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CASE REPORT

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Durable response to third-line combination therapy in a metastatic colorectal cancer patient with BRAF V600E mutation: A case report

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ABSTRACT

In metastatic colorectal cancer (mCRC), the BRAFV600E mutation subtype is one of the subtypes with the worst prognosis. The long-term abnormal activation of multiple signaling pathways caused by the BRAF V600E mutation is closely related to the formation of BRAF inhibitor resistance and drug-resistant tumor cell subpopulations. These factors significantly impact the survival and prognosis of CRC patients. Therefore, treating mCRC patients with the BRAFV600E mutation, particularly in later stages, is challenging. We reported a case of an mCRC patient with the BRAF V600E mutation in the primary and metastatic tumors. After the failure of second-line treatment, this patient received a combination therapy including immunotherapy (tislelizumab), radiotherapy, and targeted therapy (fruquintinib). Through comprehensive imaging evaluations and continuous monitoring of tumor markers, we were astonished to observe that the patient has achieved and maintained a complete response (CR) for over 12 months. This case supports the efficacy of combination therapy in mCRC patients with the BRAF V600E mutation.

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Introduction

The mitogen-activated protein kinase signaling pathway plays a pivotal role in the pathogenesis and progression of colorectal cancer (CRC). Dysregulation of this pathway can result in uncontrolled cell proliferation, inhibition of apoptosis, and disruption of cell cycle regulation, thereby facilitating tumor progression. RAF proteins, positioned downstream in the RAS/RAF/MEK/ERK cascade, transmit growth signals and regulate cellular processes such as proliferation, differentiation, and apoptosis. The BRAF-mutated metastatic colorectal cancer (mCRC) is about 8%-15%, most of which is BRAFV600E mutation.[1] mCRC with BRAF V600E mutation is more likely to occur in the right colon and elderly women, with poor prognosis.[2,3] For patients with BRAFV600E-mutated mCRC, current guidelines recommend first-line treatment with chemotherapy combined with bevacizumab. This recommendation is primarily based on data from the phase III TRIBE study, where the FOLFOXIRI plus bevacizumab regimen demonstrated a trend toward improved overall survival (OS) compared to FOLFIRI plus bevacizumab in the 28-patient BRAFV600E-mutated subgroup.[4] However, subsequent clinical studies have not consistently replicated these findings.[5] A meta-analysis published in the Journal of Clinical Oncology in 2020 also showed that three-drug chemotherapy plus bevacizumab did not significantly improve OS compared to two-drug chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab.[6] With the advancements of precision medicine, using BRAF inhibitors in CRC has achieved several breakthroughs. Currently, major authoritative guidelines consistently recommend dual-target or triple-target regimens combining BRAF inhibitors with anti-EGFR monoclonal antibodies, with or without MEK inhibitors for second-line and later-line treatments.

Despite these advancements, the prognosis for patients with BRAF V600E-mutated mCRC remains poor, underscoring the urgent need for novel combination treatment strategies to improve treatment outcomes and enhance survival for BRAFV600E-mutated mCRC patients.

Patient presentation

A 40-year-old female patient presented with hematochezia in June 2020 and was subsequently diagnosed with poorly differentiated rectal adenocarcinoma following a colonoscopy and CT examination. She then underwent laparoscopic radical resection of rectal cancer. Postoperative pathological examination confirmed poorly differentiated rectal adenocarcinoma, staged as pT2N2bM0 (stage IIIB). We utilized the Illumina NextSeq 550DX and NovaSeq 6000 platforms to evaluate full exonic coverage for 530 genes and partial intronic coverage for 28 genes, using the GRCh37/hg19 reference genome. We utilized the VENTANA PD-L1 (SP263) antibody for immunohistochemical staining to assess the expression levels of the PD-L1 protein. The results demonstrated that the patient had a BRAF V600E-mutated, microsatellite stable (MSS) subtype of CRC with negative PD-L1 expression.

The patient received 8 cycles of XELOX adjuvant chemotherapy after surgery and then was regularly reexamined until PETCT showed multiple retroperitoneal lymph node metastases in December 2021. She received bevacizumab plus

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irinotecan plus raltitrexed as the first-line treatment from December 2021 to February 2023. In March 2023, the patient's CT images showed a progression disease (PD) due to the enlarged right iliac vascular lymph nodes. Then she received radiotherapy to the right iliac vascular lymph nodes from March 2023 to April 2023. After radiotherapy, the patient continued to receive bevacizumab combined with irinotecan and raltitrexed for 2 cycles. However, in June 2023, the patient's CT examination showed an enlarged abdominal para-aortic lymph node, and the efficacy evaluation was PD.

With the emergence and development of immuno-oncology, radiotherapy is increasingly being employed as an adjuvant therapy to augment the efficacy of immunotherapy in cancer patients. In our center's prior clinical investigations, we observed that the combination of radiotherapy and immunotherapy frequently yields an anti-tumor efficacy that exceeds the sum of their individual effects. These findings have bolstered our confidence in the integrated treatment approach utilizing both modalities in clinical practice.[7,8] In our clinical practice, we select mCRC patients who exhibit good physical condition and high treatment compliance to undergo combination therapy as a third-line treatment. Therefore, considering this patient's economic situation and tolerance, we chose a novel combination treatment combining radiotherapy, targeted therapy, and immunotherapy for her as the third-line treatment. To intuitively express this patient's treatment process and efficacy, we listed the entire treatment process in Figure 1.

For her third-line treatment, she received radiotherapy for abdominal para-aortic lymph nodes (prescription dose: PTV: 2 Gy * 25f, PGTV 2.5 Gy * 25f). Then, this patient received fruquintinib 5 mg/day (d1–7), and tislelizumab 200 mg every three weeks. Following the completion of three treatment cycles, we conducted an efficacy evaluation for the patient in September 2023. The tumor volume was reduced by 85.7%, and tumor markers CEA and CA242 normalized. Encouragingly, the image of CT in December 2023 showed that the lesion almost disappeared, and the efficacy evaluation was close to a complete response (CR) (Figure 2a). Tumor markers including carcinogenic embryonic antigen (CEA), cancer Antigen 199 (CA199), and cancer Antigen 242 (CA242) in this patient returned to normal levels after the third-line treatment (Figure 2b). So far, the patient's progression-free survival (PFS) after third-line treatment has exceeded 12 months. Regarding treatment-related adverse events, the patient demonstrated overall good tolerability throughout the entire course of therapy. The primary adverse effect was a grade 2 gastrointestinal reaction, specifically nausea and vomiting, which occurred during oral administration of fruquintinib. The patient tolerated the treatment well, with manageable side effects. The primary adverse event was grade 2 gastrointestinal reactions (nausea and vomiting) during oral administration of fruquintinib, which were alleviated by adjusting the dosing schedule to alternate days. Additionally, the patient experienced mild, grade 1 thrombocytopenia.

Discussion

It is reported that mCRC Patients with BRAFV600E mutation have a poor prognosis with a median OS (mOS) of 12 months. Bevacizumab combined with chemotherapy is considered the first-line treatment for patients with BRAF V600E-mutated mCRC. Recently, the clinical trial BEACON supported the better efficacy of encorafenib combined with cetuximab with or without binimetinib. Further, the ANCHOR clinical study demonstrated the efficacy and safety of encorafenib plus binimetinib plus cetuximab as the first-line treatment for BRAFV600E mutation CRC, with a median progression-free survival (mPFS) of 5.8 months and mOS of 17.2 months.[4] The ongoing BREAKWATER clinical trial investigated the efficacy and toxicity of the combination therapy of FOLFOX6 plus encorafenib plus cetuximab as the first-line therapy in mCRC patients with BRAF V600E mutation. The final results of these clinical trials are expected to rewrite guidelines for the treatment of BRAF V600E mCRC, but the treatment of BRAF V600E mCRC is still a long way off.

Studies have demonstrated a potential synergistic mechanism between BRAF/MAPK inhibition and immune response. Optimized targeting combinations can enhance immune synergy, leading to improved clinical outcomes when combined with immune checkpoint blockers.[9] In the present case, the patient had a short duration of response to the second-line therapy after failure of the first-line therapy. For her third-line treatment plan, we selected a comprehensive treatment mode including immunotherapy, radiotherapy, and targeted therapy based on our previous experiences. The combination treatment continued to be effective, and the patient achieved a complete response, and her PFS has reached 12 months so far. Compared with conventional third-line therapy for mCRC, the combination therapy significantly extended patients' PFS and OS. Additionally, the incidence of adverse events during treatment did not show a significant increase relative to conventional therapy. Compared with previous clinical studies on mCRC with BRAFV600E mutation, such

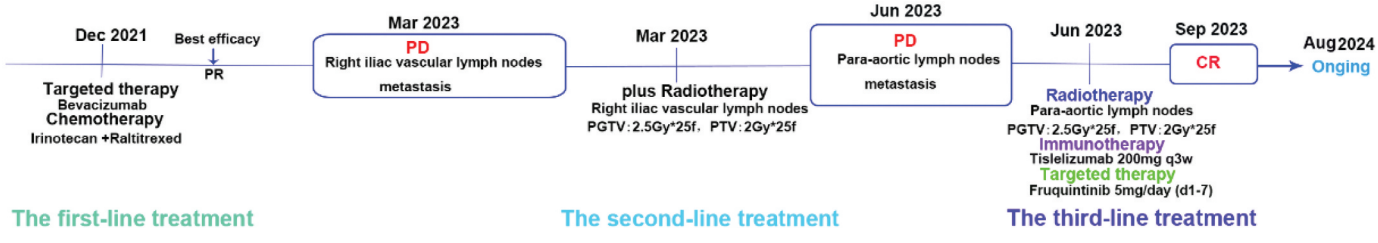

Figure 1. Clinical course including the timing of disease progression and corresponding treatment strategies. abbreviations: CR, complete response; PD, progression disease.

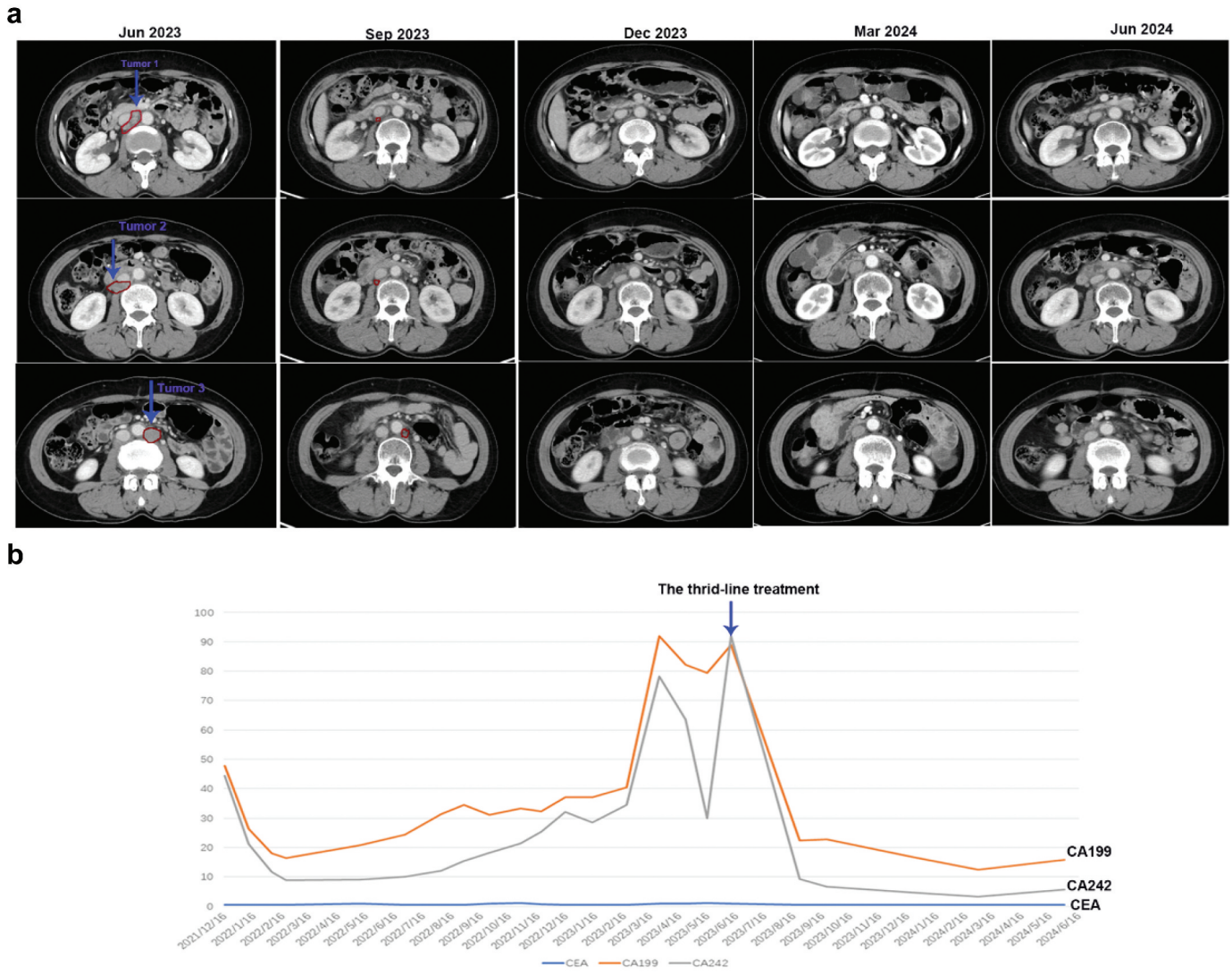

Figure 2. (a) Comparison of CT images of abdominal para-aortic lymph node metastasis before (June 2023) and after third-line treatment (Sep 2023 to June 2024). (b) Comparison of the expression levels of tumor markers including CEA, CA199, and CA242 before and after the third-line treatment.

as the BEACON and BREAKWATER trials, the current case involves a patient receiving third-line treatment. Notably, most of the medications used are covered by medical insurance, thereby significantly reducing the economic burden. This approach offers certain advantages, including a longer PFS. However, further prospective clinical studies with larger sample sizes are necessary to comprehensively evaluate the efficacy and safety of this combination therapy. Based on the observation of the efficacy and safety of this combination of "immunotherapy-targeted therapy-radiotherapy" in mCRC, we have carried out a clinical trial and are currently continuing to enroll patients to explore the clinical application of this combination treatment mode (ChiCTR2300075853).

Previous studies have shown that radiotherapy enhances the efficacy of immunotherapy primarily by inducing cancer cell death, which leads to the release of intracellular proteins that serve as tumor antigens and subsequently elicit an immune response. A recent study has uncovered an additional mechanism: radiotherapy can also induce neoantigen generation in low-mutation-load tumors, thereby increasing their sensitivity to immune checkpoint therapy.[10] Radiotherapy can trigger type I interferon (IFN) response through the cGAS-STING signaling pathway, up-regulate inflammatory cytokines, and activate anti-tumor T cell immunity.[11] In addition, radiotherapy can induce abscopal effects. Radiotherapy has shown a good synergistic effect with immune checkpoint inhibitors in solid tumors.[12] Anti-angiogenesis targeted therapy can regulate the tumor immune microenvironment, to produce synergistic effects in combination with immunotherapy. In addition, anti-angiogenesis targeted therapy can normalize vascular morphology and support T-cell infiltration. Immune checkpoint inhibitors can release the "brake" of T cells.[13]

Conclusion

Therefore, the combination treatment mode of immunotherapy, targeted therapy, and radiotherapy has sufficient theoretical and clinical practice basis. However, the clinical application of this combination strategy still needs to be verified with a larger sample size. Furthermore, additional research is required to identify and screen appropriate candidates for this combination therapy

regimen, as well as to systematically summarize the clinical data on toxicities and adverse effects associated with this treatment approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Notes on contributor

Xiaoping Qian, Ph.D, She has been engaged in clinical medicine for more than 30 years, mainly focusing on individualized anti-tumor therapy for colorectal cancer. Since 2015, she has been appointed as a doctoral supervisor in the Medical school of Nanjing University. As the first person in charge, she has undertaken 15 scientific research projects including the general project of the National Natural Science Foundation of China.

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Authors' contributions

Xiaoping Qian and Li Li contributed to the study conception and design; Qun Zhang contributed to the study monitoring and writing the manuscript.

Ethics approval and consent to participate

The patient consented to all the reported procedures when indicated, according to the approval of the Ethics Committee of Nanjing Drum Tower Hospital.

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