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CASE REPORT

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Re-exposure to immunotherapy in metastatic colon cancer: A case report

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Abstract

Re-exposure to immunotherapy in metastatic colorectal cancer may be indicated in selected patients that previously benefitted from immunotherapy with tolerable irAEs.

KEYWORDS

colon cancer, immunotherapy, microsatellite instability

1 | INTRODUCTION

Patients with metastatic colorectal cancer characterized by a deficient mismatch repair status are candidates for immunotherapy. Knowledge about reintroduction of immunotherapy, however, is missing. This case reports on the outcome of doublet immunotherapy in a patient previously exposed to monoimmunotherapy, and how these treatments may alter the expected outcome.

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide with a 5-year survival rate of 14% in patients with metastatic CRC (mCRC).[1] A minority of mCRC patients (approximately 5%) have a tumor with DNA mismatch repair deficiency and/or high microsatellite instability (dMMR/MSI-H).[2] This patient group may respond poorly to conventional chemotherapy and have shorter overall survival compared to patients with mismatch repair proficient (pMMR) tumors.[3]

The mismatch repair (MMR) system corrects spontaneous errors occurring during DNA replication. In dMMR tumors, errors accumulate resulting in microsatellite length mutation, microsatellite instability (MSI),[4] and truncated peptides that are able to activate the immune system.[5] The interest in evaluating the effect of immunotherapy in this particular patient group has therefore been tremendous.

Several studies have demonstrated durable response and disease control by single anti-programmed death PD-1 checkpoint inhibitors such as pembrolizumab and nivolumab in dMMR metastatic colon cancers, and generally, one third of the patients show objective response.[6-8] Evidence has suggested enhanced efficacy with an objective response rate of 55% when combining nivolumab and ipilimumab (a CTLA-4 inhibitor) and thereby targeting two sites of the immune-regulatory system simultaneously, although the immune-related adverse events (irAEs) are expectedly more frequent in this setting.[9] However, the safety profile of the combination is reported to be manageable with one third of the patients experiencing grade 3-4 irAEs and only 13% discontinuing treatment.[10]

Interesting evidence is emerging from studies having examined the effect of immunotherapy as first-line treatment in metastatic colon cancer[11] in conjunction with other treatment

modalities such as radiation therapy[12] and in the neoadjuvant setting.[13] A recent study demonstrated significantly longer progression-free survival with pembrolizumab compared to standard chemotherapy (16.5 vs 8.2 months) when applied as first-line treatment in patients with dMMR/MSI-H metastatic colon cancer. The rate of serious irAEs was significantly lower in the pembrolizumab group.[11]

The growing evidence on immunotherapeutic treatment of dMMR/MSI-H colon cancer has increased the number of patients receiving the treatment, and selecting the right patients is of utmost importance.[14] The expected clinical outcome of reintroduction of immunotherapy, however, remains widely unknown. Different therapeutic approaches following progression on immunotherapy are being investigated, and the clinical responsiveness to subsequent treatments may depend on previous exposure to immunotherapy. We present a case of a patient with metastatic colon cancer successfully treated with nivolumab and ipilimumab after previous progression on pembrolizumab. The outcome was quite surprising.

2 | CASE PRESENTATION

A 53-year-old man was diagnosed with BRAF V600E-mutated metastatic colon cancer with dMMR and a synchronous renal cell carcinoma in 2016. He was initially treated with standard oncology therapy as previously presented,[15] followed by 15 months of pembrolizumab monotherapy (Figure 1). Upon progression, fluorouracil and irinotecan (FOLFIRI) were reintroduced and bevacizumab added at the sixth cycle. The metastatic sites were the liver and peritoneal cavity. The combination of FOLFIRI and bevacizumab surprisingly resulted in stable disease for 8 months, despite the fact that the disease had previously progressed directly on both FOLFIRI and a bevacizumab containing regimen. At this point, an evaluation CT scan showed increasing carcinomatosis, and clinically, the patient presented with subfebrile temperature, weight loss, and increased abdominal pain.

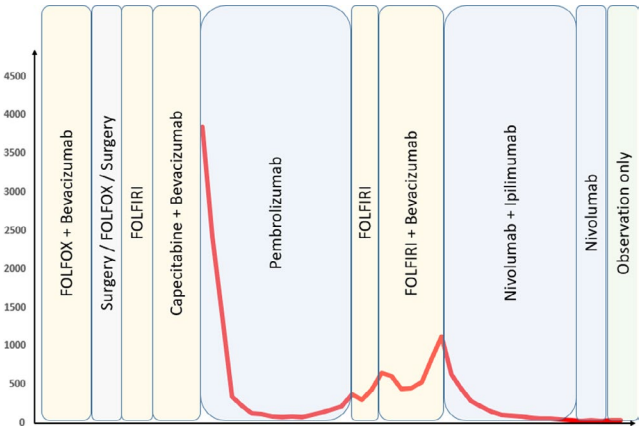

FIGURE 1 Treatment overview from the initiation of first-line FOLFOX + bevacizumab in February 2016 to the latest update in September 2020 during the first treatment break. The width of the individual "treatment column" corresponds to the duration on treatment. The red curve illustrates changes in carcinoembryonic antigen in μg/L measured continuously since the introduction of pembrolizumab

Since the patient requested further treatment and had a performance status of 0, second-line immunotherapy with nivolumab and ipilimumab was initiated in March 2019 based on approval by the National Board of Health. In a 6-week treatment cycle, the patient received nivolumab 3 mg/kg and low-dose ipilimumab 1 mg/kg on day one followed by nivolumab 3 mg/kg on days 14 and 28. Table 1 summarizes the clinical events during this treatment. Figure 1 provides an overview of the patient's treatments and their duration. The level of carcinoembryonic antigen (CEA) was measured after initiation of pembrolizumab.

During the first month of treatment the patient presented with decreased pain, a drop in CEA, and reduced consumption of opioids. At the same time, he experienced declining appetite, abdominal discomfort, and a weight loss of 1.5 kg leading to initiation of prednisolone. The second month resulted in physical improvement with weight gain, cessation of abdominal discomfort, and a further drop in CEA. Prednisolone was tapered off over 6 weeks. A CT scan after the first cycle showed progression of abdominal carcinomatosis but was interpreted as immune infiltration. The subsequent CT scan showed stable disease and no longer signs of increasing carcinomatosis. Again, the CEA level dropped. However, due to a slightly increased radiological lung pattern and mild coughing, prednisolone 5 mg daily was initiated. After the third treatment cycle, the CT scan revealed slight regression of liver metastases.

During the following 9 months, stable disease was confirmed radiologically and biochemically with a continuous drop of CEA and clinically supported by weight gain and increasing physical activity of the patient. Except for a mild skin rash treated with antihistamines and mild topical steroids, the treatment was tolerated well.

After 13 months of treatment, the CT scan showed increased bilateral ground-glass opacities. The patient was clinically unaffected and the CEA level continued dropping. The radiological changes were interpreted as side effects to long-term immunotherapy. Consequently, ipilimumab was discontinued and nivolumab continued as monotherapy. Three months later, the radiological ground-glass opacities significantly worsened, and the patient now presented with tiredness and exercise-induced dyspnea consistent with irAE grade 2-3 pneumonitis. Hospitalization was not needed, but the condition required termination of nivolumab and treatment with high-dose prednisolone of 100 mg daily tapered down over the next 3 months.

TABLE 1 Clinical overview during re-exposure to immunotherapy

Timeline	Event	Consequence
March 2019	Treatment initiation of Nivolumab and Ipilimumab	
March 2019	Dropping CEA, decreased pain, declining appetite, abdominal discomfort, weight loss 1.5 kilos	Low-dose prednisolone 10 mg daily for 1 wk and 5 mg daily in the subsequent wk
April 2019	Further drop of CEA, increased well-being, weight gain of 1 kilo, and cessation of abdominal discomfort. No longer taking opioids. Performance status 0. Dry, scaly, and itchy skin. CT scan showed increased carcinosis	Prednisolone decreased to 2.5 mg daily for 1 wk and discontinued after a total of 6 wk. Treatment with a mild topical steroid and antihistamines initiated. Results of the first CT scan interpreted as pseudoprogression
May 2019	CEA continuously dropping, performance status 0, slightly increased coughing. The second CT scan, after 12 wk, showed stable disease and increased interstitial lung pattern	Prednisolone 5 mg daily initiated (discontinued in February 2020)
July 2019	CT scan after 16 wk showed stable disease and slight regression of liver metastases	
March 2020	TSH dropped to 0.15 and T4 increased to 24. Patient experienced no symptoms of hyperthyroidism	
April 2020	CT scan showed increased bilateral ground-glass opacities. No clinical pulmonary symptoms. Thyroid count spontaneously normalized	Ipilimumab discontinued due to radiologic pulmonary changes. Nivolumab monotherapy 3 mg/kg continued every 2 wk
July 2020	The patient had clinical symptoms of tiredness and exercise-induced dyspnea, which had increased over the last 2 mo, and developed grade 2-3 immune-mediated pneumonitis. No impairment of ADL. Otherwise performance status 0. CT scan revealed severe progression of ground-glass opacities but otherwise stable disease	The patient was referred to a pulmonologist and a cardiologist. Cardiologic examination was normal. DLCO was severely reduced to 30% and Nivolumab was paused. Treatment with oral prednisolone 100 mg daily and prophylactic trimethoprim/ sulfamethoxazole was started. Prednisolone was tapered off over 3 mo
September 2020	CT scan showed stable disease and CEA is stably low. Clinically, shortness of breath worsened after prednisolone 5 mg was discontinued	Prednisolone 25 mg daily was reintroduced and tapered off over the next 6 wk

To this date, re-exposure to immunotherapy has been effective for 18 months and ongoing, with manageable side effects that did not require hospitalization. The patient is currently on a treatment break for the first time after 52 months of continuous treatments. He is clinically unaffected and had stable disease on the most recent CT scans in September and December 2020. CEA remains stable at the lowest level seen in this individual.

3 | DISCUSSION

The number of mCRC patients treated with immunotherapy is increasing due to a growing number of approved indications. Recently, pembrolizumab was approved by the U.S Food and Drug Administration as first-line treatment for patients with dMMR/MSI-H mCRC. Meanwhile, multiple studies explore novel therapeutic approaches with immunotherapy, including combinations with radiation therapy, chemotherapy, and targeted therapy and treatment for early-stage CRC in the neoadjuvant and adjuvant settings.

Consequently, there is an increasingly relevant question of how to proceed after previous progression on immunotherapy. Its reintroduction is rather new in clinical oncology and knowledge on the issue is sparse. A major concern is that re-exposure to immunotherapy may lead to multiple and severe irAEs due to a previously primed immune system in a fashion similar to allergic reactions. Also, the treatment strategy over the last years has moved from monotherapy to combination therapy with dual blockage of PD-1 and CTLA-4, which further enhances the risk of severe toxicity. The choice to reintroduce immunotherapy is therefore complex and should always be carefully balanced between the possible clinical benefit and treatment-related toxicity in the individual patient.

Our case illustrates a patient with dMMR metastatic colon cancer who achieved long-term disease stabilization on combination immunotherapy with nivolumab and ipilimumab after previous progression on pembrolizumab. FOLFIRI and bevacizumab were given for 8 months during the immunotherapy pause. The decision to reintroduce immunotherapy was based on previous clinical response and mild irAEs

during treatment with pembrolizumab and the lack of other treatment options. The combination was chosen partly since nivolumab and ipilimumab act synergistically to promote antitumor response through complementary mechanisms of action and seem to be superior to nivolumab monotherapy,[9] and partly in order to overcome a possible, acquired PD-1-resistance.

To the best of our knowledge, there is only one other and very recent case report on re-exposure of immunotherapy in mCRC. Nivolumab and ipilimumab in their case were also well tolerated and had a meaningful benefit comparable to our results.[16] Data on three additional cases with a similar outcome were reported at the Society for Immunotherapy for Cancer (SITC) conference 2020.[17] Based on these data and the present case, we propose that reintroduction of immunotherapy may be indicated in selected patients in which irAEs have previously been manageable and clinical benefit documented.

More recently, preclinical and clinical evidence has suggested a mutual, enhanced effect of immunotherapy and antiangiogenic treatment. Antiangiogenic treatment reverses tumor-induced immunosuppression in the tumor microenvironment (TME) and enhances drug delivery due to vessel normalization, thereby improving the efficacy of immunotherapy.[18] Also, immunotherapy can promote vascular normalization through a stimulation of interferon gamma (ifn-Y) released from the activated T cells.[19] In the present case, the responsiveness to FOLFIRI and bevacizumab may have been altered due to a prolonged immunogenic effect of pembrolizumab after its cessation, resulting in a synergistic effect of pembrolizumab and bevacizumab. Similarly, the subsequent response to nivolumab plus ipilimumab may have been enhanced because of recent treatment with bevacizumab.

The phase III BEACON study treated 665 BRAF-mutated mCRC patients who had previously progressed on one or two treatment regimens. They were randomized to receive encorafenib and cetuximab plus/minus binimetinib or standard treatment. The triplet and doublet treatments inhibiting BRAF, EGFR, and/or MEK resulted in significantly longer overall survival and a higher response rate compared to standard treatment.[20] To this date, our patient has been on a treatment break since July 2020. When the disease progresses, the likely next step will therefore be to target the BRAF and EGFR receptors based on data from the BEACON study.

4 | CONCLUSION

Re-exposure to immunotherapy may be indicated in selected patients with metastatic colon cancer and dMMR leading to tolerable irAEs and a meaningful clinical benefit. Reintroducing a treatment targeting the same receptor as previously (PD-1) seems to provide benefit based on the combination with a treatment targeting another regulatory side (CTLA-4). The benefit from the chemotherapy given in-between might be due to long-term effects of the initial immunotherapy.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

TRH: identified the special learning points and conceived the idea for the case report, was responsible for collection and assembly of data, drafted the manuscript, discussed the results, commented, and approved the final version of the manuscript. JKS: identified the special learning points and conceived the idea for the case report, discussed the results, commented, and approved the final version of the manuscript. BMH: identified the special learning points and conceived the idea for the case report, discussed the results, commented, and approved the final version of the manuscript. LHJ: identified the special learning points and conceived the idea for the case report, discussed the results, commented, and approved the final version of the manuscript. TFH: identified the special learning points and conceived the idea for the case report, was responsible for collection and assembly of data, co-drafted the manuscript, discussed the results, commented, and approved the final version of the manuscript.

ETHICAL APPROVAL

The patient has provided oral and written consent to this case report.

DATA AVAILABILITY STATEMENT

All relevant data are presented in the case.

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