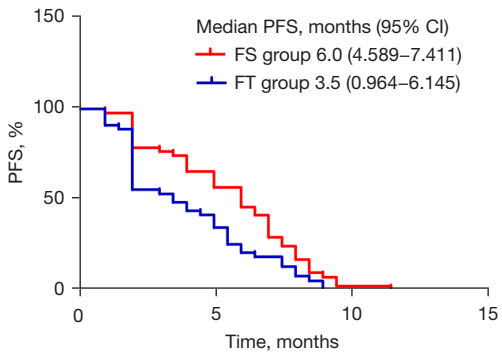

Figure 1 Kaplan-Meier curve of PFS in the FS and FT groups (P=0.009). PFS, progression-free survival; CI, confidence interval; FS, fruquintinib plus sintilimab; FT, fruquintinib plus TAS-102; TAS-102, trifluridine and tipiracil.

primary endpoint of disease progression or death. In this study, PR was observed in 14 patients, 49 patients had SD, 29 patients had PD, and CR was not observed. There were 8 patients with PR, 30 patients with SD and 9 patients with PD in the FS group. There were 6 patients with PR, 19 patients with SD and 20 patients with PD in the FT group. The DCRs of the FS group and FT group were 80.9% (38/47) and 55.6% (25/45), respectively, and the DCR of the FS group was higher than that of the FT group (P=0.009). The ORRs of the FS group and FT group were 17.0% (8/47) and 13.3% (6/45), respectively, and there was no significant difference between the FS and FT groups (P>0.05) (*Table 2*). The mPFS was 6.0 months (95% CI: 4.589–7.411) in the FS group and 3.5 months (95% CI: 0.964–6.145) in the FT group. The mPFS in the FS group was longer than that in the FT group (P=0.009) (*Figure 1*).

Subgroup analysis of predictive factors

In this study, we used multivariate Cox regression analysis to evaluate the effect on PFS of each factor, including sex (male *vs.* female), site of primary tumor (left colon *vs.* right colon), age (<65 *vs.* ≥65 years), liver metastasis (with *vs.* without), genetic status of *KRAS*, *NRAS* and *BRAF* (wild type *vs.* mutant), ECOG score, number of treatment regimens received, and whether targeted therapy (bevacizumab, cetuximab) was received. No significant differences were noted in the subgroup analysis with regard to PFS (P>0.05) (*Table 3*).

Safety

The median follow-up time of the study was 10.791 months. All patients were treated with FS or FT until unacceptable toxicity, disease progression or death occurred. No treatment-related deaths or unexpected side effects were observed in this study. Except for one patient in FS group who stopped the drug due to severe rash, the other patients did not reduce or stop the drug due to treatment-related toxic and side effects.

The majority of AEs were grade 1–2 in severity and generally well tolerated. AEs are presented in *Table 4*. The most common grade 3 or above AEs were anemia (4.3% in the FS group and 6.7% in the FT group), leukopenia (2.1% in the FS group and 4.4% in the FT group), hepatic impairment (2.1% in the FS group and 4.4% in the FT group), fatigue (4.3% in the FS group and 6.7% in the FT group), decreased appetite (2.1% in the FS group and 8.9% in the FT group), secondary hypertension (4.3% in the FS group and 2.2% in the FT group) and hand-foot syndrome (2.1% in the FS group and 4.4% in the FT group). In addition, one patient in the FS group developed a severe rash that resolved after drug discontinuation and symptomatic treatment (*Table 4*).

Discussion

CRC is a highly heterogeneous disease. At present, the strategy for the third-line or above treatment of mCRC is gene detection-based layered therapy. Immunotherapy is the recommended treatment of choice for MSI-H CRC (20-22). However, in most patients with MSS CRC, single therapy with immunotherapy and chemotherapy is virtually

Table 3 Multivariate Cox regression model analysis of factors in predicting PFS

Parameter	No. of patients (%)	HR	95% CI	P
Age (years)		1.143	0.603–2.167	0.681
≥65	18 (19.6)			
<65	74 (80.4)			
Sex		0.702	0.422–1.168	0.173
Female	44 (47.8)			
Male	48 (52.2)			
ECOG PS		0.686	0.348–1.353	0.277
0–1	80 (87.0)			
2	12 (13.0)			
Primary tumor site		0.856	0.519–1.411	0.541
Left colon	61 (66.3)			
Right colon	28 (30.4)			
With liver metastasis		1.112	0.686–1.800	0.667
Yes	53 (57.6)			
No	39 (42.4)			
Number of metastatic sites		0.965	0.594–1.566	0.884
<3	48 (52.2)			
≥3	44 (47.8)			
Treatment line		1.315	0.825–2.094	0.249
3	43 (46.7)			
≥4	49 (53.3)			
KRAS		1.523	0.871–2.663	0.140
Wild type	57 (62.0)			
Mutant	35 (38.0)			
NRAS		0.517	0.224–1.195	0.123
Wild type	84 (91.3)			
Mutant	8 (8.7)			
BRAF		2.260	0.887–5.757	0.088
Wild type	86 (93.5)			
Mutant	6 (6.5)			
Previous bevacizumab		1.347	0.768–2.364	0.298
Yes	58 (63.0)			
No	34 (37.0)			
Previous cetuximab		1.499	0.808–2.781	0.199
Yes	26 (28.3)			
No	66 (71.7)			

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4 Treatment-related adverse events

Adverse event	FS group (n=47), n (%)			FT group (n=45), n (%)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Hematologic						
Anemia	21 (44.7)	2 (4.3)	0	24 (53.3)	3 (6.7)	0
Decreased white blood count	2 (4.3)	1 (2.1)	0	5 (11.1)	2 (4.4)	0
Decreased platelet count	8 (17.0)	0	0	10 (22.2)	1 (2.2)	0
Hepatic toxicity	7 (14.9)	1 (2.1)	0	6 (13.3)	2 (4.4)	0
Nonhematologic						
Decreased appetite	12 (25.5)	1 (2.1)	0	17 (37.8)	4 (8.9)	0
Diarrhea	11 (23.4)	1 (2.1)	0	12 (26.7)	0	0
Hand-foot syndrome	6 (12.8)	1 (2.1)	0	8 (17.8)	2 (4.4)	0
Oral mucositis	5 (10.6)	0	0	7 (15.6)	0	0
Rash	5 (10.6)	0	1 (2.1)	2 (4.4)	0	0
Hypothyroidism	6 (12.8)	1 (2.1)	0	1 (2.2)	0	0
Fatigue	13 (27.7)	2 (4.3)	0	15 (33.3)	3 (6.7)	0
Pneumonitis	2 (4.3)	0	0	0	0	0
Proteinuria	4 (8.5)	0	0	3 (6.7)	0	0
Secondary hypertension	5 (10.6)	2 (4.3)	0	4 (8.9)	1 (2.2)	0

FS, fruquintinib plus sintilimab; FT, fruquintinib plus TAS-102; TAS-102, trifluridine and tipiracil.

ineffective. Fruquintinib, a novel VEGFR inhibitor, is used to treat a variety of malignancies. The safety and efficacy of fruquintinib as third-line or follow-up treatment were evaluated in 416 mCRC patients in the FRESCO study. The mOS was 9.3 months (2.7 months longer than placebo), and the mPFS was significantly prolonged in patients receiving fruquintinib compared with placebo, improving from 1.8 to 3.7 months (23). Based on these findings, current guidelines recommend fruquintinib as a third-line treatment for mCRC.

Based on the benefits of monotherapy, antiangiogenic therapy combined with chemotherapy, immunotherapy and local treatment can exert synergistic effects to further improve patient survival benefits. In *in vivo* experiments, the synergistic antitumor effects of the combination of anti-PD-1 therapy and fruquintinib were observed in animal models of homologous mouse MSS CRCs established by subcutaneous transplantation of CT26 cells (24). Zheng *et al.* also found that potent anti-PD-1 could increase vascular perfusion by promoting the aggregation of $CD8^+$ T cells and IFN-γ production, suggesting a potential synergistic effect between VEGF/VEGFR and anti-PD-1 (25). In the combination therapy of anti-VEGF/VEGFR and anti-PD-1, dose- and time-dependent normalization of tumor vasculature by fruquintinib is critical for efficacy (26). Wang *et al.* reported a case of MSS mCRC in which the disease progressed after treatment with irinotecan, fluorouracil, and oxaliplatin as well as after higher-line treatments, including chemotherapy combined with bevacizumab, regorafenib monotherapy, and combined chemotherapy, but responded rapidly after treatment with anti-PD-1 combined with fruquintinib (24). The previously reported data on the treatment of MSS endometrial cancer with lenvatinib and pembrolizumab were consistent (27). The mechanism of action of this combination therapy may include elimination of anti-PD-1 resistance due to fruquintinib or synergistic enhancement of the efficacy of the two drugs; anti-PD-1 has been reported to enhance antitumor immunity triggered by VEGF/VEGFR inhibition (28,29). The phase IB of Abstract 2514 trial of fruquintinib combined with sintilimab for advanced colorectal cancer was released by the American Society of Clinical Oncology (ASCO) in 2021 (30). This

study confirmed that mOS was 11.8 months, mPFS was 6.9 months, ORR was 27.3%, and DCR was 95.5% for mCRC patients treated with oral fruquintinib 5 mg qd. In our previous studies, we found that the majority of patients were intolerant to oral administration of fruquintinib 5 mg qd (the majority of AEs included hepatic toxicity, hand-foot syndrome, etc.); therefore, in this study, fruquintinib was administered orally 4 mg qd, d1–21, every 28 days as a cycle. The mPFS was 6 months, and the DCR and ORR were 80.9% and 17.0%, respectively.

TAS-102 is indicated for mCRC patients who have received chemotherapy with fluorouracil, irinotecan, and oxaliplatin or who have received or are not suitable for anti-EGFR or anti-VEGF therapy. In the TERRA study, which involved 406 mCRC patients with at least a prior second-line standard chemotherapy regimen, TAS-102 significantly improved OS (7.1 to 7.8 months) and PFS (1.8 to 2.0 months) (31). Therefore, current guidelines recommend TAS-102 as a third-line treatment for mCRC (class 1A). In a phase II trial, TAS-102 plus bevacizumab significantly improved PFS and OS compared with TAS-102 alone in chemotherapy-resistant mCRC patients (32). Bevacizumab, a recombinant humanized monoclonal antibody, normalizes tumor vasculature by inhibiting VEGF and angiogenesis. Bevacizumab combined with TAS-102 increases the concentration of trifluridine in tumor DNA without increasing the toxicity and systemic exposure of trifluridine. In a preclinical study, investigators used TAS-102 plus bevacizumab to treat CRC xenografts and found that the combination therapy inhibited tumor growth significantly better than monotherapy, and the concentration of phosphorylated trifluridine in tumor tissue was higher in the TAS-102 plus bevacizumab group than in the TAS-102 monotherapy group (33). As a new VEGFR blocker, fruquintinib and TAS-102 can also be used as third-line treatments for mCRC, and their combination is theoretically feasible. In this study, the ORR and DCR values for the FT group were 13.3% and 55.6%, respectively, with an mPFS of 3.5 months. As of press time, the majority of patients were alive and had not yet reached OS in this study.

In summary, targeted VEGF or VEGFR biological agents combined with chemotherapy and anti-PD-1 treatment can bring longer survival benefits to patients than the application of a single drug, but the effectiveness and safety of these two combined modes still need to be comprehensively considered. In this study, we used the VEGFR inhibitor fruquintinib as the research drug and compared the efficacy and safety of fruquintinib in combination with sintilimab and fruquintinib in combination with TAS-102 in the third-line and above treatment of mCRC. We enrolled 92 MSS or pMMR mCRC patients who received FS or FT as third-line or higher-level treatment after progression on two or more regimens. As of November 2022, patients in the FS and FT groups had DCRs of 80.9% and 55.6% (P=0.009) in this study, but there was no significant difference in ORRs between the FS group and FT group (P>0.05). This result may be mainly related to 30 patients and 19 patients with curative effect of SD (FS and FT). For patients with mCRC who fail or are intolerant to second-line or above treatment, it was also a gratifying result for researchers to achieve SD in third-line or above treatment. Fifty-three patients with liver metastasis were included in this study. In the FS and FT groups, there was no statistical difference in ORR between patients with liver metastasis and patients without liver metastasis (P>0.05), which was inconsistent with the findings of Zhang *et al.* (34) (whether it was related to different doses of fruquintinib). Meanwhile, mPFS was 6.0 months in the FS group and 3.5 months in the FT group, and mPFS was longer in the FS group. The above results show that FS worked better than FT. The toxicities and side effects of the combined therapy for advanced mCRC cannot be ignored. Both combination regimens were well tolerated in this study, comparable to observations in previous studies (35-37). The most common AEs of grade 3 or above were anemia, leukopenia, fatigue, decreased appetite, and diarrhea. One patient in the FS group developed a severe rash that resolved after drug discontinuation and symptomatic treatment. In addition, 18 patients (19.6%) were older than or equal to 65 years old, including 12 patients (25.5%) in FS group and 6 patients (13.3%) in FT group. Compared with studies such as FRESCO-2 (38), 46% of patients older than or equal to 65 years old were treated with fruquintinib, younger patients were included in this study.

However, the number of patients enrolled is small in this study, so large-scale clinical trials are needed to further verify the effectiveness and safety of FS or FT as third-line or higher treatment for MSS mCRC.

Conclusions

Compared to FT, treatment with FS provides a longer mPFS and is well tolerated in patients with MSS mCRC who progress after receiving second-line or higher

chemotherapy regimens.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-867/rc

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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). This study was approved by the Ethics Committee of the Chongqing University, Cancer Hospital. The patients in this study signed a written informed consent form.

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