Original article

Efficacy and Safety Comparison of Regorafenib and Fruquintinib in Metastatic Colorectal Cancer-An Observational Cohort Study in the Real World

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Abstract

Regorafenib and fruquintinib are tyrosine kinase inhibitors that have been approved in the management of refractory metastatic colorectal cancer (mCRC) in China. However, limited data on the better treatment option has been reported for these mCRC patients. This ambispective observational cohort study evaluated the differences of efficacy and safety between regorafenib and fruquintinib. This study found that regorafenib and fruquintinib had similar efficacy for mCRC patients in a real-world setting. The toxicity profiles of the two drugs were also similar, but the frequency varied. Additionally, regorafenib followed by fruquintinib showed longer overall survival than the reverse, but the sequence needs to be further confirmed.

Background: Regorafenib and fruquintinib are tyrosine kinase inhibitors that are recommended for refractory colorectal cancer (CRC) in China. However, to date, no head-to-head trials have been conducted to guide clinical practice. **Methods and Patients:** An ambispective observational cohort study was conducted in Beijing Cancer Hospital. Patients with metastatic CRC who received regorafenib or fruquintinib were retrospectively collected between January 2018 and April 2020, and prospectively enrolled between May 2020 and February 2021. The primary outcome was time-to-treatment failure (TTF), and secondary outcomes were overall survival (OS) and adverse events. An additional goal of the study was to explore the appropriate sequence of regorafenib and fruquintinib treatment. **Results:** A total of 366 patients with metastatic CRC were enrolled to receive regorafenib ($n = 260$) or fruquintinib ($n = 106$) between January 2018 and February 2021. No difference was observed for median TTF (regorafenib 2.7 months vs. fruquintinib 3.1 months, $P = .200$) or median OS (regorafenib 13.8 months vs. fruquintinib 11.3 months, $P = .527$). The propensity score analysis showed similar results for median TTF and median OS between the 2 groups, as did the results of subgroup analysis for prospective set ($n = 146$). For sequence analysis, patients with regorafenib followed by fruquintinib ($n = 84$) showed longer OS than that with the reverse ($n = 29$) (28.1 months vs. 18.4 months, $P = .024$). Most patients tolerated regorafenib at a reduced dose (93.1%), and most patients tolerated fruquintinib at a standard dose (68.9%). The incidences of most adverse events were similar between the two groups, while any grade of hand-foot skin reaction and hyperbilirubinemia were more frequently observed in the regorafenib group and $\geq$grade 3 hypertension was more common in the fruquintinib group. **Conclusion:** Regorafenib and fruquintinib had similar efficacy and toxicity profiles with various frequency. Regorafenib followed by fruquintinib showed longer OS than the reverse, but the sequence needs to be further confirmed.

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the third most common cause of cancer-related deaths in the world.[1]

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Approximately 22% of CRC patients are diagnosed at the metastatic stage, with only 14% achieving 5-year relative survival.[1] Although significantly improved survival had been attained in some patients who were suitable for local ablative treatment, for most multiple metastatic CRC patients, systemic therapy remained the cornerstone through the whole process of management.[2]

Regorafenib, an oral multi-kinase inhibitor against several angiogenic receptors, including vascular endothelial growth factor receptors (VEGFR) 1/2/3, has been approved in patients with mCRC who failed standard therapies, based on the results of the CORRECT trial and the CONCUR trial, in western countries in 2012 and in China in 2017.[3-6] Fruquintinib, a highly selectively tyrosine kinase inhibitor (TKI) of VEGF 1/2/3, had also been recommended for refractory mCRC patients, based on the FRESCO trial in China in 2018.[7,8] TAS-102 is another option for refractory mCRC patients; however, though it has been approved since August 2019 in China, it is still outside the scope of medical insurance and has high cost.[9,10]

There have been several meta-analyses comparing the efficacy and safety of regorafenib and fruquintinib; however, no head-to-head trials have been conducted to provide clinicians with evidence for the best treatment option for refractory mCRC patients.[11-14] Here, we conducted an observational trial to compare the efficacy and safety of regorafenib and fruquintinib in real-world practice.

Patients and Methods

Study Design and Patients

This was an ambispective observational cohort study conducted at Beijing Cancer Hospital (NCT04431791). Patients who received regorafenib or fruquintinib were retrospectively collected between January 2018 and April 2020, and prospectively enrolled between May 2020 and February 2021. The informed consent of patients in the historical cohort was not required because of the retrospective design, while the patients in the prospective cohort were required to provide written informed consent. The study was approved by the Beijing Cancer Hospital ethics committee in May 2020, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The observation period was the time from the first administration of regorafenib or fruquintinib until death, loss to follow-up, or the end of the study. Patients' follow-up was until September 2021.

The main eligibility criteria were as follows: histologically confirmed metastatic colorectal cancer; previously treated with, or who could not tolerate, the standard chemotherapy, and for whom a decision was made by a treating physician to treat with regorafenib or fruquintinib; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2; adequate organ function. The key exclusion criteria were: a history of administration of regorafenib or fruquintinib; uncontrolled medical disorders.

Treatment

The standard dose was 160 mg for regorafenib and 5 mg for fruquintinib, once daily for 21 days of a 28-day cycle. Dose modification by treating physicians was permitted. Patients were allowed to receive combination therapy in the form of operation, radiother-apy, intervention therapy, chemotherapy, or immune checkpoint inhibitor (ICI), at the discretion of the treating physician.

Assessment

Tumor assessments were conducted according to the routine practice of the treating physician. Effectiveness and safety were assessed by the treating physician and the investigator. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version. 1.1. Adverse events (AEs) were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

The investigator collected demographic data and characteristics from medical records or by interview at baseline. Treatment-related data, including the dose of medication, AEs, and tumor status, were collected during follow-up visits every 2 months from first administration. After treatment discontinuation, the time of treatment failure, the reason, and the subsequent treatments were recorded, and survival was assessed every 3 months.

Endpoints

The primary outcome measured was time-to-treatment failure (TTF), which was defined as the time from first administration of treatment to the date of treatment discontinuation for any reason, including disease progression, treatment toxicity, or death. The secondary outcome was overall survival (OS), which was defined as the time from first administration of treatment until death; AEs were also measured as a secondary outcome. The appropriate sequence of regorafenib and fruquintinib was explored. For the patients who received crossover treatment after the first TTF, we defined TTF1 as the interval from the first administration of the primary treatment to the first TTF events, and TTF2 was defined as the interval from the starting of the second treatment to the second TTF events.

Statistical Analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were used to summarize data. Median (range) and number (proportion) of patients were used to present categorical variables and continuous variables, respectively. Chi-square test, Fisher's exact test, and Mann-Whitney U test were used to assess the difference among baseline characteristics stratified by the treatment group. Median TTF and OS were estimated using the Kaplan-Meier method. Median follow-up was calculated by the reverse Kaplan-Meier method. Univariate and multivariate Cox proportional hazards regression were used to evaluate the association between TTF and treatment effects for all patients (the observational set). Similar analyses were performed for OS. The assumption of proportionality was checked using Schoenfeld partial residual plots.

As an observational study, the present analyses suffered from selection bias. Thus, we conducted the propensity score matching analysis to reduce selection bias. Patients receiving regorafenib and fruquintinib were paired by a 3:1 nearest available score matching algorithm using the propensity score (propensity score set) with IBM SPSS 26.0 software (IBM, Inc). Patients in the two groups were matched with a difference of propensity score within 0.25. The

| Figure 1 | Flow diagram of patient selection. |
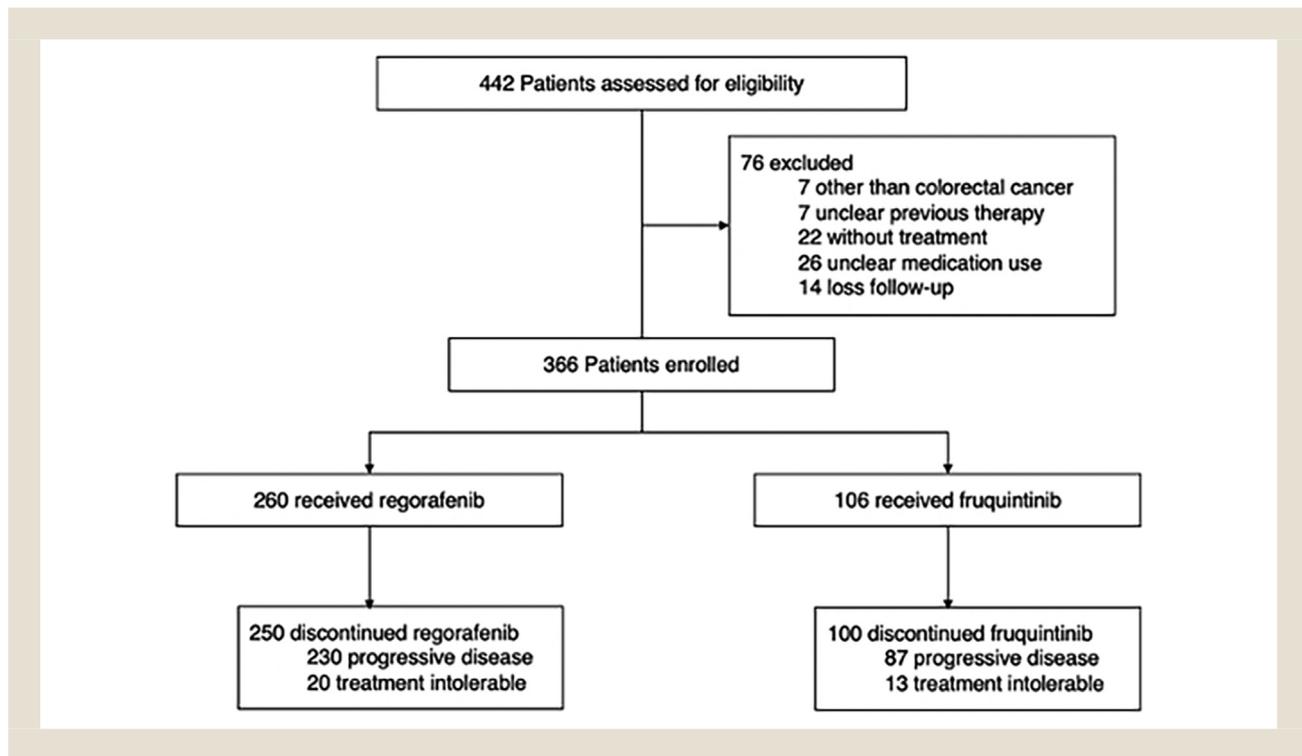
propensity score was calculated with all available baseline variables. Statistical tests were two-sided with a $P \leq .05$ significance level.

Results

In total, 442 patients were screened, and 366 patients who met all criteria were enrolled to receive regorafenib ($n = 260$) or fruquintinib ($n = 106$) (Figure 1), of which 146 patients were prospectively enrolled and 220 patients were retrospectively enrolled. Most baseline characteristics were similar between regorafenib and fruquintinib groups (Table 1); however, a higher proportion of patients in the regorafenib group had lymph node metastasis compared with the fruquintinib group. Additionally, 76.5% and 76.4% of patients in the regorafenib group and fruquintinib group had received previous anti-VEGF therapy, respectively. In RAS and BRAF wild-type patients, 63.7% (72/113) in the regorafenib group and 59.2% (29/49) in the fruquintinib group received anti-EGFR therapy. The median follow-up time was 17.9 months in the regorafenib group and 13.5 months in the fruquintinib group ($P = .392$).

Treatment

Among patients, 70.4% (183/260) and 75.5% (80/106) received single-agent regorafenib or fruquintinib, respectively ($P = .326$). The proportion receiving some combination of local therapy (surgery, radiotherapy, and interventional therapy) was similar between 2 groups (10.8% vs. 15.1%, $P = .248$). However, combination with ICI was more frequent in the regorafenib group (17.7% vs. 2.8%, $P < .001$), while combination with chemotherapy tended

to be more common in the fruquintinib group (4.2% vs. 9.4%, $P = .052$).

The rate of initial dose reduction was significantly more common in the regorafenib group than in the fruquintinib group (97.3% vs. 27.4%). Most patients started regorafenib with 80 mg/d (56.5%); only 2.7% of patients initially received the standard dose of 160 mg/d. A majority of patients started fruquintinib with the standard dose of 5 mg (72.6%) (Figure 2); 12.3% (32/260) of patients in the regorafenib group and 5.7% (6/106) of patients in the fruquintinib group tolerated a lower final dose than the initial dose that they received. In the combination therapy subgroup, 81.2% (63/77) of patients received 80 mg/d as an initial dose, while 57.7% (15/26) of patients in the fruquintinib group received 5 mg/d as an initial dose.

Efficacy

At the planned cutoff date, 250 TTF events and 139 deaths were observed in the regorafenib group, and 100 TTF events and 57 deaths in the fruquintinib group. The median TTF was 2.7 months (95% CI 2.2-3.0) and 3.1 months (95% CI 2.8-4.0) in the regorafenib and the fruquintinib groups, respectively (adjusted HR 1.61, 95% CI, 0.92-1.48, $P = .200$) (Figure 3A). The median OS was 13.8 months (95% CI 10.6-15.9) in the regorafenib group and 11.3 months (95% CI 8.1-14.7) in the fruquintinib group (adjusted HR 0.89, 95% CI 0.62-1.28, $P = .527$) (Figure 3B). In the efficacy-evaluable set, 3 patients in the regorafenib group and 1 patient in the fruquintinib group achieved partial response, and the disease control rate (DCR) was 52.0% and 57.0%, respectively (Table 2).

In the subgroup analysis, with balanced baseline characteristics (Table S1), the results of median OS in the prospective set and the

Table 1   Patient Characteristics

Characteristics	Regorafenib (N = 260)		Fruquintinib (N = 106)		P
	N	%	N	%	
Age (years, median (range))	61 (21 - 89)		59.5 (28 - 84)		.958
< 65 y	173	66.5	70	66.0	.927
≥ 65 y	87	33.5	36	34.0	
Sex					.711
Male	154	59.2	65	61.3	
Female	106	40.8	41	38.7	
ECOG PS					.796
0-1	247	95.0	100	94.3	
2	13	5.0	6	5.7	
Histology					.373
Well/moderately differentiated	201	77.3	77	72.6	
Low differentiated/mucinous/signet ring	48	18.5	26	24.5	
Unknown	11	4.2	3	2.8	
Primary tumor site					.567
Right colon[a]	57	21.9	24	22.6	
Left colon[b]	83	31.9	28	26.4	
Rectum	120	46.2	54	50.9	
RAS mutation status					.221
Wild-type	128	49.2	57	53.8	
KRAS mutation	121	46.5	42	39.6	
NRAS mutation	4	1.5	5	4.7	
Unknown	7	2.7	2	1.9	
BRAF V600E status					.712
Wild-type	233	89.6	96	90.6	
Mutation	15	5.8	7	6.6	
Unknown	12	4.6	3	2.8	
MMR					.574
dMMR	7	2.7	3	2.8	
pMMR	239	91.9	100	94.3	
Unknown	14	5.4	3	2.8	
Main metastatic sites at study entry					
Liver	163	62.7	64	60.4	.679
Lung	161	61.9	63	59.4	.658
Lymph node	113	43.5	34	32.1	.044
Peritoneum	60	23.1	23	21.7	.755
Number of metastatic sites at study entry					.502
1-2	162	62.3	70	66.0	
≥ 3	98	37.7	36	34.0	
Status of primary tumor at treatment start					.424
Resected	231	88.8	91	85.8	
Unresected	29	11.2	15	14.2	
Time from diagnosis of metastatic disease at study start					.434
< 18 mo	127	48.8	47	44.3	
≥ 18 mo	133	51.2	59	55.7	
Prior systemic anti-cancer therapy					
Fluoropyrimidine	257	98.8	105	99.1	.861
Oxaliplatin	242	93.1	98	92.5	.833

(continued on next page)

Table 1	(continued)					
	Regorafenib (*N* = 260)		Fruquintinib (*N* = 106)			*P*
Characteristics	*N*	%	*N*	%		
Irinotecan	221	85.0	88	83.0		.635
Anti-VEGF antibody	199	76.5	81	76.4		.980
Anti-EGFR antibody	80	30.8	29	27.4		.517
Number of prior systemic anti-cancer therapies						.325
1	57	21.9	16	15.1		
2	158	60.8	69	65.1		
≥ 3	45	17.3	21	19.8		

dMMR = deficient MMR; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; MMR = mismatch repair; pMMR = proficient MMR; VEGF = vascular endothelial growth factor.
Percentages might not total 100% because of rounding.
[a] Cecum, ascending colon, and right-sided transverse colon.
[b] Left-sided transverse colon, descending colon, and sigmoid colon.

retrospective set were consistent with those in the overall cohort, respectively (Table S2). Median TTF was significantly longer for patients with fruquintinib [3.5 months (95%CI 3.0-5.1)] than those with regorafenib [2.7 months (95%CI 2.3-3.1)] in the retrospective set (adjusted HR 1.43, 95% CI 1.02-1.99, *P* = .037), however, no difference of median TTF was observed in the prospective set (Table S2). Additionally, in the single-agent therapy set, in which the baseline characteristics were similar between two groups (Table S3), patients receiving regorafenib and fruquintinib also had similar median TTF (Figure S1A and Table S4) and median OS (Figure S1B and Table S5).

In the propensity score analysis for TTF and OS, all available baseline variables were included to calculate the propensity score. For this analysis, 186 patients in the regorafenib group and 98 patients in the fruquintinib were matched, and no significant difference was observed between 2 groups in median TTF (*P* = .208), or in median OS (*P* = .178) (Figure S2).

Safety

Overall, 85.0% (221/260) of patients had at least one AE considered to be regorafenib-related, while 79.2% (84/106) of patients had at least one AE considered to be fruquintinib-related (Table 3). Of these, 8.8% (20/250) and 13.0% (13/100) of patients in the regorafenib group and the fruquintinib group, respectively, discontinued treatment for AE. The frequency of any grade of hand-foot skin reaction (HFSR) and hyperbilirubinemia in the regorafenib group was significantly greater than the frequency in the fruquintinib group (43.8% vs. 26.4%, *P* = .002; 21.5% vs. 12.3%, *P* = .040). Any grade of proteinuria was more frequent in patients on fruquintinib therapy (20.8% vs. 13.5%); however, the result did not reach statistical significance (*P* = .081). Most of ≥ grade 3 AEs were similar between the two groups, while fruquintinib was associated with a higher rate of ≥ grade 3 hypertension (5.0% vs. 11.3%, *P* = .030).

Treatment Sequence

For treatment sequence analysis, 113 patients received regorafenib followed by fruquintinib (R-F group, *n* = 84) or vice versa (F-R group, *n* = 29). The median number of previous treatments when entering the sequence treatment was 3 in the R-F group (range 2-8) and F-R group (range 2-6). The median TTF1 was 3.1 months (95% CI 2.2-4.0) in the R-F group and 4.4 months (95% CI 3.6-6.3) in the F-R group (adjusted HR 1.39, 95% CI 0.88-2.18, *P* = .157) (Figure 4A). However, the median TTF2 in the R-F group [3.6 months (95% CI 2.8-4.4)] was significantly longer than that in the F-R group [1.7 months (95% CI 1.4-2.8)] (adjusted HR 0.22, 95% CI 0.21-0.55, *P* < .001) (Figure 4B). The OS, which was calculated from first enrollment (adjusted HR 0.59, 95% CI 0.38-0.93, *P* = .024) [28.1 months (95% CI 19.6-NR) vs. 18.4 months (95% CI 12.9-NR)] (Figure 4C), showed the same trend.

Discussion

To our knowledge, this was the first study to compare the efficacy and safety of regorafenib and fruquintinib, both of which have been recognized as standard treatments for refractory mCRC patients in China. With limited options for mCRC patients, it is critical to explore whether they could benefit from another drug with a similar mechanism after receiving one of the current therapies.

Our study showed that regorafenib and fruquintinib had similar median TTF (2.7 vs. 3.1 months) and median OS (13.8 vs. 11.3 months) in the observational set and propensity score set. In clinical practice, patients might receive a combination of regorafenib or fruquintinib with other therapies, including local therapy and ICI, to improve the disease control rate, alleviate tumor-associated symptoms, and prolong survival. In order to reflect the real-word situation, we did not exclude this segment of patients. This could be one of the reasons that the median TTF and median OS of regorafenib were longer than on previous real-world reports (TTF 1.6-2.2 months, OS 5.6-9.3 months).[15-19] In addition, some patients enrolled as receiving first- or second-line therapy, and most of patients receiving subsequent treatment instead of best-support care, might also contribute to the longer survival. However, data for fruquintinib were limited.

In our study, median OS was significantly better with regorafenib followed by fruquintinib than with fruquintinib followed by regorafenib (28.1 vs. 18.4 months); the same was true for TTF2 (3.6 vs. 1.7 months). This was similar to the result of the REVERCE study, in which regorafenib followed by cetuximab was associated

Figure 2 | Initial and last daily dose of regorafenib and fruquintinib.
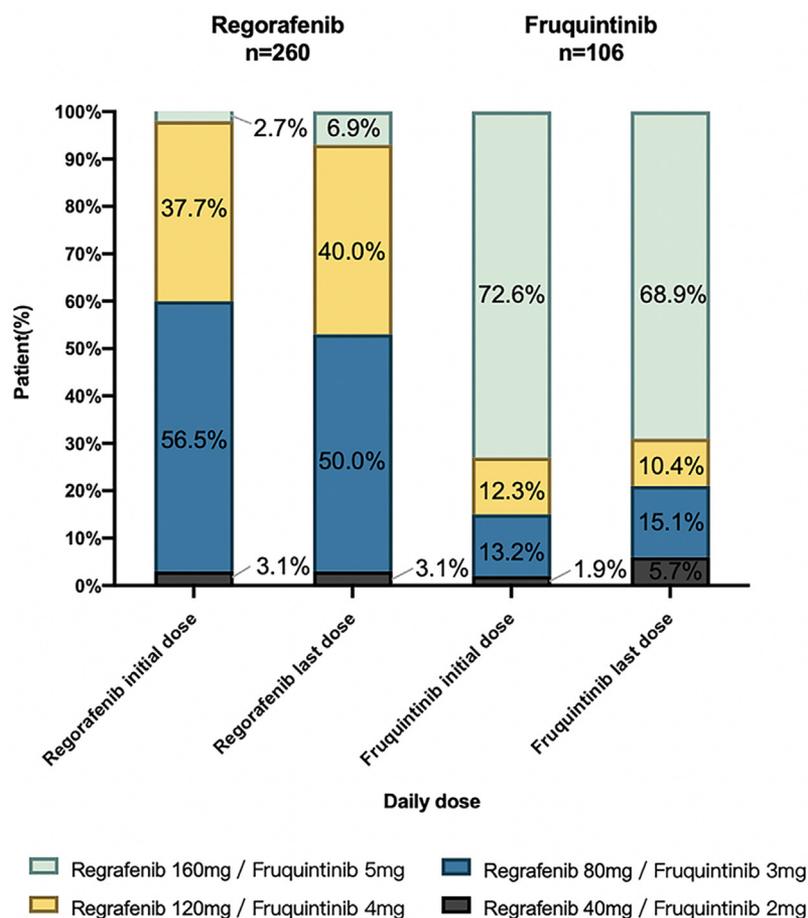
**Table 2 | Clinical Response of Efficacy Evaluable Group**

Response	Regorafenib ($N = 225$)		Fruquintinib ($N = 93$)	
	N	%	N	%
Best of response				
Complete response	0	0.0	0	0.0
Partial response	3	1.3	1	1.1
Stable disease	114	50.7	52	55.9
Progressive disease	108	48.0	40	43.0
Objective response rate	3	1.3	1	1.1
Disease control rate	117	52.0	53	57.0

with longer OS than was cetuximab followed by regorafenib, as well as PFS2, and similarly with PFS1.[20] Furthermore, previous work had reported anti-tumor activity when subsequent chemotherapy was given after regorafenib or reintroduced with regorafenib.[21-23] However, as a specific anti-vascular drug, fruquintinib is totally different from cetuximab or cytotoxic chemotherapy. Whether the sequential use of regorafenib and fruquintinib will cause these drugs to interact with each other is unclear, and this needs to be confirmed in the prospective study.

In our study, most patients (95%) received initial regorafenib at the reduced dose of 80 mg/day (57% of the full dose). Although nearly half of these patients (42.9%) received combination therapy, which could lead the physician to choose a more tolerable dose, still 49.2% (90/183) of patients received the reduced dose as their

Figure 3 Kaplan-Meier analysis for time-to-treatment failure and overall survival in the observation set. (A) Median TTF was 2.7 months (95% CI 2.2-3.0) in the regorafenib and 3.1 months (95% CI 2.8-4.0) in the fruquintinib. (B) Median OS was 13.8 months (95% CI 10.6-15.9) in the regorafenib and 11.3 months (95% CI 8.1-14.7) in the fruquintinib. OS = overall survival; TTF = time-to-treatment failure.
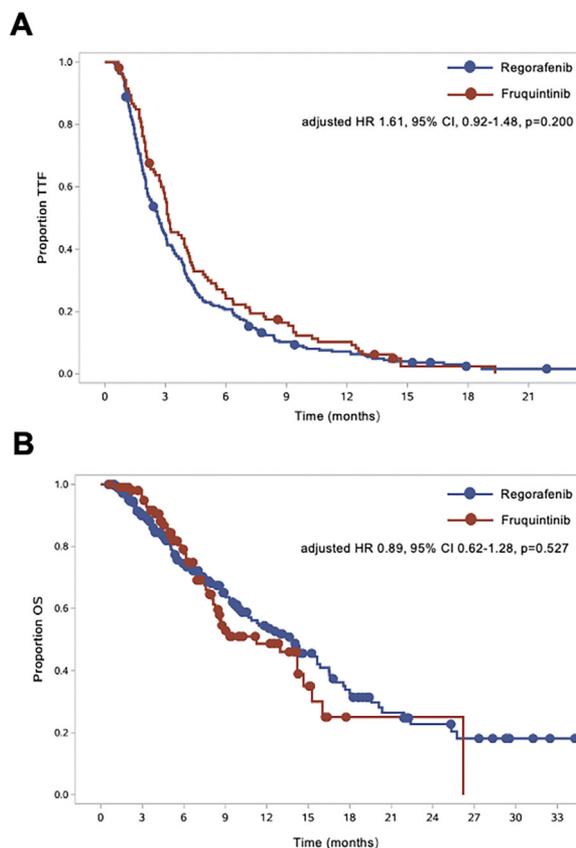
final dose in single-agent therapy. Although the CONCUR study confirmed the tolerance of 160 mg/d in Asian patients, including the Chinese population, patients enrolled in the clinical trial were generally in better condition.[4,24] In a prospective observational study, most patients from Taiwan (71.8%) started regorafenib with a dose lower than 160 mg/d, and 80% of patients received a reduced dose as their final dose.[25] According to the subgroup analysis of the CORRECT study, the frequencies of adverse events were significantly different in the Japanese and non-Japanese subgroups, which may partially explain the lower tolerance observed in patients in our study relative to those in most western studies.[26-28] Additionally, a dose-escalation strategy based on the ReDos study is the most commonly used in clinical practice, in which patients start with a dose of 80 mg/day and receive weekly dose escalation if no significant drug-related toxicities are observed, up to 160 mg/d.[29] However, the efficacy and the dose of regorafenib is controversial. In our study of the single-agent set, the median TTF of patients with a final dose of 160 mg/d and reduced dose was 3.9 and 2.7 months (*P* = .140), and the DCR in the two subgroups was 71.4% and 57.7% (*P* = .321), respectively. In another dose-escalation study,

patients who received 120 mg/d and failed to escalate to 160 mg/d showed a lower DCR (22%) than those who were escalated to 160 mg/d (75%).[30] It is not rare that both physicians and patients were unwilling to risk adverse events if a dose lower than 160 mg/d was well tolerated in clinical practice.

Limited data about fruquintinib in real-world practice has been reported. In our study, 69% of patients received 5 mg/d as their final dose, while 42.4% of patients with a reduced dose as their final dose received combination therapy. It seemed that fruquintinib was more tolerable than regorafenib. Although most patients with regorafenib received a reduced dose, any grade of HFSR and hyperbilirubinemia were more frequently observed in the regorafenib group. However, ≥grade 3 hypertension was more common in the fruquintinib group.

In general, the frequencies of AEs in our study were lower than the reports of randomized controlled trials.[3,4] Reasons for this may include: physicians' ability to treat with TKI-associated AE gradually matured after the accumulation of clinical experience; flexible dose selection was permitted, especially for regorafenib, for which most patients did not reach the standard dose. Furthermore, as this

Table 3   Comparison of the Frequency of Common Treatment-Related Adverse Events

Adverse Events	Regorafenib n = 260				Fruquintinib n = 106				P-value (Any grade)	P-value (Grade ≥3)
	Any grade		≥ Grade 3		Any grade		≥ Grade 3			
	N	%	N	%	N	%	N	%		
Any TRAE	221	85.0	55	21.2	84	79.2	24	22.6	.180	.754
Clinical adverse events										
HFSR	114	43.8	18	6.9	28	26.4	4	3.8	.002	.250
Hypertension	81	31.2	13	5.0	33	31.1	12	11.3	.997	.030
Fatigue	41	15.8	5	1.9	15	14.2	1	0.9	.696	.829
Diarrhea	26	10.0	4	1.5	8	7.5	1	0.9	.463	1.000
Anorexia	28	10.8	2	0.8	12	11.3	1	0.9	.878	1.000
Weight loss	21	8.1	0	0.0	7	6.6	0	0.0	.631	NA
Voice changes	19	7.3	0	0.0	3	2.8	0	0.0	.102	NA
Rash	15	5.8	1	0.4	5	4.7	0	0.0	.688	1.000
Oral mucositis	26	10.0	2	0.8	9	8.5	1	0.9	.656	1.000
Nose bleed	11	4.2	0	0.0	5	4.7	0	0.0	.785	NA
Fever	5	1.9	0	0.0	1	0.9	0	0.0	.829	NA
Nausea/Vomiting	12	4.6	0	0.0	4	3.8	0	0.0	.940	NA
Muscle pain	7	2.7	1	0.4	4	3.8	1	0.9	.832	.496
Colonic perforation	3	1.2	3	1.2	2	1.9	2	1.9	.959	.959
Laboratory abnormalities										
Leukopenia/Neutropenia	24	9.2	5	1.9	11	10.4	1	0.9	.735	.829
Anemia	10	3.8	1	0.4	3	2.8	0	0.0	.869	1.000
Thrombopenia	15	5.8	3	1.2	10	9.4	1	0.9	.207	1.000
ALT/AST increase	43	16.5	5	1.9	18	17.0	2	1.9	.918	.829
Hyperbilirubinemia	56	21.5	7	2.7	13	12.3	2	1.9	.040	.937
Proteinuria	35	13.5	4	1.5	22	20.8	5	4.7	.081	.159

ALT = alanine aminotransferase; AST = aspartate transaminase; HFSR = hand-foot skin reaction; TRAE = treatment-related adverse event.

is an observational study, some of the data are retrospective, which may affect the results.

This study had several limitations. This was a real-world observational study characterized by bias, in which we collected as many variables as possible that might affect the results, and used propensity scoring to analyze the data. Under these conditions, neat conclusions were difficult to draw. We chose TTF as the primary endpoint; compared with progressive-free survival, TTF also reflects tolerance to the drugs. However, TTF may be affected by the observation time. Considering that a substantial number of patients received a sequenced treatment of the two drugs, in order to reflect the respective efficacy of these drugs, we chose TTF instead of OS. For sequence analysis, more patients received regorafenib first followed by fruquintinib, because the latter was approved later; therefore, treatment sequence requires careful consideration and prospective study to further validate.

Conclusion

The present study investigated the differences of efficacy and safety between regorafenib and fruquintinib for mCRC patients. We found that regorafenib and fruquintinib had similar efficacy and toxicity profiles with various frequency in a real-world setting. Additionally, regorafenib followed by fruquintinib showed longer overall survival than the reverse. These results should be further investigated in prospective randomized clinical trials, and the exploration of molecular mechanism might provide more convincing evidence for precise treatment of mCRC.

Clinical Practice Points

- Precious indirect meta-analyses have showed similar efficacy and toxicity profiles of regorafenib and fruquintinib.
- There is no randomized controlled trial directly comparing regorafenib and fruquintinib.
- We compared regorafenib and fruquintinib, and explored the appropriate sequence in real-world set in Chinese mCRC patients.
- The regorafenib group and the fruquintinib group showed similar efficacy, and regorafenib followed by fruquintinib showed longer overall survival than the reverse.
- We performed propensity score-matched analysis, and subgroup analysis of single-agent therapy for sensitivity analysis, and the result did not change.
- Most of patients received regorafenib with reduced dose, while received fruquintinib with standard dose.
- Most AEs were similar, while any grade of HFSR and hyperbilirubinemia were more frequently observed in the regorafenib group

Figure 4 Kaplan-Meier analysis for time-to-treatment failure (TTF) and overall survival (OS) in the sequence population. (A) Median TTF1 was 3.1 months (95% CI 2.2-4.0) in the R-F group during regorafenib therapy and 4.4 months (95% CI 3.6-6.3) in the F-R group during fruquintinib therapy. (B) Median TTF2 was 3.6 months (95% CI 2.8-4.4) in the R-F group during fruquintinib therapy and 1.7 months (95% CI 1.4-2.8) in the F-R group during regorafenib therapy. (C) Median OS was 28.1 months (95% CI 19.6-NR) in the R-F group and 18.4 months (95% CI 12.9-NR) in the F-R group.
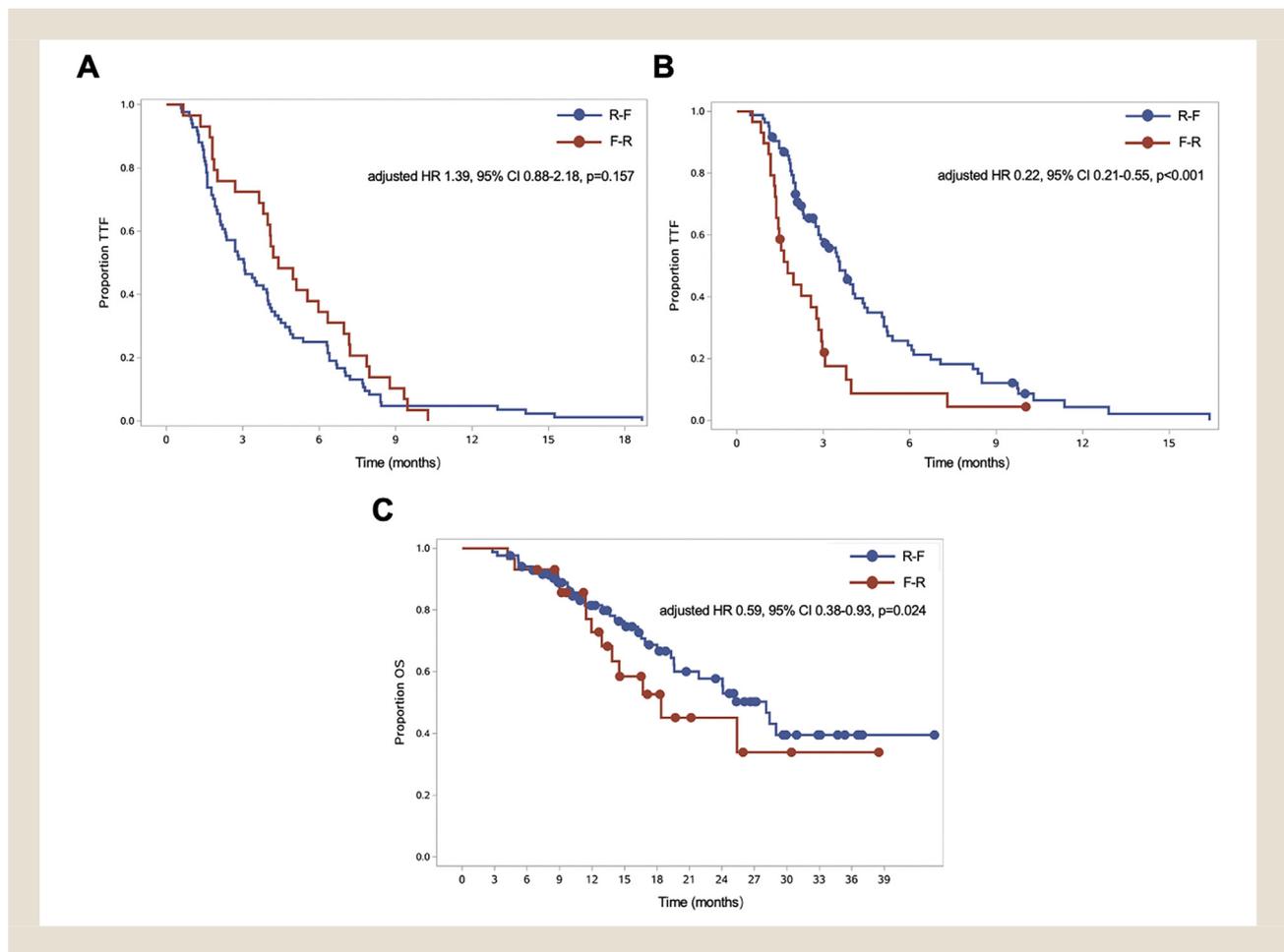
- and ≥grade 3 hypertension was more common in the fruquintinib group.
- Regorafenib followed by fruquintinib may prolong OS over fruquintinib followed by regorafenib, and the strategy to improve the tolerance of regorafenib are desperately needed.

Compliance with Ethical Standards

This study was approved by the Beijing Cancer Hospital Ethics Committee (No. 2020YJZ26). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

The informed consent of patients in the historical cohort was not required because of the retrospective design, while the patients in the prospective cohort were required to provide written informed consent.

Author Contributions

Qi Zhang: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing; Mifen Chen: Formal analysis, Methodology, Writing – original draft; Zhenghang Wang: Formal analysis, Methodology, Writing – review & editing; Changsong Qi: Resources, Writing – review & editing; Yanshuo Cao: Resources, Writing – review & editing; JunYan Zhang: Writing – review & editing; Zhi Peng: Resources, Writing – review & editing; Xicheng Wang: Resources, Writing – review & editing; Ming Lu: Resources, Writing – review & editing; Lin Shen: Resources, Writing – review & editing; Jian Li: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Data Availability Statement

The data that support the findings of our study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.01.007.

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