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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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CASE REPORT

Oral fruquintinib combined with tegafur-gimeracil-oteracil potassium for advanced colorectal cancer to obtain longer progression-free survival: A case report

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Abstract

BACKGROUND

After the failure of second-line standard therapy, effective treatment options for metastatic colorectal cancer are limited, and the duration of remission cannot meet clinical needs. In addition, associated drug toxicity may lead to treatment interruption that may affect patient outcomes. Therefore, more safe, effective and convenient treatments are urgently needed.

CASE SUMMARY

Here, we describe a patient with advanced colorectal cancer with multiple metastases in both lungs. Oxaliplatin combined with 5-fluorouracil or capecitabine was given as the first-line treatment, and bevacizumab combined with irinotecan was given as the second-line treatment after disease progression. However, treatment was interrupted due to recurrent grade 2 nausea and grade 1 diarrhea. He received targeted therapy with fruquintinib starting on August 26, 2020 and responded well for 12 mo. After slow progression of the lung metastases, progression-free survival was again achieved over 13.5 mo by continued treatment of fruquintinib in combination with tegafur-gimeracil-oteracil potassium chemotherapy. Overall treatment duration was more than 25.5 mo. The treatments delayed tumor progression, reduced drug side effects, maintained a good quality of life, and further extended overall survival.

CONCLUSION

This case report detailed preliminary evidence showing that the combination of fruquintinib with tegafur-gimeracil-oteracil potassium chemotherapy double oral therapy may result in longer progression-free survival in patients with advanced colorectal cancer.

Key Words: Fruquintinib; Tegafur-gimeracil-oteracil potassium (S-1); Advanced colorectal

cancer; Progression-free survival; Case report

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Core Tip: After the failure of second-line standard therapy, effective treatment options for metastatic colorectal cancer (CRC) are limited. Here, we describe a patient with CRC with multiple lung metastases. Disease progression occurred after oxaliplatin + 5-fluorouracil or capecitabine as first-line treatment and bevacizumab + irinotecan as second-line treatment. The patient received targeted therapy with fruquintinib and responded well for 12 mo. Progression-free survival was again achieved over 13.5 mo by continuing fruquintinib in combination with tegafur-gimeracil-oteracil potassium chemotherapy. This case detailed preliminary evidence showing that the combination of fruquintinib with tegafur-gimeracil-oteracil potassium resulted in longer progression-free survival in patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide and the second most common cause of cancer-related deaths worldwide[1,2]. The most common cause of death in patients with CRC is distant metastasis, with approximately 25%-40% of patients with CRC already having metastases at the time of initial diagnosis[3,4].

Treatment recommendations for metastatic CRC (mCRC) include single or combination chemotherapy [5-fluorouracil (5-FU), capecitabine, oxaliplatin, and irinotecan] with or without targeted therapy (bevacizumab and cetuximab)[5]. These regimens are generally used for first-line and second-line treatments. The median overall survival for advanced CRC has now reached 30 mo by rational drug distribution[6]. For patients who do not respond to first-line and second-line standard therapies, the drugs approved for third-line treatment of mCRC in China currently include regorafenib, fruquintinib and garcia-carbonero (TAS-102), but the efficacy of these three regiments is limited[7,8,10].

5-FU combined with anti-vascular therapy showed synergistic efficacy and increased antitumor activity in refractory mCRC. The toxicity of the combined regimen was considered tolerable[11]. However, the use of bevacizumab needs to be carried out in the hospital. If the combination of two oral drugs is selected, it may reduce the inconvenience of repeated visits to the hospital and improve patient compliance and quality of life.

CASE PRESENTATION

Chief complaints

A 58-year-old male presented for treatment in March 2018 due to continuous increased frequency of defecation. Colonoscopy and biopsy revealed sigmoid adenocarcinoma, while chest computed tomography (CT) during the same period indicated multiple pulmonary nodules, which was considered metastasis.

History of present illness

He underwent laparoscopic radical resection of the left half colon on March 28, 2020. The postoperative pathological examination showed: (Sigmoid lesion) moderately differentiated adenocarcinoma; tumor size: 6.5 cm × 4.5 cm; invasion of the whole layer; and 19 lymph nodes around the intestine were negative for cancer metastasis. Immunohistochemistry examinations revealed the following: MSH2 (+), MLH1 (+), PMS2 (+), MSH6 (+), and suggestive pMMR. Genetic testing revealed *KRAS*, *NRAS*, *BRAF* wildtype, microsatellite stable, and *UGT1A1* GG type.

History of past illness

He had a history of hypertension and paroxysmal atrial fibrillation for 3 years.

Imaging examinations

In April 2018, reexamination by chest CT 1 mo after surgery revealed that the pulmonary nodules were larger than before, and abdomen CT showed no active findings.

FINAL DIAGNOSIS

The patient was diagnosed with stage IV sigmoid adenocarcinoma with multiple lung metastases.

TREATMENT

The patient refused to use bevacizumab and cetuximab because of concerns about adverse events such as hypertension and rash associated with targeted drug therapy. Instead starting in April 2018, the patient received six cycles of first-line treatment with mFOLFOX6 regimen (oxaliplatin 165 mg IV on day 1 + leucovorin 0.6 g IV on day 1 + 5-FU 0.75 g IV on day 1 + 5-FU 4.5 g CIV 46 h q2w), during which the intrapulmonary metastases were stable. In August 2018, the patient voluntarily stopped taking the mFOLFOX6 regimen due to personal reasons and did not receive maintenance treatment. Follow-up CT examination during drug withdrawal indicated slow progression of lung lesions.

In February 2019, the patient began the XELOX protocol (oxaliplatin 200 mg IV on day 1 +capecitabine 1.5 g PO bid on days 1–14 q3w) for five cycles of intermittent treatment. After the lung lesions were stable for a period of time, the patient stopped treatment again in July 2019. CT reexamination in October 2019 indicated that the lesions in the lung were enlarged. We judged the efficacy as progressive disease, and the progression-free survival (PFS) time of first-line treatment was 19 mo.

The major adverse events during treatment were grade 2 nausea and vomiting after chemotherapy, myelosuppression (grade 1 leukopenia and neutropenia and grade 2 thrombocytopenia), grade 1 liver dysfunction, and grade 1 numbness of the hands and feet. These adverse reactions and the inconvenience of repeated visits to the hospital were the main reasons the patient decided to stop treatment many times. The patient had no coughing and wheezing during treatment and maintained an Eastern Cooperative Oncology Group performance score of 0.

The patient was still unable to receive cetuximab due to anxiety about the rash. Second-line bevacizumab combined with irinotecan was initiated in November 2019 for a total of eight cycles. Bevacizumab (500 mg) and irinotecan (350 mg) were given every 3 wk. During second-line treatment, the patient's treatment was interrupted for 2 mo due to the coronavirus disease 2019 pandemic. The treatment evaluation was stable disease. However, grade 2 nausea and vomiting and grade 1 diarrhea occurred repeatedly during the treatment, and the patient could not tolerate these adverse events. Second-line treatment continued until July 2020. Due to no signs of disease progression (Figure 1A-C), the patient again requested that the treatment be discontinued and replaced with oral medication.

Therefore, treatment with oral fruquintinib [5 mg once a day (qd) on days 1–21 every 4 wk] was administrated as a third-line treatment starting on August 26, 2020. CT reexamination after 3 mo of treatment showed no significant change in the size of the metastatic lesions in both lungs, but the cavity in the lesions increased (Figure 1D-F). Subsequent follow-up and CT examination of the lung lesions remained stable (Figure 1G-I), while the main toxicity experienced by the patient during this period was hypertension, which could be well managed.

After 12 mo, some lesions in the lung slowly enlarged again (Figure 1J-L). After communication with the patient, the patient refused to receive intravenous therapy. Considering the slow growth of the lesions and no new metastatic lesions after comprehensive evaluation, our treatment group suggested that the patient should continue fruquintinib in combination with another oral chemotherapy drug: tegafur-gimeracil-oteracil potassium capsules (S-1). After repeated consultations with the patient and the signing of informed consent, the regimen of fruquintinib + S-1 was initiated as fourth-line treatment in September 2021. Fruquintinib (5 mg) was given once daily, 2 wk on and 1 wk off; S-1 (60 mg) was given twice daily, 2 wk on and 1 wk off.

During administration, the patient experienced grade 2 leukocyte decline and grade 1 diarrhea. Considering the patient's high quality of life requirements, we decided to adjust the dose of S-1 based on toxicity 9graded according to National Cancer Institute CTCAE V.4.0) and possible benefits. S-1 was adjusted from 60 mg twice daily to 40 mg in the morning and 60 mg in the evening. At the same time, nifedipine sustained release tablets and skin moisturizing care were given regularly to monitor the adverse reactions (grade I hypertension, grade I hand-foot syndrome). Follow-up during medication was regular, and chest CT examination showed stable lung metastases until August 2022 (Figure 2). The patient maintained good quality of life, and the Eastern Cooperative Oncology Group score was 0.

Unfortunately, another chest CT examination in October 2022 revealed the enlargement of pulmonary metastases and the appearance of multiple new lesions (Figure 2), which was judged to be disease progression. In addition, abdomen CT still showed no active findings. PFS of 13.5 mo was achieved by fruquintinib S-1.

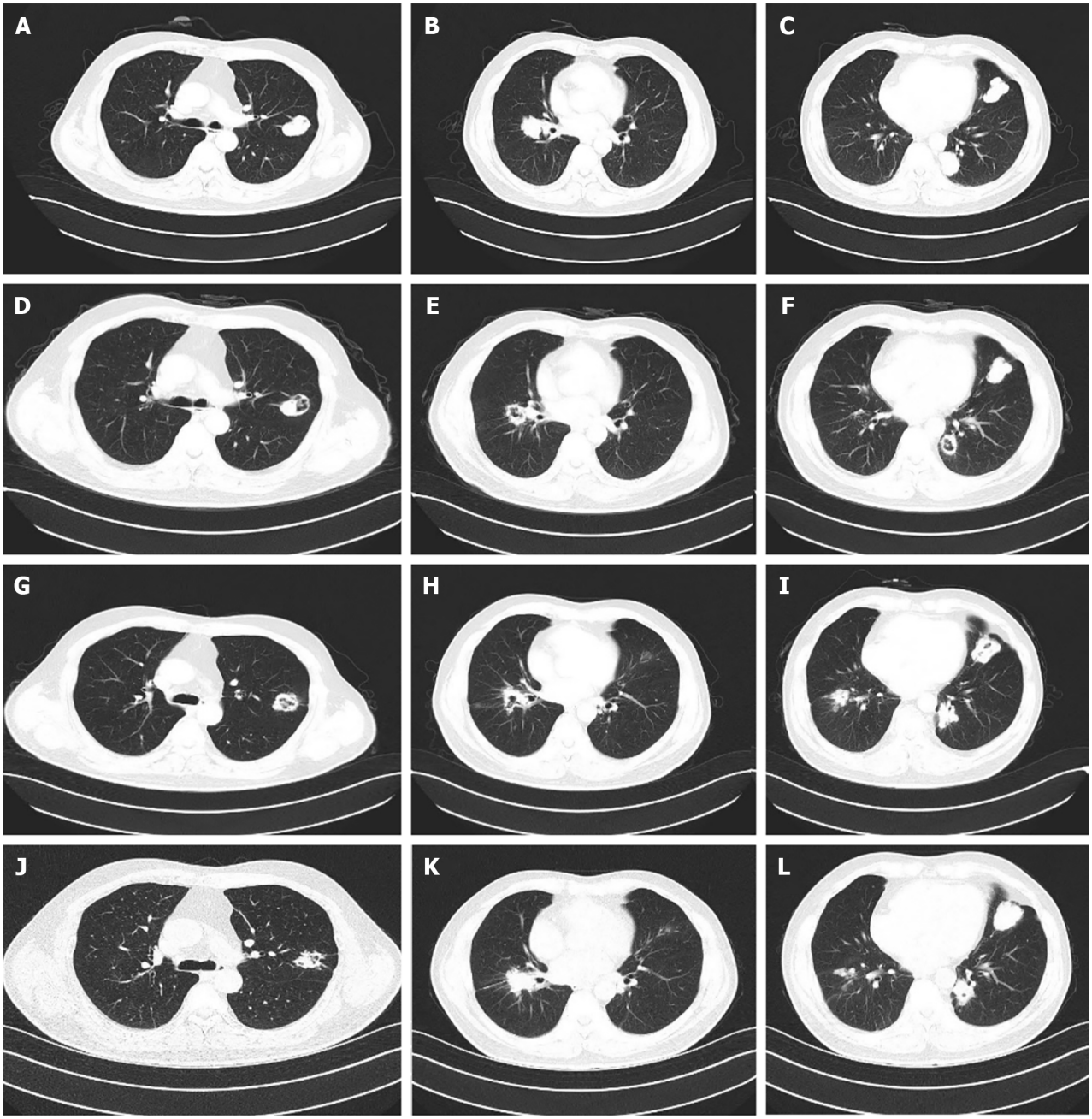

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Figure 1 Chest computed tomography before and after treatment with fruquintinib showed multiple metastases in both lungs. A-C: A baseline chest computed tomography (CT) scan before fruquintinib treatment on August 24, 2020; D-F: CT after fruquintinib treatment was given for 3 mo (November 30, 2020); G-I: CT after fruquintinib treatment was given for 8 mo (May 31, 2021); J-L: CT after fruquintinib treatment was given for 12 mo (August 31, 2021).

OUTCOME AND FOLLOW-UP

The patient achieved a continuous survival benefit from continued treatment with fruquintinib monotherapy after diagnosis of mCRC and subsequent combination therapy with S-1, including at least 25.5 mo of PFS and 30 mo of overall survival (Figure 3).

Considering that the second-line treatment of irinotecan had not shown resistance combined with the genetic test results of the patient, we started the cetuximab plus irinotecan regimen as the fifth-line treatment starting in October 2022. The efficacy of this regimen was not available by the submission date.

In this case report, informed consent was obtained before each treatment. The therapeutic effect was evaluated by the Response Evaluation Criteria in Solid Tumors criteria. The nature and severity of adverse events were evaluated according to the National Cancer Institute CTCAE 4.0.

Informed consent for treatment was signed by the patient before each treatment, and written informed consent was obtained from the patient in order to publish relevant clinical and imaging data. These situations are in line with the ethical standards to be implemented in research involving human

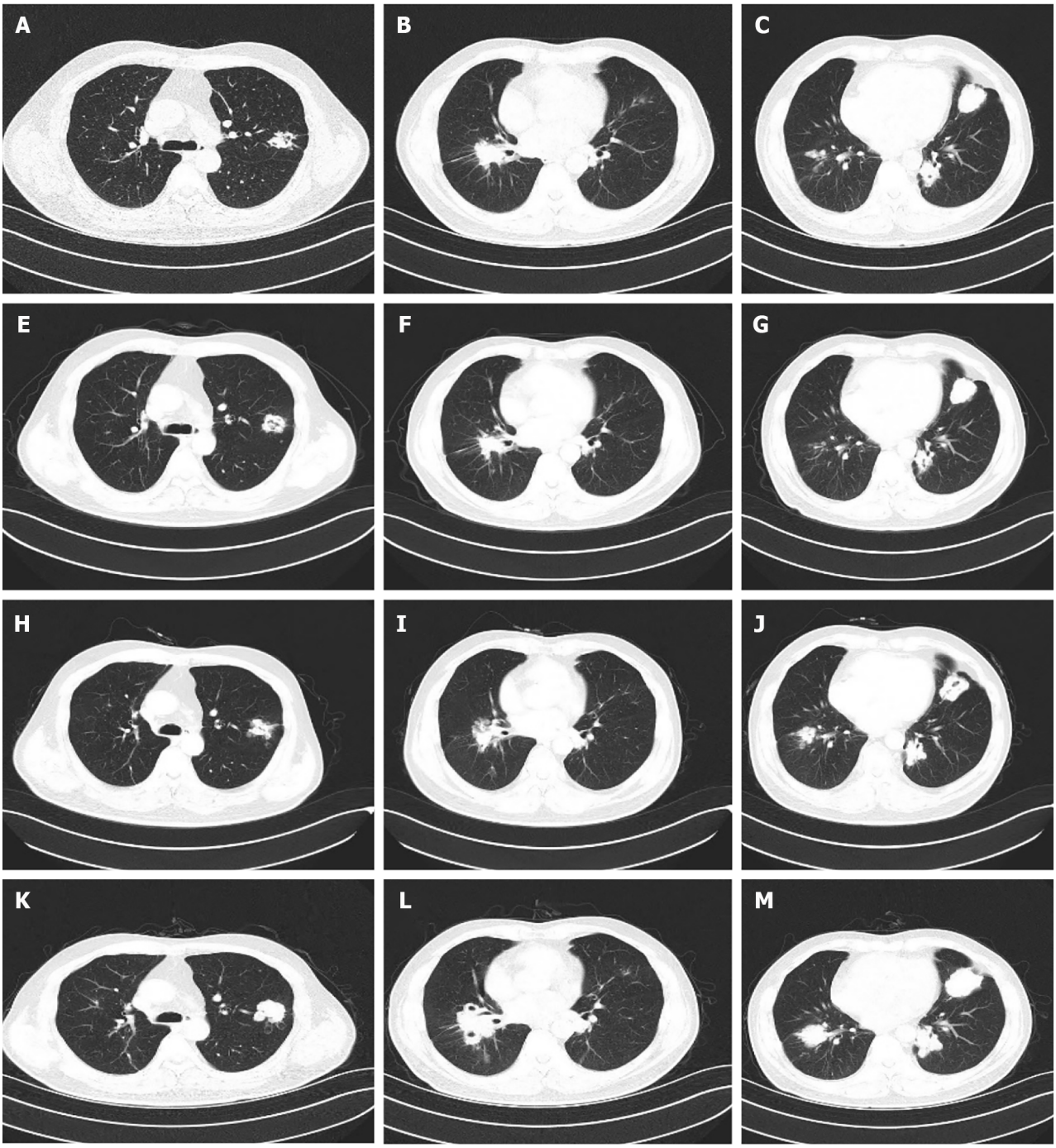

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Figure 2 Chest computed tomography before and after treatment with fruquintinib plus tegafur-gimeracil-oteracil potassium showed multiple metastases in both lungs. A-C: Computed tomography (CT) before fruquintinib plus tegafur-gimeracil-oteracil potassium (S-1) treatment (August 31, 2021); D-F: CT after fruquintinib plus S-1 treatment was given for 2 mo (November 1, 2021); G-I: CT after fruquintinib plus S-1 treatment was given for 10 mo (June 13, 2022); J-L: CT after fruquintinib plus S-1 treatment was given for 13.5 mo (October 12, 2022).

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DISCUSSION

Angiogenesis plays a critical role in the neoplastic growth, progression, and metastasis of CRC[12]. It was reported that vascular endothelial growth factor (VEGF) secreted by tumor cells can stimulate endothelial cell survival and proliferation, causing changes in vascular permeability and promoting neo-angiogenesis[12]. Anti-angiogenetic therapy is an important strategy for mCRC treatment. Anti-

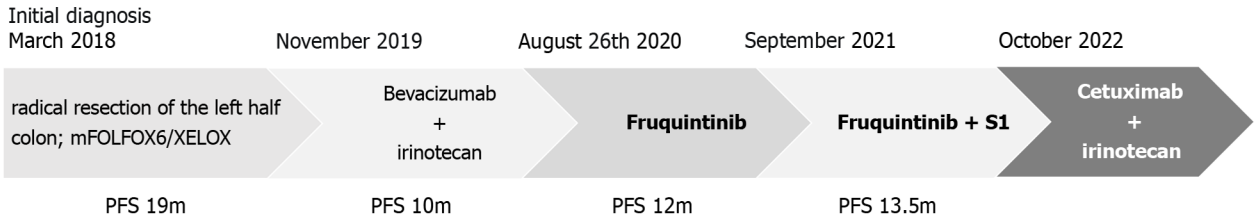

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Figure 3 Treatment timeline of the patient. mFOLFOX6: Oxaliplatin, leucovorin, and 5-FU; PFS: Progression-free survival; S1: Tegafur-gimeracil-oteracil potassium; XELOX: Oxaliplatin and capecitabine.

angiogenic agents include the small molecule inhibitors that block the activity of VEGF receptor kinases and the neutralization antibody of VEGF (monoclonal antibodies), which inhibit angiogenesis, cause vascular degeneration, and normalize tumor blood vessels[14]. Bevacizumab is the most successful antibody for neutralizing VEGF, and it has been authorized for mCRC first-line and second-line treatment combined with chemotherapy[5,15,16]. Nonetheless, there are some disadvantages associated with the use of bevacizumab as a monoclonal antibody, including immunogenicity and intravenous administration.

Fruquintinib is a highly selective and potent small-molecule inhibitor against VEGF receptor 1, 2, and 3[17]. It originated and was developed by Hutchison MediPharma and was authorized for third-line treatment in mCRC in China. Fruquintinib is a highly selective inhibitor of the VEGF signaling pathway, which can decrease cell proliferation of human umbilical vein endothelial cells and human lymphatic endothelial cells. It also decreases tumor angiogenesis and lymphangiogenesis, effectively reduces blood vessel density, inhibits tumor proliferation and migration, and has strong antitumor activity[17].

In clinical studies, fruquintinib has shown a survival benefit in mCRC patients. In the phase III FRESCO trial, the fruquintinib group had significantly prolonged median overall survival compared with the placebo group [9.3 mo; 95% confidence interval (CI): 8.2-10.5 *vs* 6.6 mo; 95%CI: 5.9-8.1]. The median PFS of fruquintinib was also significantly increased (3.7 mo; 95%CI: 3.7-4.6 *vs* 1.8 mo; 95%CI: 1.8-1.8)[8]. Fruquintinib also showed an acceptable safety and tolerability profile[8,9].

Our patient chose fruquintinib after drug resistance and intolerance of first-line and second-line treatments. He achieved 12 mo of PFS with monotherapy while maintaining a good quality of life. However, fruquintinib also faced the challenge of drug resistance.

In addition to molecular targeted therapy drugs, chemotherapy is still the main treatment for patients with advanced CRC, among which 5-FU based chemotherapy combined with oxaliplatin or irinotecan is the preferred standard treatment for patients with advanced or recurrent CRC[18]. However, if a patient does not respond to chemotherapy or has a toxic reaction, there are few remaining options.

In 2017, another oral drug, trifluridine-tipiracil (TAS-102), was approved by the United States Food and Drug Administration, which finally offered another potential option for patients with mCRC[19]. TAS-102 has shown a significant overall survival benefit compared with placebo in patients with chemorefractory mCRC in the phase III RECOURSE trial, with a longer median overall survival (7.1 mo *vs* 5.3 mo) and a longer median PFS (2.0 mo *vs* 1.7 mo) in the TAS-102 group[10]. Unfortunately, neither fruquintinib nor TAS-102 gave patients with refractory mCRC a satisfactory PFS[8,10].

Considering that targeted anti-angiogenic drugs combined with chemotherapy play a synergistic antitumor role by inhibiting neovascularization, inducing vascular normalization, and enhancing cytotoxic drug delivery, anti-angiogenic therapy combined with chemotherapy drugs have been explored for refractory CRC. Pfeiffer *et al*[11] conducted a phase II clinical study after previous studies achieved good results and continued to explore the safety and effectiveness of the combination of bevacizumab and TAS-102. The median PFS was 2.6 mo in the TAS-102 group and 4.6 mo in the TAS-102 + bevacizumab group. TAS-102 combined with bevacizumab showed significant clinically relevant improvement in PFS with tolerable toxicity compared to TAS-102 monotherapy.

Based on these results, continuous anti-vascular targeted therapy combined with cytotoxic drugs may have clinical significance in patients with refractory advanced CRC. This combination therapy may change practice in the future, but we do not yet understand the characteristics of patients most suitable for second-line post-combination therapy. At present, the price of TAS-102 is relatively high in China, and it is not covered by medical insurance. Meanwhile, bevacizumab requires intravenous infusion. Therefore, a safe, effective, and more convenient and economical treatment plan is urgently needed in clinic.

S-1, a novel oral 5-FU derivative developed by Taiho Pharmaceuticals Company (Japan), has been widely used in the treatment of gastrointestinal malignancies[20]. S-1 monotherapy has an effectiveness rate of 19%-39% in the treatment of advanced CRC[21,22] and has been shown to be as effective as 5-FU and capecitabine[23,24]. In these studies, the toxicity of S-1 treatment was primarily hematological, while hand-foot syndrome was more common in the capecitabine group. However, there was no statistically significant difference between the two groups. Therefore, S-1 is also an option for the treatment of

advanced CRC[22,23,24].

Based on the above information, it is reasonable to conclude that fruquintinib combined with S-1 may be superior to fruquintinib or S-1 alone in some patients with refractory CRC who do not respond to standard therapy. The therapeutic mechanism of this combination regimen may be associated with the synergistic antitumor action in addition to the respective antitumor effects of fruquintinib and S-1.

In this case, some lung metastases slowly enlarged after 12 mo of monotherapy with fruquintinib. Combined with the results of the above related studies and after repeated communication with the patient and signing the informed consent, the patient began treatment with the combination of fruquintinib and cytotoxic drug S-1. The patient gained 13.5 mo of PFS, and the lung metastases were again well controlled. Only grade 2 leukopenia, grade 1 diarrhea, grade 1 hypertension, and grade 1 hand-foot syndrome were observed during the treatment period.

In the phase III CORRECT, FRESCO, and RECOURSE trials, the median PFS of patients in the regorafenib group, fruquintinib group, and TAS-102 group were 1.9 mo, 3.7 mo, and 2.0 mo, respectively[7,8,10]. Considering that the absolute PFS benefit time of third-line treatment was shorter in previous clinical trials, we hypothesize that the combination of fruquintinib and S-1 caused the longer survival benefit. At the same time, the combination of the two oral drugs reduced the inconvenience of repeated visits to the hospital and improved the patient's quality of life. This treatment combination may have potential clinical significance in future salvage treatment of advanced CRC. Since China is still a developing country, we also need to consider the factors of pharmacoeconomics to reduce the economic burden of patients as much as possible[25]. The strategy of using oral drugs also reduced the risk of exposure to coronavirus disease 2019 during the pandemic. To our knowledge, this is the first time that fruquintinib combined with S-1 in the treatment of advanced CRC has been reported with a good efficacy.

CONCLUSION

In conclusion, the prognosis of CRC after advanced multiline therapy is extremely poor, and survival after existing third-line and post-third-line therapies is limited. Therefore, it is very important to explore suitable therapies for patients with refractory advanced CRC to prolong the overall survival time of patients and enhance the quality of life of patients as much as possible.

Although fruquintinib combined with S1 is not currently the standard treatment for mCRC, this case provides evidence for its antitumor activity and safety. Given that only 1 patient was observed in this report and the clinical data is very limited, further investigation and accumulation of more experience are needed. Further clinical studies can be conducted to demonstrate the efficacy and safety of this combination regimen.

FOOTNOTES

Author contributions: Qu FJ, Wu S, and Kong Y were responsible for collecting data, analyzing data, and writing the article; Kong Y was responsible for guiding the writing and participating in the revision of the article; All authors read and approved the final manuscript.

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