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Dual Checkpoint Inhibition with Ipilimumab plus Nivolumab After Progression on Sequential PD-1/PDL-1 Inhibitors Pembrolizumab and Atezolizumab in a Patient with Lynch Syndrome, Metastatic Colon, and Localized Urothelial Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Immune checkpoint blockade (ICB) is an approved therapy for advanced metastatic mismatch repair (MMR)-deficient cancer regardless of tissue of origin. Although therapy is effective initially, recurrence rates are significant, and long-term outcomes remain poor for most patients. It is not currently recommended to give sequential ICB for advanced MMR-deficient colorectal cancer (CRC) or for patients with metastatic cancer from Lynch syndrome. The need for subsequent therapy options in advanced MMR-deficient cancer beyond the first ICB regimen arises in clinical practice, and there are often no effective standard chemotherapies or other targeted therapies. We report the case of a Lynch syndrome patient with metastatic CRC and urothelial cancer who was treated sequentially with pembrolizumab (targeting PD1), atezolizumab (targeting PD-L1), brief rechallenge with pembrolizumab, and finally the combination of ipilimumab (targeting CTLA-4) and nivolumab (targeting PD1). Over a 28-month period the patient experienced prolonged disease control with each different regimen the first time it was given, including metabolic response by positron emission tomography and computed tomography scanning and tumor marker reductions. The case suggests that some patients with advanced MMR-deficient CRC may experience meaningful clinical benefit from multiple sequential ICB regimens, a strategy that can be further tested in clinical trials. ***The Oncologist*** 2019;24:1416–1419

Key Points

- The case exemplifies clinical benefit from sequential immune checkpoint blockade in a patient with Lynch syndrome with advanced metastatic colorectal cancer and urothelial cancer.
- Metabolic response, with decreased fluorodeoxyglucose avidity on positron emission tomography and computed tomography, and reductions in tumor markers, such as carcinoembryonic antigen, were helpful in this case to monitor disease status over a 28-month period of therapy.
- The concept of sequential immune checkpoint blockade in patients with advanced mismatch repair-deficient cancer merits further study to determine which patients are most likely to benefit.

Background

Impaired mechanisms of DNA mismatch repair (MMR) either by mutation in or promoter methylation of essential genes lead to highly mutated repetitive DNA sequences (microsatellites) across the genome. Microsatellite instability (MSI) contributes to different tumor types. Although an inherited form of MMR deficiency (Lynch syndrome) accounts for ~3% of colorectal cancers (CRCs), MMR deficiency accounts for ~15% of all CRCs via somatic mutation [1].

MSI-high (MSI-H) CRC has a high tumor mutation burden, increasing neoantigen presentation [2]. Within the tumor microenvironment, MSI-H CRC tumors are enriched with type 1 T helper cells and cytotoxic T lymphocytes,

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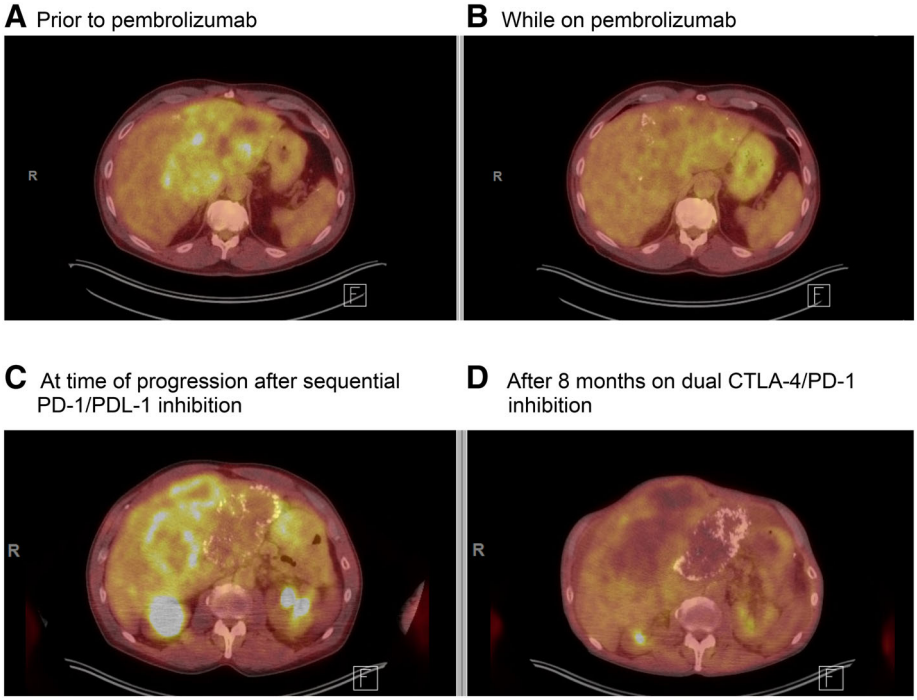

Figure 1. Positron emission tomography and computed tomography (PET/CT) throughout treatment. **(A):** PET/CT prior to initiating pembrolizumab. **(B):** PET/CT after 5 months of immunotherapy indicating a partial response with decrease in standardized uptake value (SUV) of liver mass from 6.5 down to 4.6. **(C):** PET imaging at time of progression after atezolizumab and pembrolizumab with maximum SUV of 6.5. **(D):** PET obtained after 8 months on ipilimumab plus nivolumab for four doses followed by nivolumab alone showed a response to combination therapy with a maximum SUV of 3.6.

indicating an ongoing immune response [3]. However, this is counterbalanced by increased immune checkpoint expression with upregulation of PD-1/PDL-1 and CTLA-4, inhibiting the immune response, thereby allowing tumor growth [2, 3]. Immune checkpoint inhibitors relieve this block and restore antitumor immune function. Trials of these drugs in patients with MSI-H CRC previously treated with chemotherapy have yielded significant responses, and these drugs are approved by the U.S. Food and Drug Administration (FDA) to treat MSI-high CRC in the second line [4–6].

Immune checkpoint therapies have been studied as a single line of treatment in MSI-high metastatic CRC (mCRC). If checkpoint inhibition does not work or stops working, sequential treatment is not recommended. We present a case of a patient treated effectively with sequential PD-1/PDL-1 inhibitors as well as dual checkpoint inhibition beyond progression with good disease control. The patient agreed for his case to be published in the literature.

Patient Story

The patient was a 64-year-old man diagnosed with stage IIIA colon cancer 11 years prior to establishing care at our institution. Immunohistochemistry revealed absent MSH-2 and MSH-6 expression. The patient completed adjuvant chemotherapy and remained disease free until recurrence 10 years later with a 16.5-cm mass in the liver, after which he was treated with FOLFIRI (leucovorin calcium, fluorouracil, irinotecan hydrochloride) and bevacizumab, followed by irinotecan and cetuximab at disease progression with interval growth in liver lesions and metastatic lymphadenopathy (for full details of his prior therapy, please refer to our earlier publication on this patient) [7]. Five months later, his disease progressed in the liver and lymph nodes with new hydroureteronephrosis bilaterally. Workup revealed localized urothelial carcinoma via right ureteral cytology, also lacking MSH-2 and MSH-6 expression.

The patient established care in our clinic in 2016. Given the MMR deficiency evident in his colon tumors, we performed germline testing, which revealed an *MSH-2* mutation (*IVS1* + 2T > G) in some but not all of his cells confirming the diagnosis of a mosaic attenuated Lynch syndrome, consistent with his later age of presentation. The patient was started on compassionate use pembrolizumab initially at a dose of 2 mg/kg, which was rotated to a flat dose of 200 mg every 3 (q3) weeks. Carcinoembryonic antigen (CEA) subsequently declined, and a partial response was seen on positron emission tomography and computed tomography (PET/CT; Fig. 1A–B) with decreased metabolic activity and improvement in the patient's abdominal pain. After 9 months of treatment, the patient's CEA rose, and increased fluorodeoxyglucose activity was noted in his liver metastasis on a PET/CT, along with activity in the ureters, bilaterally. Repeat cystoscopy demonstrated high-grade T1 urothelial carcinoma of the bladder in addition to his ureteral urothelial carcinoma. Given the approval of atezolizumab for patients with urothelial carcinoma, the patient was treated with atezolizumab 1,200 mg q3 weeks with stability of his urothelial tumors on repeat cystoscopy and 8 months of CRC disease control before progressive disease in the liver. He was briefly retreated with pembrolizumab 200 mg q3 weeks for an additional 3 months, given that on re-review of his CEA trends it was unclear if there was a decline on pembrolizumab just before atezolizumab started. However, after four additional cycles

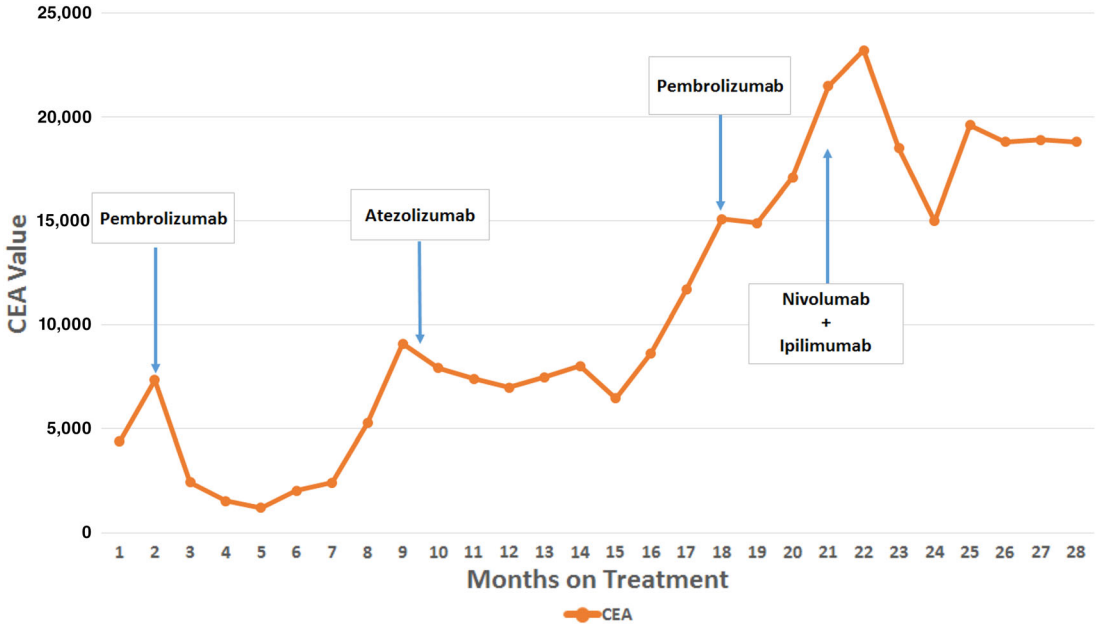

Figure 2. CEA trend over time during treatment.
Abbreviation: CEA, carcinoembryonic antigen.

of pembrolizumab, the patient's right upper quadrant pain worsened, CEA rose from 15,100 to 21,500, and PET/CT imaging showed progression of his liver tumor (Fig. 1C). Therefore, pembrolizumab was discontinued.

The patient then began treatment with off-label compassionate use nivolumab 3 mg/kg and ipilimumab 1 mg/kg q3 weeks based on a study published in the *Journal of Clinical Oncology* showing activity of combination PD-1 and CTLA-4 blockade in MSI-H tumors [4]. With this combination, the patient's CEA level remained stable at ~18,000, and PET/CT imaging revealed a metabolic response (Fig. 1D) with decline in uptake in his primary tumor as well in other metastatic implants and shrinkage of urothelial tumors. After four cycles of the combination, the patient continued single agent nivolumab 3 mg/kg once every 4 weeks with continued disease control for a total of 7 months on this therapy. At that time, a rise in bilirubin to 5.3 was noted, which was attributed to an immunotherapy-related adverse event, and the patient was treated with high-dose steroids. During his steroid taper, the patient chose to discontinue all therapy and subsequently passed away.

Discussion

The development and approval of PD-1/PDL-1 and CTLA-4-specific therapies have revolutionized oncology, yet the full utility of these drugs to treat mCRC is still being elucidated. Anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1 (avelumab, durvalumab, atezolizumab), and anti-CTLA4 (ipilimumab) targeted drugs have been studied in mCRC. In patients with MSI-H mCRC, immune checkpoint therapy has shown responses in a substantial proportion of patients. Overall response rates (ORR) with pembrolizumab or nivolumab range between 30% and 40%, with disease control achieved in >50% of treated patients, and these drugs are approved in the second line for MMR-deficient/MSI-H mCRC [5, 6]. In patients with MSI-H mCRC, the addition of CTLA-4 inhibitor ipilimumab to nivolumab increased ORR to 55% [4]. However, the utility of sequential immunotherapy after progression is unknown. For the five PD1/PDL-1 inhibitors currently FDA approved, preclinical data suggest the drugs bind different epitopes on PD-1/PDL-1, and therefore it may be reasonable to sequence them [8]. The current literature on sequential PD-1/PDL-1 inhibition is mixed, with some reports showing continued progression of disease in patients who had previously responded to PD-1 inhibition [9]. Although there are emerging data to add CTLA-4 inhibition to a PD-1 inhibitor upon progression on single checkpoint blockade in multiple tumor types other than colorectal carcinoma, this is not yet standard of care [10–14].

Our patient with Lynch syndrome was treated with sequential PD-1/PDL-1 inhibitors with response, followed by the combination of a CTLA-4 and PD-1 inhibitor at the time of progression with significant disease control. His disease was controlled by single as well as dual checkpoint inhibition, both on PET/CT imaging (Fig. 1) and by stabilization in his CEA (~18,000 for 8 months while he was on dual immunotherapy; Fig. 2). Prolonged disease control suggests possible utility in sequencing immunotherapy medications in patients with MSI-H mCRC, and studies are needed to help determine who may benefit from receiving multiple immunotherapy-based treatments.

Author Contributions

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Disclosures

The authors indicated no financial relationships.

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For Further Reading:
Claudia Maletzki, Maja Hühns, Ingrid Bauer et al. Suspected Hereditary Cancer Syndromes in Young Patients: Heterogeneous Clinical and Genetic Presentation of Colorectal Cancers. ***The Oncologist*** 2019;24:877–882.

Abstract:
Colorectal cancer (CRC) is rare in young patients without a confirmed family history of cancer. Reports of an increased prevalence of POLD1/POLE mutations in young patients with colorectal cancer have raised awareness and support routine genetic testing for patients with early-onset tumors. In cases of CRC without proven MMR-germline mutation, molecular analyses are warranted to confirm or rule out other familial CRC syndromes. This article describes the cases of two young male patients, who presented with locally advanced and metastatic CRC, and reports the results of the germline mutational analyses done for both patients. These cases demonstrate the importance of special care and molecular diagnostic procedures for young patients with CRC.

Key Points:
- Patients with colorectal cancer who are younger than 50 years at initial diagnosis (early onset) should routinely undergo genetic testing.
- Early- and very-early-onset patients (younger than 40 years) with absence of microsatellite instability should be considered for tumor mutation burden testing and/or DNA polymerase proofreading mutation.
- The mutational signature of HSP110 within mismatch repair deficiency-related tumors may help to identify patients likely to benefit from 5-fluorouracil-based chemotherapy.
- Intensified, maintained, and specific surveillance may help to reduce secondary tumor progression.