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Rapid Reduction of CEA and Stable Metastasis in an *NRAS*-mutant Rectal-Cancer Patient Treated With FOLFIRI and Bevacizumab Combined With Oral Recombinant Methioninase and a Low-Methionine Diet Upon Metastatic Recurrence After FOLFIRI and Bevacizumab Treatment Alone

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Abstract. *Background/Aim: The choice of chemotherapy agents for RAS-mutant colorectal cancer is limited, and prognosis is poor compared to RAS-wild-type colorectal cancer. The purpose of the present study was to evaluate the effectiveness of methionine restriction combined with chemotherapy in a patient with NRAS-mutant rectal cancer. Patients and Methods: A 59-year-old female was diagnosed with lung-metastatic recurrence of NRAS-mutant rectal cancer two and a half years after resection of the primary tumor. She started chemotherapy, which consisted of fluorouracil, irinotecan (FOLFIRI), and bevacizumab, in October 2020. Eight months later, stereotactic body radiation therapy (SBRT) was performed to treat the lung metastases. She stopped chemotherapy at this point and had blood tests and computed tomography (CT) scans regularly. Her CEA level increased to 139.91 ng/ml and her lung metastasis became larger by September 2022. Therefore, she was reintroduced to FOLFIRI and bevacizumab in October 2022, and also started a low-methionine diet and oral recombinant methioninase (o-rMETase) as a supplement. Results: After starting the combination therapy with o-rMETase, a low-methionine diet, FOLFIRI, and bevacizumab, blood CEA levels very rapidly decreased and were almost within the normal limits five months later. CT findings showed the lung metastasis did not grow. Conclusion: Methionine restriction comprising o-rMETase and a low-methionine diet combined with first-line chemotherapy was effective in a patient with NRAS-mutant rectal cancer in which metastasis had re-occurred after first-line chemotherapy alone.*

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Colorectal cancer (CRC) is the second most-common cause of cancer death in the United States (1). Median survival time of CRC patients with metastatic disease is approximately 30 months, regardless of intensive chemotherapy (2). Especially in patients with *RAS*-mutant colorectal cancer, due to the limited efficacy of chemotherapy, the prognosis is poor, compared to *RAS*-wild-type patients (3, 4).

The addiction to methionine is a fundamental and general hallmark of cancer, known as the Hoffman effect (5-11). Methionine addiction of cancer cells is due, at least in part, to elevated transmethylation reactions (10-11), which greatly increase the demand for methionine, compared to normal cells. Therefore, cancer cells cannot survive in the absence of exogenous methionine (5-11), despite high rates of methionine biosynthesis by the cancer cells (5-7, 11, 12). Our laboratory has developed recombinant methioninase (rMETase) to target methionine addiction (13). When administered orally, this enzyme degrades methionine in the intestines, resulting in a decrease in methionine in the circulation and in tumors (14).

Preclinical research has shown that methionine addiction is a potent colorectal-cancer therapeutic target (15-17). We

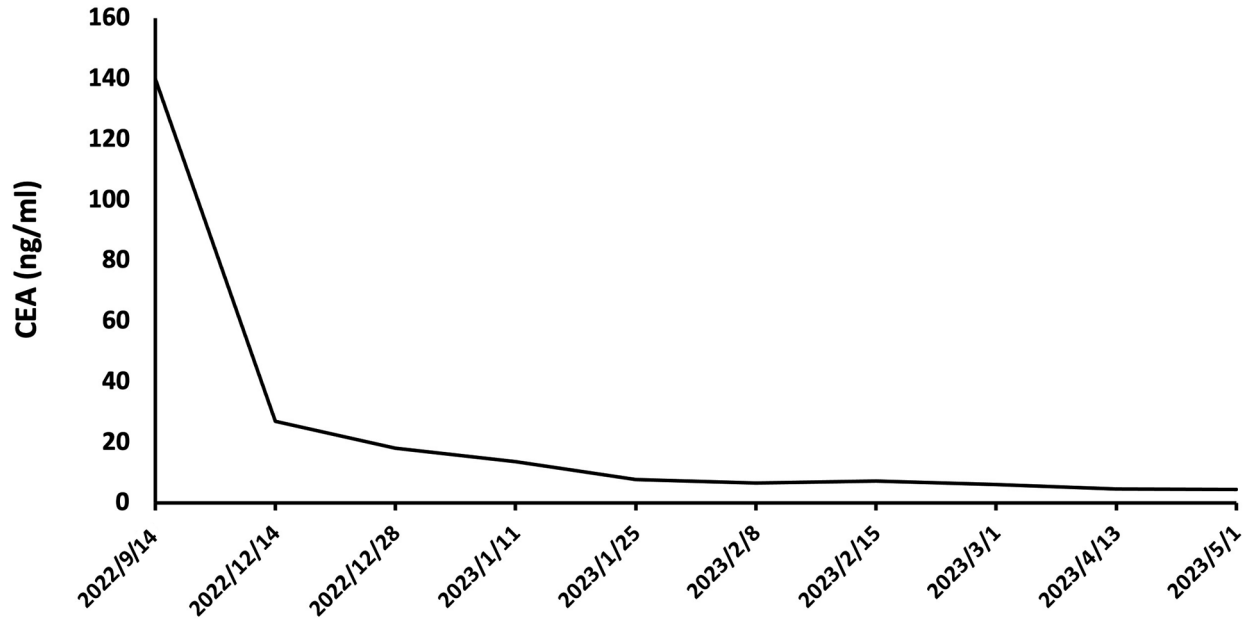

Figure 1. *Time course of patient's CEA levels (ng/ml). Treatment with FOLFIRI, bevacizumab, o-rMETase, and a low-methionine diet began in September 2022.*

previously showed the synergistic efficacy of oral rMETase (o-rMETase) combined with 5-fluorouracil and oxaliplatinum (FOLFOX) on a patient-derived orthotopic xenograft (PDOX) nude-mouse model of colorectal-cancer liver metastasis (17).

Durando *et al*. demonstrated the feasibility of the combination of dietary methionine restriction with the FOLFOX regimen in a small phase I/II human clinical trial with colorectal-cancer patients. They demonstrated acceptable toxicity and tumor response, but the patients did not continue methionine restriction because the medical low-methionine diet was not palatable (18).

We believe that a low-methionine plant-based diet combined with o-rMETase is the solution to this problem. We previously showed that a rectal cancer patient taking o-rMETase and a low-methionine diet had stable carcino-embryonic antigen (CEA) for more than 15 months (19).

In the present case report, a 59-year-old female with recurrent *NRAS*-mutant rectal cancer treated with 5-fluorouracil and irinotecan (FOLFIRI), combined with dietary methionine restriction and o-rMETase, as a supplement, showed strong efficacy: CEA levels were reduced by 97% and metastatic disease in the lung was stabilized.

Patients and Methods

rMETase production and formulation. Fermentation of recombinant *Escherichia coli* transformed with the methioninase gene from *Pseudomonas putida* was used to produce rMETase (20). rMETase was purified using a high-yield method involving a 60˚C heat step, polyethylene glycol precipitation, and diethylaminoethyl (DEAE)-Sepharose FF column chromatography (20).

Methionine restriction and o-rMETase administration. The patient went on a methionine-restricted, low-methionine diet in accordance with the Nutritional Oncology Research Institute (NORI) protocol, which suggests a daily methionine intake of 2 mg/kg body weight (21). As a dietary supplement, 250 units of o-rMETase were administered orally twice daily.

Results

Case report. A 59-year-old female was diagnosed with Stage IIA (T3, N0, M0) rectal adenocarcinoma on January 9, 2018. After neoadjuvant chemo-radiotherapy (capecitabine and radiation of 50.4 Gy), she received abdomino-perineal resection (APR) in May of the same year. Because lymph-node metastasis was demonstrated pathologically, she was given adjuvant chemotherapy (5-fluorouracil [5-FU] and oxaliplatinum, FOLFOX) for 6 months.

However, computed tomography (CT) revealed four lung metastases in August 2020. The patient then started chemotherapy, which consisted of 5-FU and irinotecan (FOLFIRI), and bevacizumab, in October 2020. This regimen was used due to genetic profiling of the tumor, which demonstrated an *NRAS*-mutation. Eight months later, stereotactic body radiation therapy (SBRT) was performed to treat the lung metastases. After that, the blood CEA level decreased within the normal limits. The patient stopped chemotherapy at this point and CEA was measured and CT performed on a regular basis.

The patient's CEA level rapidly rose by July 2022, and increased to 139.91 ng/ml in September 2022. Positron emission tomography (PET) CT showed the patient's lung metastases were larger on September 14, 2022 compared to August 2020. Therefore, she re-introduced FOLFIRI and bevacizumab in October 2022 in combination with a low-methionine diet and o-rMETase as a supplement. After starting this combination regimen, blood CEA levels decreased rapidly (Figure 1). Five months later, the CEA level was almost within the normal limits on May 1, 2023, having decreased by 97%. A CT scan showed that the patient's lung metastases had not grown since the previous scan on January 28, 2023. The patient also took pro-oxidant supplements.

Discussion

In *RAS*-mutant metastatic colorectal cancer, a fluoropyrimidine and oxaliplatinum (oxaliplatinum-based doublet) or a fluoropyrimidine and irinotecan (irinotecan-based doublet) or a fluoropyrimidine, oxaliplatinum and irinotecan (triplet) plus bevacizumab are the standard of care in the first-line setting (22-24). If an oxaliplatinum-based doublet is selected in the first-line setting, the standard of care in the second-line setting is an irinotecan-based doublet plus an anti-angiogenetic agent, such as bevacizumab, aflibercept or ramucirumab (25-27). In the second-line-chemotherapy setting, the treatment efficacy is limited, with progression- free survival (PFS) between 4.1 and 6.9 months, and an objective response-rate (ORR) between 3.9% and 19.8%. In the present case, the patient received FOLFIRI plus bevacizumab for recurrence after FOLFOX, but two years later lung metastases grew and the CEA level increased to 139.91. In September 2022 the patient resumed FOLFIRI plus bevacizumab, but this time in combination with o-rMETase and a low-methionine diet. This treatment resulted in a strong reduction of CEA levels by 97% to near-normal levels and arrest of the growth of her lung metastases.

We originally discovered that methionine restriction is synergistic with chemotherapy (28). Thereafter, numerous studies have demonstrated the synergy between methionine restriction, including methionine restriction with rMETase, and chemotherapy of all types (29). Cancer cells selectively arrest in late S/G_2 of the cell cycle when methionine is depleted (30, 31). Therefore, chemotherapeutic agents acting on S-phase are especially effective in combination with methionine restriction. In the present case, because 5-FU and irinotecan act in S-phase, this combination therapy was synergistic with methionine restriction. Combining methionine restriction with chemotherapy is termed the Hoffman protocol (28,29).

In *Ras*-mutant colorectal cancer, chemotherapy drugs are limited because anti-EGFR antibodies are not effective. Recently, RAS inhibitors have been developed for each mutation type, but they have only modest efficacy (32). Sotorasib, which is a *KRAS G12C* inhibitor, showed a response rate of 7.1% in a Phase I clinical trial and 9.7% in a Phase II clinical trial (33). Neo-*RAS* wild-type colorectal cancer results from a change from *RAS*-mutant disease to *RAS*-wild type disease in circulating tumor DNA and is associated with long-term improvement of overall survival (34).

The present results suggest that methionine restriction combined with standard first-line chemotherapy is promising for *RAS*-mutant colorectal cancer, possibly because methionine restriction targets the fundamental basis of cancer (5-11, 35-37). Further clinical studies, are needed (38).

Conflicts of Interest

The Authors declare no competing interests in relation to this work.

Authors' Contributions

YK and RMH wrote the article. QH produced methioninase. SM reviewed the manuscript.

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