Case Report

Preliminary experience of oral fruquintinib-capecitabine as a new maintenance treatment strategy for advanced colorectal cancer in the era of coronavirus disease 2019 (COVID-19): case report and literature review

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Background: Bevacizumab combined with fluorouracil is the currently recommended maintenance treatment for metastatic colorectal cancer, but the use of bevacizumab needs to be carried out in hospitals, which invisibly increases the risk of patients' exposure to coronavirus disease 2019 (COVID-19) during the COVID-19 epidemic. Therefore, except of the advantage of convenience, all oral drugs as the maintenance treatment can reduce hospitalization and potential exposure risk during the COVID-19 epidemic, which is worth further exploration.

Case Description: First case was a 49-year-old male with stage IV colon adenocarcinoma and abnormal liver function who was given bevacizumab with FOLFOXIRI (8-cycles), following which his liver function recovered. Oxaliplatin was stopped upon thrombocytopenia development. The patient was finally maintained on oral fruquintinib and capecitabine therapy since November 2020, and has been progression-free for >15 months. Grade 2 leukopenia, neutropenia, and thrombocytopenia; grade 1 terminal nerve injury; and grade 1 hand and foot numbness were observed. The second case was a 48-year-old male with advanced colon cancer who underwent laparoscopic sigmoidectomy. Post-surgery, the patient was commenced on fluorouracil and leucovorin (1-cycle), followed by conversion therapy with cetuximab and chemotherapy (6-cycles). The patient underwent left hemi-hepatectomy, partial hepatectomy of the right lobe, and intraoperative radiofrequency ablation, following which he continued to receive cetuximab and chemotherapy. The patient was maintained on oral fruquintinib and capecitabine since December, 2020 and has been progression-free for >14 months. Grade1 myelosuppression, leukopenia, and neutropenia, grade 2 thrombocytopenia were observed.

Conclusions: This case report based on preliminary evidence advocates oral fruquintinib-capecitabine maintenance treatment as an alternative to bevacizumab-capecitabine standard therapy for CRC patients, especially in the era of COVID-19 epidemic. This scheme can reduce hospitalization and potential COVID-19 contact, and is more convenient than intravenous administration. Which should be further explored in future studies.

Keywords: Case report; capecitabine; colorectal cancer (CRC); fruquintinib; maintenance therapy

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Introduction

Colorectal cancer (CRC) remains the second-most common cause of mortality worldwide. The pharmacological treatment for these patients is far from satisfactory, with a survival rate, especially for advanced metastasis, of only 14.7% (1). Targeted therapy with the anti-epidermal growth factor receptor (anti-EGFR) agent cetuximab and the anti-angiogenesis agent bevacizumab have shown improved survival rates in patients with CRC (2). However, anti-cancer drugs are associated with adverse side effects, which, in turn, can negatively affect patients' quality of life. This has led oncologists to focus more closely on the patient's overall treatment experience, taking into account the drug therapy administration route (3). Though oral treatment options might not be available for all types of cancer, the development of cancer drugs that can be administered efficaciously through oral as well as the traditional intravenous (IV) route is becoming increasingly common (4). In particular, during the coronavirus disease 2019 (COVID-19) pandemic, oral medication can minimize the hospitalization of patients, thus reducing the risk of exposure to COVID-19, which is crucial for tumor patients with relatively lower body resistance or impaired immune function. Intravenous administration of anti-cancer drugs has to require patients dealing with it in the hospital, which invisibly increases the economic burden, contact risk and many other inconveniences of patients in round trips to the hospital. In view of the important position of maintenance treatment in colorectal cancer patients and the consideration of convenience and safety, we adopted the oral maintenance treatment scheme of fruquintinib combined with capecitabine, which has initially shown good effectiveness and safety, and has well avoided repeated hospitalization of patients. Taking into account not only convenience but also safety, which is particularly important during the period of COVID-19, this oral scheme is worth further exploration in follow-up studies. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-824/rc).

Case presentation

Case 1

A 49-year-old male was admitted to a local hospital in April 2020 with persistent complaints of abdominal pain in the right upper quadrant and increased frequency of passing stools for more than 3 months. Magnetic resonance imaging (MRI) showed multiple space-occupying lesions in the liver and a slight thickening of the rectal wall (*Figure 1*). Colonoscopy and biopsy revealed metastatic CRC (mCRC), following which the patient was referred to our hospital for subsequent treatment. We diagnosed stage IV colon adenocarcinoma with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 1 and an abnormal liver function. The laboratory examinations showed elevated levels of carcinoembryonic antigen (CEA) 9,875 ng/mL, cancer antigen-125 (CA-125) 22.80 U/mL, CA-19-9 6,749 U/mL, CA-72-4 38.6 U/mL, serum cytokeratin-19 fragment (CYFRA 21-1) 128 ng/mL, neuron-specific enolase (NSE) 114 ng/mL, and CA-50 141.26 U/L. Based on these tests and other contraindications, the patient was commenced on a mFOLFOX6 regimen [oxaliplatin 165 mg on day 1, IV + leucovorin 0.8 g, IV on day 1 + 5-FU 0.78 g IV bolus on day 1 + 5-FU 4.7 continuous intravenous infusion (CIV) 46 h every 2 weeks (q2w)]. In May 2020, genetic examination revealed the presence of microsatellite stable (MSS) KRAS wild type and NRAS amplified UGT1A1 GG type. Hence, the patient was started on bevacizumab targeted therapy (0.4 g IV on day 1) combined with chemotherapy. From May 27, 2020, to September 11, 2020, the patient was given bevacizumab with a FOLFOXIRI regimen (irinotecan 0.29 g IV at day 1 + oxaliplatin 165 mg IV at day 1 + leucovorin 0.78 at day 1 + 5-FU 0.78 at day 1 + 5-FU 4.7 CIV 46 h q2w) as the first-line chemotherapy for eight cycles as palliative treatment, following which his liver function recovered and tumor markers decreased significantly. The patient developed thrombocytopenia during this course of treatment. The entire course of treatment was 12 cycles. Considering the risk of myelosuppression and thrombocytopenia after chemotherapy, oxaliplatin was stopped in the last two cycles, and the previous treatment was continued till September 2020. Since November 2020, the patient has been maintained on oral fruquintinib therapy [5 mg once a day (qd) on days 1–14 every 3 weeks (q3w)] and oral capecitabine [1.5 g twice a day (bid) on days 1–14 q3w] with progression-free survival (PFS) >15 months (*Figure 2*). After therapy, the levels of biomarkers reduced as follows: CEA 18.3 ng/mL, CA-125 3.7 U/mL, CA-19-9 15.1 U/mL, CA-72-4 3.1 U/mL, serum CYFRA 21-1 2.5 ng/mL, NSE 11.9 ng/mL, and CA-50 7 U/L. The treatment was well tolerated except for myelosuppression, with no abnormal liver function during maintenance therapy. Grade 2 leukopenia, neutropenia, and thrombocytopenia; grade1 terminal nerve injury; and grade

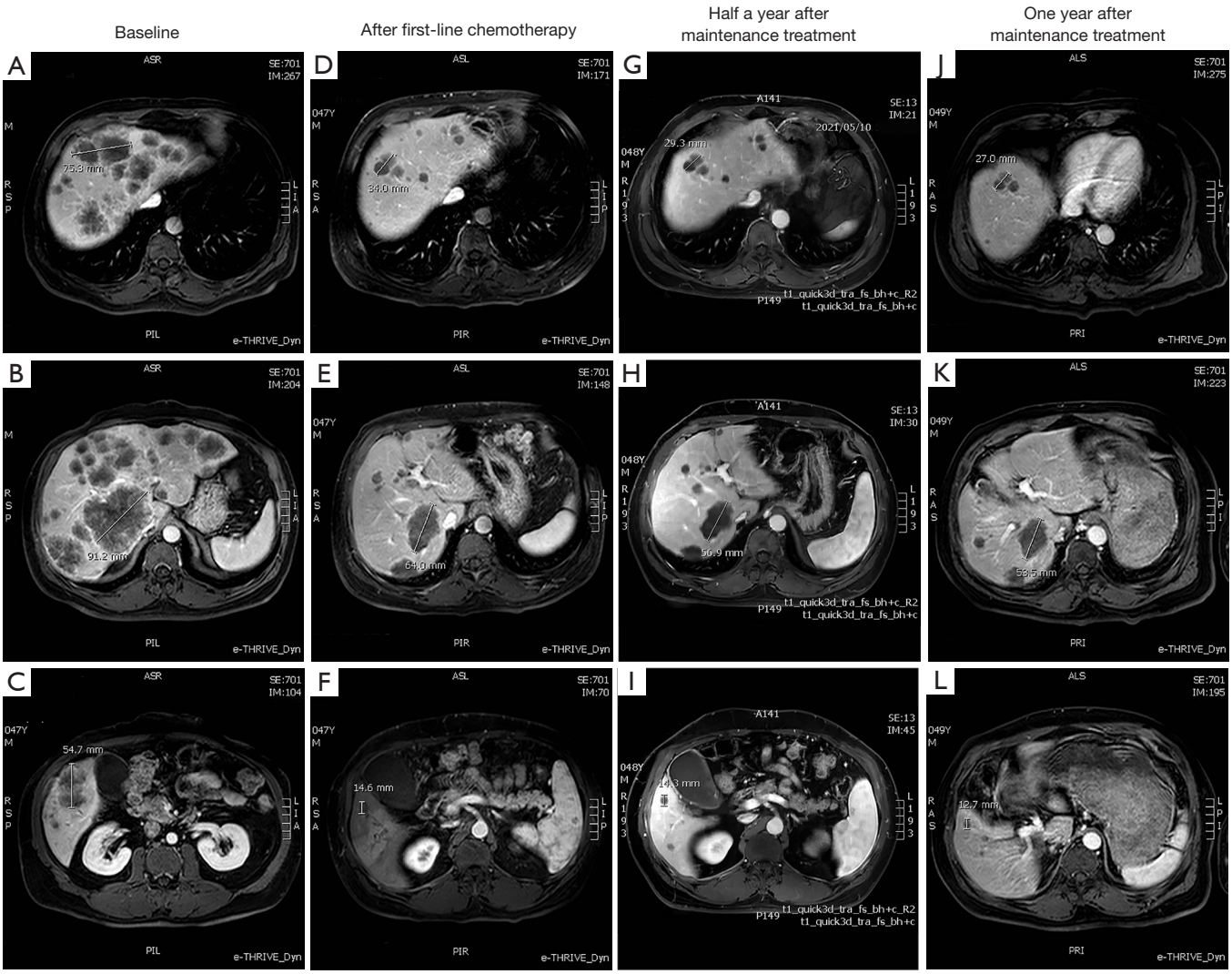

Figure 1 MRI scans of patient 1. (A-C) Shows the baseline status where the patients has a very large liver tumor burden and multiple liver metastases; (D-F) shows that after the first-line chemotherapy for 12 cycles, the tumor size was significantly reduced; (G-I) shows the tumor size was still shrinking after maintenance therapy with fruquintinib and capecitabine for half a year; (J-L) shows the tumor was still reduced and no new growth is observed after 1-year maintenance therapy. MRI, magnetic resonance imaging.

1 hand and foot numbness was also observed.

Case 2

A 48-year male complained of constipation. Auxiliary tests found the presence of advanced colon cancer, and he underwent laparoscopic sigmoidectomy in April 2020. The post-operative pathological examination showed colonic tumor foci with grade II adenocarcinoma (4×4×1.5 cm) infiltrating the intestinal wall, extra serous fibrous adipose tissue, and 4/15 mesenteric lymph nodes and 1/3 paraintestinal lymph nodes displaying cancer metastasis. Immunohistochemistry examinations revealed the following: A3: KI67 (70%), P53 (individual +), MSH2 (+), MLH1 (+), PMSII (+), MSH6 (+), and BRAF (–); B3: KI67 (60%), P53 (40% +), MSH2 (+), MLH1 (+), PMSII (partial +), MSH6 (+), and BRAF (–). MRI showed a clear indication of liver metastasis and a PS score of 1 post-surgery with KRAS, NRAS, BRAF wild-type, APC, TP53 mutation, and MSS. The patient showed elevated levels of CA-19-9 79.33 U/mL, CA-24.2 30.32 U/mL, CEA 3.580 ng/mL, and AFP 11.1 ng/mL. On May 7, 2020,

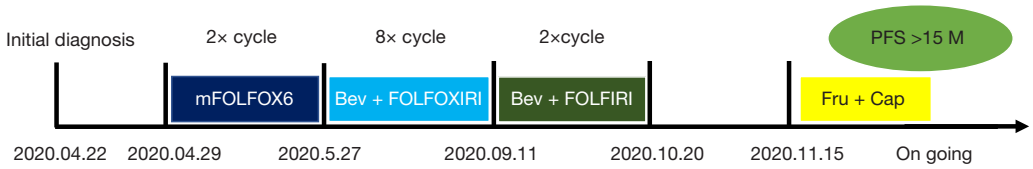

Figure 2 Treatment timelines of patient 1. Bev, bevacizumab; Fru, fruquintinib; Cap, capecitabine; PFS, progression-free survival.

the patient was started on fluorouracil combined with leucovorin as palliative chemotherapy for one cycle. During treatment, genetic tests showed KRAS, NRAS, BRAF wild-type, APC, and TP53 mutations. On May 12, 2020, the patient came to our department for treatment. An MRI scan showed an abnormal increase in the FDG metabolism of multiple liver nodules and multiple lymph nodes in the retroperitoneal and left clavicular area, suggesting multiple liver and lymph node metastases (*Figure 3*). After eliminating contraindications for chemotherapy, the patient was given cetuximab 980 mg IV on day 1 and FOLFOXIRI (irinotecan 0.294 g IV on day 1 and oxaliplatin 166 mg IV on day 1 + leucovorin 0.78 g IV on day 1 + fluorouracil 0.78 g IV on day 1 + fluorouracil 4.7 g CIV 46 h q2w) for six cycles. After reexamination in August 2020, the patient underwent left hemi-hepatectomy, partial hepatectomy of the right lobe, and intraoperative radiofrequency ablation. Post-surgery, the patient continued to receive palliative first-line chemotherapy with cetuximab combined with a mFOLFOX6 regimen for six cycles. The tumor burden decreased significantly after surgery; hence, irinotecan was stopped. Since December 15, 2020, the patient has been on maintenance therapy with oral fruquintinib (5 mg qd on days 1–14 q3w) and oral capecitabine therapy (1.5 g bid on days 1–14 q3w). The levels of CA-19-9, CA-24.2, CEA, and ATP improved to 18.1 U/mL, 6 U/mL, 2.1 ng/mL, and 6.8 ng/mL, respectively, following this therapy. The main adverse event during maintenance treatment was myelosuppression after chemotherapy and grade 1 abnormal liver function. Grade 1 leukopenia and neutropenia and grade 2 thrombocytopenia were also observed. Currently, the patient remains progression-free for >14 months (*Figure 4*).

Ethical statement

All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

The Pan-Asian adapted European Society for Medical Oncology (ESMO) consensus guidelines recommend combining fluoropyrimidine and bevacizumab as maintenance therapy in patients with mCRC (5). Similarly, the Chinese Society of Clinical Oncology (CSCO) recommends maintenance therapy consisting of 5-fluorouracil/leucovorin or capecitabine due to low toxicity (6). FOLFOX and FOLFIRI regimens in combination with EGFR monoclonal antibodies (panitumumab or cetuximab) can be given for patients with wild-type KRAS/NRAS only (7). In patients with KRAS wild-type but NRAS-amplified CRC, the EGFR monoclonal antibody cetuximab is not indicated; hence, bevacizumab combined with chemotherapy was selected in our case. For patients with mCRC responding to chemotherapy in combination with targeted agents, the clinically evident benefits of bevacizumab plus capecitabine maintenance therapy were observed (8). The advent of COVID-19 has seen a paradigm shift in the choice of patient approaches toward disease. Also, traditional patient-centered research methodologies have taken a back seat during social distancing. Most patients prefer telecommunication and online discussion over physical consultation for their treatment. Given such a scenario and the complexity of IV-administered therapy, our study showed that continuous anti-angiogenesis combined with oral chemotherapy could be used as an alternative to classic bevacizumab combined with capecitabine. Vascular endothelial growth factor (VEGF) plays a vital role in tumor angiogenesis. Hence, drugs targeting VEGF and its receptors (VEGFRs) can be beneficial for various malignancies, including CRC, as they inhibit new

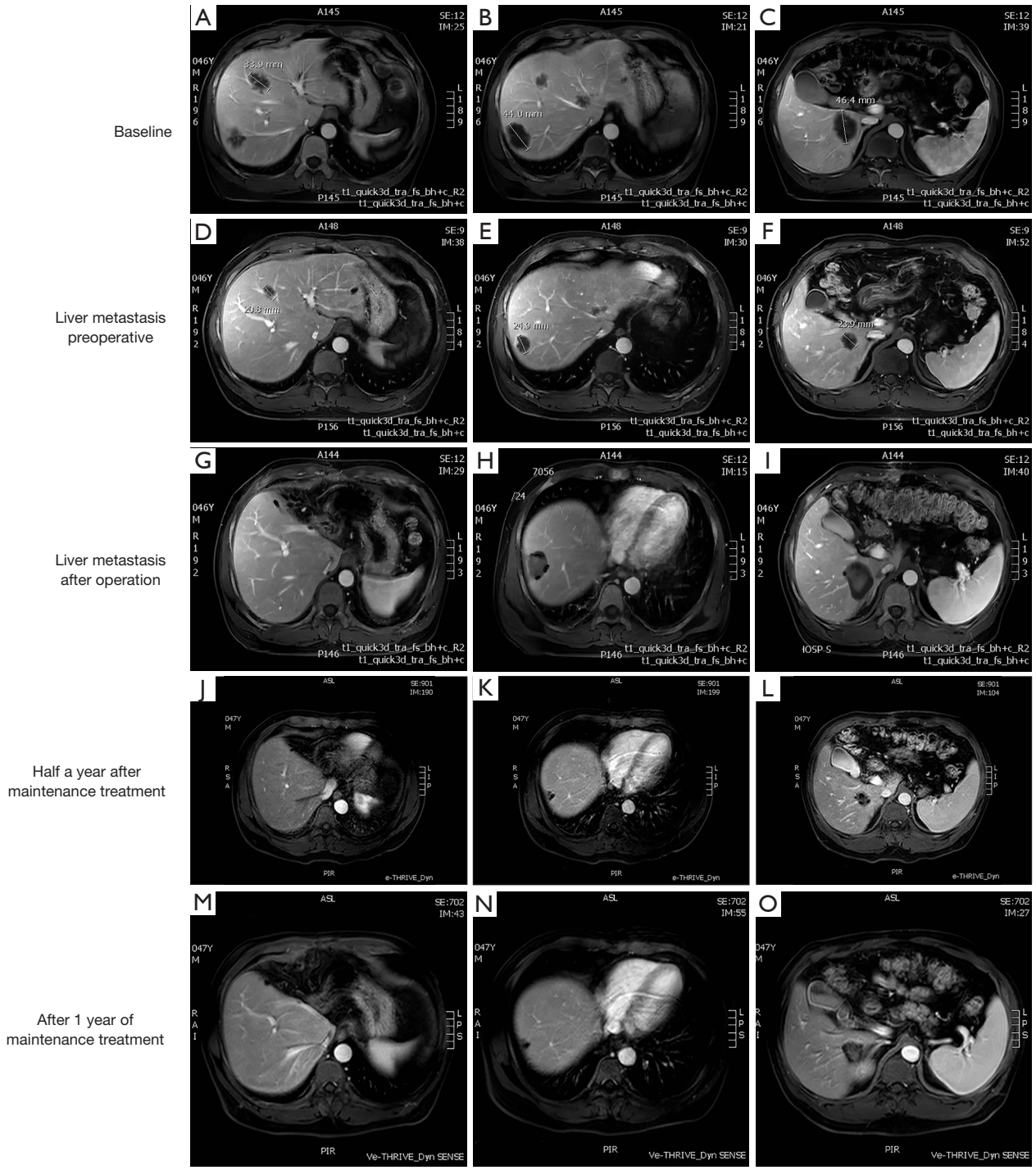

Figure 3 MRI scans of patient 2. (A-C) Shows the baseline status where the patients manifested as multiple occlusions of the liver after sigmoidectomy; (D-F) after 6cycles of cetuximab targeted therapy combined with first-line chemotherapy, the imaging showed that the tumor burden was significantly reduced; (G-I) patient with liver metastases postoperative imaging manifestations, some lesions tumor radiofrequency postoperative manifestations; (J-L) after half-year of maintenance therapy, no tumor activity was found in the lesions after radiofrequency ablation; (M-O) after 1-year maintenance therapy, no new tumor growth was observed. MRI, magnetic resonance imaging.

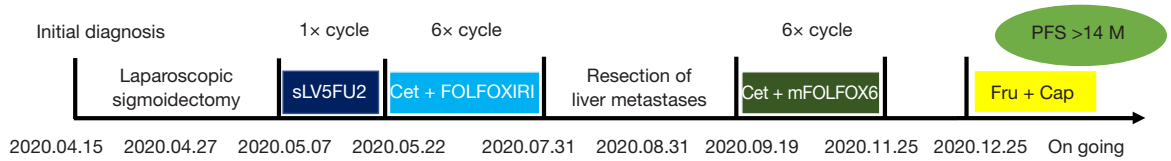

Figure 4 Treatment timelines of patient 2. Cet, cetuximab; Fru, fruquintinib; Cap, capecitabine; PFS, progression-free survival.

blood vessel growth and result in vascular regression, normalization, and constriction (9). In 2018, the National Medical Products Administration of China and in 2020, the US Food and Drug Administration (under fast track) granted approval of fruquintinib for treating patients with mCRC. This study showed that for mCRC patients with both wild and mutant RAS types (case 1: KRAS wild- and NRAS-amplified type, case 2: RAS wild-type), treatment with oral fruquintinib and capecitabine maintenance therapy was well tolerated and reduced the risk of disease progression.

A retrospective analysis of 35 patients with high-risk resected CRC revealed that 8/17 patients treated with capecitabine therapy for <30 months developed progressive disease, while five patients with resected stage 4 disease who received capecitabine as maintenance therapy were alive >5 years after surgery. The findings suggest that maintenance capecitabine therapy reduces the risk of disease progression and cancer-related death (10). A randomized clinical trial with fruquintinib improved the median PFS by 3.7 months compared to placebo (mPFS 1.8 months) in mCRC patients (11). As both drugs have proven efficacy in improving the survival rate and progression of the disease, it is justifiable to combine these drugs for a better synergistic effect. Preliminary observation showed that biomarker levels after maintenance therapy were drastically reduced, with significant tumor reduction in both patients with and without surgery. In addition, with the new oral maintenance treatment mode, PFS was more than 1 year, which was no worse than the previous optimal 11.3 months. It is expected to further prolong PFS, which is worthy of future exploration as a clinical study. KRAS, NRAS, and other gene mutations were detected in both patients in our study. Fruquintinib and capecitabine therapy in these patients were found to be effective, suggesting the feasibility of this regimen for patients with RAS-mutant or wild-type CRC. In addition, except for myelosuppression, this maintenance therapy regimen was well tolerated with only mild grade 1 or 2 adverse events. Future clinical studies with large sample sizes on maintenance therapy using this combination will help to strengthen the study's findings. Considering the convenience and safety, we propose oral fruquintinib-capecitabine as a new maintenance treatment strategy for patients with mCRC.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-824/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-824/coif). The authors have no conflicts of interest to declare.

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. All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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