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ORIGINAL ARTICLE **CME**

Early Local Community Data on Safety and Efficacy of Fruquintinib in Metastatic Colorectal Cancer

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ABSTRACT

Introduction: *Fruquintinib, a selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3 tyrosine kinases, is indicated for late-line treatment of metastatic colorectal cancer (mCRC). This retrospective study aimed to review the safety and efficacy of fruquintinib in the Hong Kong population.*

Methods: *Patients with mCRC who had failed at least two standard chemotherapy regimens were treated with fruquintinib at two tertiary centres in Hong Kong between December 2021 and July 2023. We reported overall survival, event-free survival (EFS), disease control rate, and toxicity. EFS was defined as the time from starting treatment to an event, which could be disease progression, discontinuation of treatment for any reason, or death.*

Results: *A total of 26 mCRC patients were treated with fruquintinib. The median overall survival and median EFS were 8.9 months and 4.2 months, respectively. Among the 22 patients who experienced an event, 15 (57.7%) had disease progression, six (23.1%) discontinued treatment for any reason, and one (3.8%) died. The disease control rate was 38.5%, including two (7.7%) patients with partial response and eight (30.8%) patients with stable disease. Grade ≥3 adverse reactions occurred in 69.2% of patients, the most common of which were hypertension (53.8%), hand-foot syndrome (19.2%), and diarrhoea (11.5%). There were no treatment-related deaths.*

Conclusion: *Fruquintinib demonstrated reasonable clinical efficacy and a manageable safety profile, consistent with the findings of international clinical studies. It is a valid option for later-line mCRC patients.*

Key Words: *Carcinoembryonic antigen; ErbB receptors; Hand-foot syndrome; Vascular endothelial growth factor A*

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Ethics Approval: This research was approved by the Central Institutional Review Board of Hospital Authority, Hong Kong (Ref No.: CIRB-2023-006-2). Informed patient consent was waived by the Board due to the retrospective nature of the research and the use of anonymised data.

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中文摘要

使用呋喹替尼治療轉移性大腸癌的安全性及有效性的早期本地社區數據

蘇衍錕、劉芷珊、黃善敏、唐雯、黃嘉杰、岑翠瑜

引言：呋喹替尼是一種血管內皮生長因子受體（VEGFR）-1、-2及-3酪胺酸激酶選擇性抑制劑，適用於轉移性大腸癌的後期治療。本回顧性研究旨在調查於香港人口使用呋喹替尼的安全性及有效性。

方法：經歷最少兩次標準化療方案失敗的轉移性大腸癌患者於2021年12月至2023年7月期間在香港兩所三級醫療機構接受呋喹替尼治療。我們報告整體存活期、無事件存活期、疾病控制率及毒性數據。無事件存活期的定義為開始治療起計至有事件發生的時間，可能包括病情惡化、因任何原因導致停止治療或死亡。

結果：共有26名轉移性大腸癌患者接受呋喹替尼治療。整體存活期中位數及無事件存活期中位數分別為8.9個月及4.2個月。在22名有事件發生的患者當中，15名（57.7%）病情惡化，6名（23.1%）因任何原因導致停止治療，1名（3.8%）死亡。疾病控制率為38.5%，包括兩名（7.7%）部分反應患者及8名（30.8%）反應穩定患者。共有69.2%患者出現三級或以上不良反應，最常見為高血壓（53.8%）、手足症候群（19.2%）及腹瀉（11.5%）。本研究沒有與治療有關的死亡個案。

結論：呋喹替尼具有合理的臨床有效性及易於管理的安全狀況，與國際臨床研究結果一致，是後期轉移性大腸癌患者的有效選項。

INTRODUCTION

Globally, colorectal cancer is the third most common type of cancer and the second leading cause of cancer-related deaths.[1] In Hong Kong, colorectal cancer was not only the second most common cancer but also the second most common cause of cancer-related deaths in 2020.[2]

The primary treatment for metastatic colorectal cancer (mCRC) is chemotherapy, often supplemented by targeted therapy and, in certain cases, immunotherapy for patients with mismatch repair deficient tumours. For chemotherapy, standard chemotherapy regimens include 5-fluorouracil (or its oral prodrug capecitabine) plus either oxaliplatin or irinotecan, or both.[3,4] Targeted therapy agents include bevacizumab and aflibercept, which target the vascular endothelial growth factor (VEGF) pathway; and cetuximab and panitumumab, which target the epidermal growth factor receptor (EGFR) pathway.[3,4] Later-line treatment regimens include trifluridine-tipiracil[5] and regorafenib.[6] These two agents offer only modest improvements in overall survival (OS) and progression-free survival. However, even after failure on multiple different treatment strategies, patients may still maintain good performance status. This underscores the necessity for more safe and effective treatment options.

Fruquintinib is a selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 tyrosine kinases.[7] In the phase III FRESCO randomised clinical trial (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients), fruquintinib significantly improved the median overall survival (mOS) compared with that of the placebo group (9.3 months [95% confidence interval (CI) = 8.2-10.5] vs. 6.6 months [95% CI = 5.9-8.1]) in Chinese patients with mCRC who progressed after at least two prior chemotherapy regimens (i.e., third- or later-line use).[8] It was approved in Mainland China in 2018 and was granted a fast-track designation by the US Food and Drug Administration in June 2020 for the above indication.[9] Another recent phase III FRESCO-2 randomised clinical trial also showed significant improvement in mOS with fruquintinib compared with placebo (7.4 months [95% CI = 6.7-8.2] vs. 4.8 months [95% CI = 4.0-5.8]).[10] Fruquintinib received its approval from the US Food and Drug Administration on 8 November 2023, for adult patients

with mCRC who had previously received 5-fluorouracil, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if the tumour was RAS-wild type).[11]

The FRESCO trial recruited 416 Chinese patients from Mainland China, where fruquintinib was developed.[8] On the other hand, the FRESCO-2 trial included patients from North America, Europe, Australia and Japan, but Japanese patients comprised <10% of the trial population.[10] The FRESCO trial excluded patients who had been previously exposed to regorafenib,[8] while patients who progressed on or were intolerant to trifluridine-tipiracil or regorafenib could enter the FRESCO-2 trial.[10] Hong Kong was not a study site in either trial, and local experience in the use of fruquintinib was scarce.

This study aimed to analyse the safety and efficacy of fruquintinib in mCRC patients. To the best of our knowledge, this is the first retrospective study of fruquintinib in public healthcare setting in the local population.

METHODS

Data Collection and Participants

Clinical data from 26 patients who received fruquintinib between 31 December 2021 and 22 July 2023 were retrospectively reviewed and collected from the institutional databases of two tertiary centres in Hong Kong, namely, Princess Margaret Hospital and Tuen Mun Hospital. The inclusion criteria for fruquintinib use were modified from the FRESCO[8] and FRESCO-2[10] trials, which were as follows: (1) age ≥18 years; (2) an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1; (3) histologically confirmed mCRC; (4) failure (progressive disease or intolerance) on at least two standard chemotherapy regimens using fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF antibodies (bevacizumab and aflibercept), or anti-EGFR antibodies (cetuximab or panitumumab); (5) measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (6) adequate bone marrow reserve (absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥100 × 10^9/L, and haemoglobin level ≥9.0 g/dL); (7) renal function (serum creatinine level ≤1.5 × upper limit of normal [ULN] or creatinine clearance ≥60 mL/min; urine dipstick protein of ≤1+ or 24-hour urine protein level <1.0 g/24 h); and (8) liver function (serum total bilirubin level ≤1.5 × ULN; alanine aminotransferase and aspartate aminotransferase level ≤2.5 × ULN in subjects without hepatic metastases; and alanine aminotransferase and aspartate aminotransferase level ≤5 × ULN in subjects with hepatic metastases). There were no exclusion criteria involving prior use of trifluridine-tipiracil or regorafenib.

Study Design

This was a local, single-arm, retrospective analysis of patients with mCRC conducted at two tertiary centres in Hong Kong. These patients had either progressed or shown intolerance after receiving at least two lines of chemotherapy. The included patients underwent repeated 28-day treatment cycles of fruquintinib, with a schedule of 3 weeks on the medication (5 mg oral daily) followed by a 1-week break. This treatment cycle was continued until disease progression, death, occurrence of unacceptable toxicity, or discontinuation by the physician. Dose reduction was allowed to manage treatment-related adverse effects and followed the protocol of the FRESCO trial.[8]

Clinical Assessment Outcomes and Endpoints

The primary endpoint was OS, defined as the time from the start of treatment using fruquintinib to death from any cause. Tumour response assessment was performed at intervals subject to the availability of imaging and physician discretion, and response was defined by RECIST version 1.1. The secondary endpoints were event-free survival (EFS) [defined as the time from starting treatment to an event, which could be disease progression defined as the first documentation of disease progression assessed by the investigator according to RECIST version 1.1, discontinuation of treatment for any reason, or death], duration of treatment (defined as the time from starting treatment to last study treatment dose), objective response rate (defined as confirmed complete or partial response), disease control rate (defined as the sum of the complete response, partial response and stable disease rates), and carcinoembryonic antigen (CEA) response. EFS was selected instead of progression-free survival because the imaging intervals in real-world settings vary. In heavily pretreated patients, quality of life (QoL) is important, and discontinuation of treatment for any reason can also indicate the tolerability of a drug. For CEA response, a definition modified from the RECIST criteria was used to evaluate treatment response, and responses were classified into three groups, namely, CEA-RD (responsive disease), CEA-SD (stable disease), and CEA-PD (progressive disease).[12,13] CEA-RD was defined as a decrease of >30% from the original

level; CEA-PD was defined as an increase of >20% from the original level.[12,13] A change in the CEA level that did not meet the criteria for CEA-RD and CEA-PD was defined as CEA-SD.[12,13]

Adverse events (AEs) were recorded throughout the study from the start of treatment to the end of the study period or the start of the next line of treatment. They were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[14]

Statistical Analysis

For OS and EFS, the Kaplan-Meier method was used to estimate the median survival time and 95% CI. Relationships between individual patient characteristics and OS or EFS were analysed using the Cox proportional hazards model to estimate hazard ratios (HRs) and 95% CIs. All analyses were performed using commercial software SPSS (Windows version 28.0; IBM Corp, Armonk [NY], US). A p value of < 0.05 was considered statistically significant.

RESULTS

The baseline demographics and disease characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of the study population (n = 26).*

Age, y	
Median (range)	63.5 (38-74)
≥65	12 (46.2%)
Sex	
Female	11 (42.3%)
Male	15 (57.7%)
ECOG performance status score	
0	16 (61.5%)
1	10 (38.5%)
Primary site at first diagnosis	
Left colon	20 (76.9%)
Right colon	6 (23.1%)
Site of metastasis	
Liver	19 (73.1%)
Lung	19 (73.1%)
Brain	0
>1 site	12 (46.2%)
RAS status	
Wild type	13 (50.0%)
K/N-RAS mutant	13 (50.0%)
BRAF V600E mutation	
No	18 (69.2%)
Yes	0
Unknown	8 (30.8%)
MSI or MMR status	
MSS or pMMR	9 (34.6%)
MSI-H or dMMR	0
Unknown	17 (65.4%)
No. or previous treatment lines in metastatic disease	
Median (range)	2 (2-4)
≤3	21 (80.8%)
>3	5 (19.2%)
Previous therapies	
VEGF inhibitors	19 (73.1%)
EGFR inhibitors	11 (42.3%)
Immune checkpoint inhibitor	0
BRAF inhibitors	0
Previous trifluridine-tipiracil or regorafenib	
Trifluridine-tipiracil	13 (50.0%)
Regorafenib	2 (7.7%)
Both	2 (7.7%)

Abbreviations: dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; MMR = mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability–high; MSS = microsatellite stable; pMMR = proficient mismatch repair; VEGF = vascular endothelial growth factor.
* Data are shown as No. (%), unless otherwise specified.

Survival Outcomes and Duration of Treatment

The median duration of treatment was 4.3 months (range, 0.6-15.4) and the median number of treatment cycles was 3 (range, 1-17). The median follow-up time was 7.3 months. The mOS was 8.9 months (95% CI = 4.5-13.3). The Kaplan-Meier plot for OS is shown in Figure 1. The proportion of patients still alive at 6 months was 78.7% and that at 12 months was 41.2%.

The median EFS was 4.2 months (95% CI = 2.5-5.9). Among the 22 of 26 patients who experienced an event, 15 (57.7%) had disease progression, six (23.1%) discontinued treatment for any reason, and one (3.8%) died. The Kaplan-Meier plot for EFS is shown in Figure 2.

Subgroup analyses of OS and EFS were carried out with a Cox proportional hazards model (simple and multivariable), but only a few clinical, tumour, or treatment factors exhibited a statistically significant correlation (Tables 2 to 4). Simple analysis also revealed that OS was worse for patients with liver metastasis and with multiple sites of metastasis (Table 2). Patients with an ECOG performance status score of 0 had better EFS (HR = 0.34; 95% CI = 0.14-0.85) [Table 4 and Figure 3]. Previous use of trifluridine-tipiracil, regorafenib, or both did not significantly affect OS or EFS (Tables 2 and 4).

The starting dose of fruquintinib was 5 mg daily (3 weeks on, 1 week off). 11 patients had their dose reduced, with 5 patients (19.2%) being reduced to 4 mg daily and 6

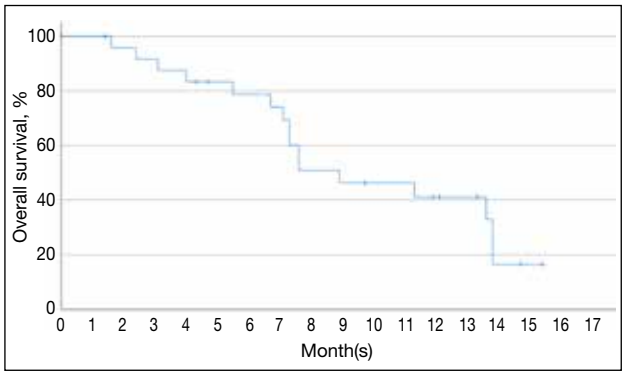

Figure 1. Kaplan-Meier estimates for overall survival in patients with metastatic colorectal cancer receiving fruquintinib.

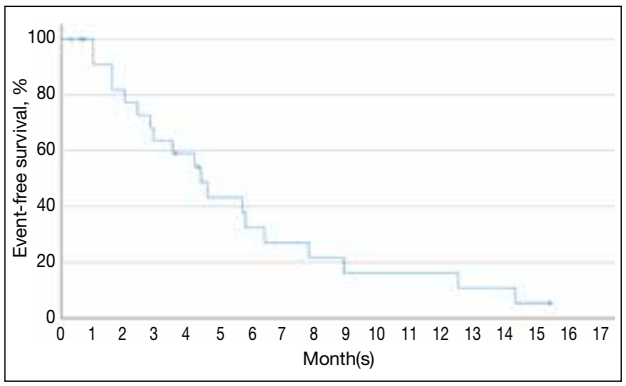

Figure 2. Kaplan-Meier estimates for event-free survival in patients with metastatic colorectal cancer receiving fruquintinib.

patients (23.1%) being reduced to 3 mg daily. Dose reduction of fruquintinib was associated with better OS (HR = 0.19, 95% CI = 0.05-0.72; p = 0.014) [Table 2 and Figure 4], but not in EFS (HR = 0.52, 95% CI = 0.22-1.21; p = 0.129) [Table 4].

Radiological Response

In patients treated with fruquintinib, the disease control rate was 38.5% (10 of 26 patients), which included two (7.7%) patients with partial response and eight patients (30.8%) with stable disease. There was no patient with complete response.

Carcinoembryonic Antigen Response

Regarding serum CEA responses, the differences in OS and EFS were not statistically significant between patients with CEA-RD, CEA-SD and CEA-PD. Numerically, patients with CEA-RD had better OS and EFS than patients with CEA-PD (Tables 2 and 4).

Table 2. Simple analysis of risk factors associated with overall survival.

	Hazard ratio (95% CI)	p Value
Age, y		
<65	1	
≥65	1.13 (0.41-3.10)	0.811
Sex		
Female	1	
Male	2.52 (0.81-7.83)	0.111
ECOG performance status score		
0	0.37 (0.13-1.06)	0.064
1	1	
Primary site at first diagnosis		
Left colon	1	
Right colon	1.15 (0.36-3.68)	0.815
Site of metastasis		
Liver metastasis	3.52 (1.07-11.57)	0.038
Lung metastasis	1.28 (0.37-4.51)	0.697
>1 site	5.45 (1.57-18.94)	0.008
RAS status		
Wild type	1	
K/N-RAS mutant	0.89 (0.33-2.37)	0.810
No. of previous treatment lines in metastatic disease		
≤3	1	
>3	0.98 (0.31-3.04)	0.966
Previous therapies		
VEGF inhibitors	0.74 (0.26-2.15)	0.584
EGFR inhibitors	0.89 (0.33-2.38)	0.809
Previous trifluridine-tipiracil or regorafenib		
Trifluridine-tipiracil	1.19 (0.44-3.22)	0.739
Regorafenib	0.98 (0.22-4.41)	0.980
Both	0.98 (0.22-4.41)	0.980
CEA response		
Responsive disease	0.63 (0.22-1.76)	0.373
Stable disease	1.68 (0.36-7.74)	0.507
Progressive disease	1.37 (0.45-4.14)	0.581
Dose reduction		
No	1	
Yes	0.19 (0.05-0.72)	0.014

Abbreviations: 95% CI = 95% confidence interval; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor.

Table 3. Multivariable analysis of risk factors associated with overall survival.

	Hazard ratio (95% CI)	p Value
Liver metastasis	1.56 (0.33-7.43)	0.579
>1 site of metastases	3.87 (0.86-17.35)	0.077
Dose reduced	0.23 (0.06-0.90)	0.035

Abbreviation: 95% CI = 95% confidence interval.

Adverse Events

Twenty-five of 26 patients (96.2%) had at least one AE of any grade (Table 5). The most frequently reported

Table 4. Simple analysis of risk factors associated with event-free survival.

	Hazard ratio (95% CI)	p Value
Age, y		
<65	1	
≥65	1.11 (0.45-2.72)	0.817
Sex		
Female	1	
Male	0.86 (0.36-2.07)	0.743
ECOG performance status score		
0	0.34 (0.14-0.85)	0.022
1	1	
Primary site at first diagnosis		
Left colon	1	
Right colon	1.41 (0.54-3.69)	0.490
Site of metastasis		
Liver metastasis	2.30 (0.87-6.08)	0.092
Lung metastasis	0.64 (0.23-1.80)	0.394
>1 site	1.73 (0.68-4.44)	0.253
RAS status		
Wild type	1	
K/N-RAS mutant	0.79 (0.34-1.83)	0.574
No. of previous lines of treatment for metastatic disease		
≤3	1	
>3	1.57 (0.60-4.13)	0.358
Previous therapies		
VEGF inhibitors	0.67 (0.25-1.79)	0.422
EGFR inhibitors	1.10 (0.48-2.56)	0.821
Previous trifluridine-tipiracil or regorafenib		
Trifluridine-tipiracil	1.58 (0.64-3.86)	0.319
Regorafenib	1.46 (0.33-6.54)	0.623
Both	1.46 (0.33-6.54)	0.623
CEA response		
Responsive disease	0.89 (0.36-2.21)	0.799
Stable disease	2.35 (0.60-9.16)	0.219
Progressive disease	0.80 (0.30-2.15)	0.661
Dose reduction		
No	1	
Yes	0.52 (0.22-1.21)	0.129

Abbreviations: 95% CI = 95% confidence interval; CEA = carcinoembryonic antigen; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor.

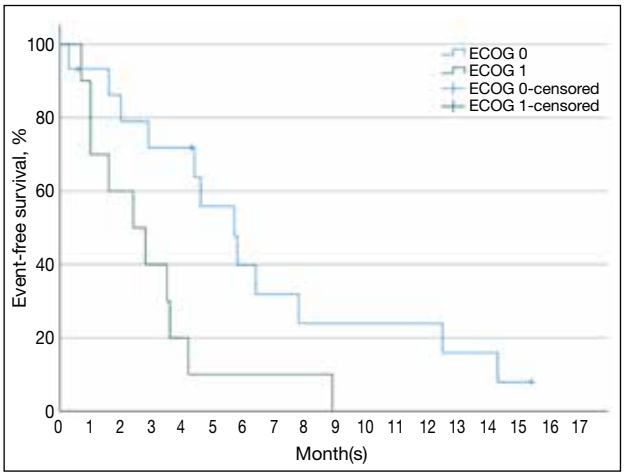

Figure 3. Kaplan-Meier estimates for event-free survival in patients with metastatic colorectal cancer receiving fruquintinib (with Eastern Cooperative Oncology Group performance status score of 0 and 1).
Abbreviation: ECOG = Eastern Cooperative Oncology Group.

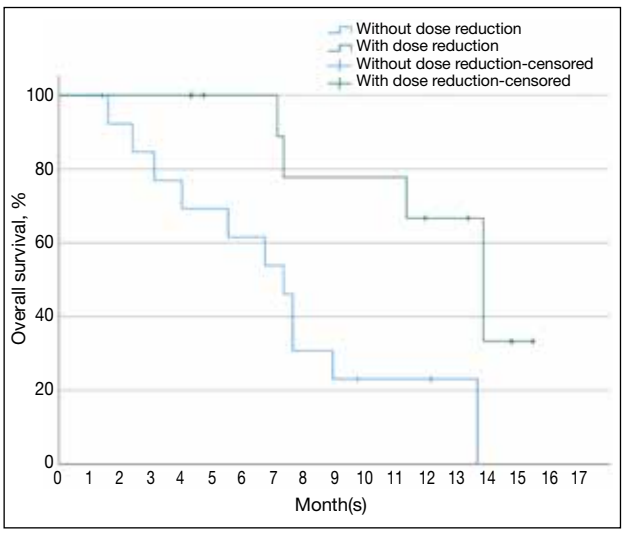

Figure 4. Kaplan-Meier estimates for overall survival in patients with metastatic colorectal cancer receiving fruquintinib (with or without dose reduction).

AEs of any grade were hypertension (84.6%), proteinuria (57.7%), hand-foot syndrome (HFS) [50%], and hypothyroidism (50%). Severe AEs (grade ≥3) occurred in 18 patients (69.2%), with the most common being hypertension (53.8%), HFS (19.2%), and diarrhoea (11.5%) [Table 5]. There were no treatment-related deaths in the study population.

Six of 26 patients (23.1%) discontinued fruquintinib due to treatment-related AEs. The most frequent AE that led to treatment discontinuation was HFS, in two patients (7.7%). Treatment interruption due to AEs occurred in five patients (19.2%), and the most common AE associated with treatment interruption was hypertension, in two patients (7.7%). Dose reduction due to AEs occurred in 11 patients (42.3%). The most frequent AEs leading to dose reductions were HFS (11.5%), proteinuria (11.5%), and diarrhoea (7.7%).

DISCUSSION

This retrospective study investigated the local population treated with fruquintinib at two tertiary

Table 5. Adverse events of the study population (n = 26).*

	Any grade	Grade ≥3
Any	25 (96.2%)	18 (69.2%)
Hypertension	22 (84.6%)	14 (53.8%)
Proteinuria	15 (57.7%)	2 (7.7%)
Hand-foot syndrome	13 (50.0%)	5 (19.2%)
Hypothyroidism	13 (50.0%)	0
Elevated ALT level	11 (42.3%)	0
Diarrhoea	8 (30.8%)	3 (11.5%)
Fatigue	7 (26.9%)	0
Elevated bilirubin level	6 (23.1%)	1 (3.8%)
Weight loss	6 (23.1%)	0
Stomatitis	5 (19.2%)	1 (3.8%)
Thrombocytopenia	5 (19.2%)	0
Decreased appetite	5 (19.2%)	0
Bone pain	4 (15.4%)	0
Bleeding	3 (11.5%)	1 (3.8%)
Dysphonia	3 (11.5%)	0

Abbreviation: ALT = alanine aminotransferase.
* Data are shown as No. (%).

institutions in Hong Kong, which included patients who had experienced disease progression following at least two lines of chemotherapy. This study did not have a placebo arm; the analysis of the results focuses on early experience of safety and efficacy in our locality.

Efficacy

In this study, the mOS was 8.9 months and the median EFS was 4.2 months, with a disease control rate of 38.5%. In Hong Kong, third-line or beyond monotherapy options for mCRC include trifluridine-tipiracil and regorafenib. In the RECOURSE trial (trifluridine-tipiracil vs. placebo in patients with previously treated mCRC), the treatment group had an mOS of 7.1 months and a disease control rate of 44%.[5] In the CONCUR trial (regorafenib vs. placebo in Asian patients with previously treated mCRC), the treatment group had an mOS of 8.8 months and a disease control rate of 51%.[6] Our data suggest that fruquintinib is a feasible monotherapy option in the third line and beyond setting for mCRC patients in Hong Kong.

OS and EFS analyses did not reveal any statistically significant differences in most of the subgroups (Tables 2 to 4), although OS was shown to worsen when patients had liver metastasis or more than one site of metastasis (Table 2). EFS was shown to be related to ECOG performance status score (Table 4). There was no statistically significant correlation between CEA response and OS or EFS (Tables 2 and 4), although OS tended to improve in patients with CEA-RD and tended to worsen in patients with CEA-PD.

In terms of the radiological and CEA (tumour marker) response, there were more patients with CEA-RD than there were with an objective response. This could be due to less intensive imaging schedules in public hospital settings, such that metabolic or relatively short-lived treatment responses could not be captured radiologically. Further study is needed to confirm the correlation between CEA response and survival, and studying the CEA response could help determine whether it can supplement the suboptimal scanning schedule in assessing the treatment response.

Adverse Events

The incidence of AEs and serious AEs was considerably high in the study population. The most frequently reported grade ≥3 AEs were hypertension, HFS, and diarrhoea (Table 5). These AEs were manageable by supportive measures and dose modification. The discontinuation of fruquintinib in this study was 26.9%, whereas the rate in FRESCO and FRESCO-2 were 15.1%[8] and 20%,[10] respectively. Further QoL analysis would be valuable to correlate the relatively high incidence of AEs and their impact on patient's QoL.

Baseline hypertension was a strong risk factor for high-grade hypertensive toxicity. Among the 14 patients who experienced grade ≥3 hypertension, all had preexisting hypertension at baseline. The baseline hypertension rate (88.4%, n = 23) was relatively high when compared to that of the general population (57.4% in the 65-84 age-group).[15] The odds ratio associated with grade ≥3 hypertension was 7.00 for patients with baseline hypertension of any grade (95% CI = 0.34-144.06; p = 0.20). Of those patients with baseline hypertension, only eight (34.8%) received intervention. Home blood pressure monitoring was started or ensured in seven patients, while antihypertensive therapy was started or titrated only in one patient. Of the eight patients who underwent intervention, seven (87.5%) still developed grade ≥3 hypertension. These findings suggested that more aggressive intervention by managing oncologists is needed for patients with baseline hypertension.

According to the evidence from regorafenib, which is also a VEGFR inhibitor, when encountering grade 2 hypertension, treating physicians can consider starting a single antihypertensive agent (such as an angiotensin-converting enzyme inhibitor).[16] For grade 3 hypertension, an additional agent (such as a beta blocker) should be considered, and if it remains refractory, a third agent (such as a calcium channel blocker) may be added.

Diuretics should be avoided because diarrhoea is also a common side-effect of fruquintinib, which may cause dehydration.

Another important adverse reaction was HFS. In HFS management, preventive measures include reducing skin friction, reducing exposure to heat, using skin barriers and early identification of skin abrasions.[17] The use of urea-based cream in combination with sorafenib (also a VEGFR inhibitor) has been shown to reduce the incidence of HFS.[18] Other commonly used measures include analgesics, topical anaesthetics, topical high-potency corticosteroids, keratolytic, and emollients.[17] If the above supportive measures are not able to improve tolerance, physicians can consider reducing the dose according to the drug's prescription information.

A total of 99% of the patients experienced any grade of AE in the fruquintinib (FRESCO-2) trial,[10] 97% in the regorafenib (CONCUR) trial[6] and 98% in the trifluridine-tipiracil (RECOURSE) trial,[5] with 63%, 54%, and 69% of patients experiencing grade ≥3 AEs, respectively. For specific grade ≥3 AEs, we compared the same class of drugs (i.e., fruquintinib vs. regorafenib), and the two drugs had similar severe AE profiles. Compared with drugs of a different class (i.e., fruquintinib vs. trifluridine-tipiracil), the toxicity profiles of these agents clearly differed, with the chemotherapy class (trifluridine-tipiracil) having more haematological toxicity, as one would expect. The most common severe AEs associated with trifluridine-tipiracil were neutropenia (38%), leukopenia (21%), and anaemia (18%).[5]

Patients in whom the dose was reduced had better OS and tended to improve EFS. As the dose reduction was mainly in response to toxicity, toxicity may be a predictor of the VEGFR inhibitor treatment response. A similar phenomenon was observed with anti-EGFR therapy, and a worse skin reaction was proven to be associated with a better response. In the OPUS study (untreated EGFR-expressing advanced colorectal cancer, FOLFOX4 vs. FOLFOX plus cetuximab),[19] patients with grade 3 to 4 skin toxicity had a 66.7% response rate, while grade 1 patients and grade 0 patients had response rates of 42.2% and 13%, respectively. In the EPIC study (The European Prospective Investigation into Cancer and Nutrition, second-line treatment after oxaliplatin-based therapy, cetuximab plus irinotecan versus irinotecan),[20] the median survival was 5.8 months for grade 0 toxicities, 11.7 months for grade 1 to 2 toxicities, and 15.6 months for grade 3 to 4 toxicities. However, further studies are needed to confirm this hypothesis in fruquintinib therapy.

Limitations

This study has several limitations. First, this was a retrospective study based only on data from two public tertiary centres in Hong Kong. Second, the sample size was small, and some subgroup analyses did not show statistical significance. Third, QoL data were not collected in this study.

CONCLUSION

Fruquintinib demonstrated reasonable clinical efficacy and a manageable safety profile and is a valid option for later-line mCRC patients. Hypertension is the most common high-grade toxicity, and preexisting hypertension is a strong risk factor. Proactive management of hypertension is strongly advocated. Prompt AE management can optimise its clinical utility, and dose reduction did not compromise efficacy. Further study of treatment sequence and patient QoL among the approved third-line or beyond options is needed.

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