Neoadjuvant Immunotherapy in Microsatellite-Instability High Nonmetastatic Colorectal Cancer: A Single-institute Experience and Review of the Literature.

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Clinical Practice Points

- Colorectal cancer is the third most common cancer in the United States and is composed of a heterogeneous group of tumors. A small subset of tumors are known to be microsatellite-unstable or deficient in mismatch repair proteins.
- Treatment with immune checkpoint inhibitors targeting programmed cell death 1 and cytotoxic T-lymphocyte antigen 4 results in improved overall survival in patients with microsatellite-unstable colorectal cancer in the metastatic setting.
- The role of immunotherapy in non-metastatic resectable colon cancer is yet to be determined.

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Keywords: Checkpoint inhibitor, Lynch syndrome, Mismatch repair deficient (MMR-d), Programmed cell death

Introduction

Colorectal cancer is the third most common cancer among both men and women in the United States.[1] It is composed of a heterogeneous group of tumors with multiple identified gene mutations as well as recognized predisposing environmental factors. All patients, regardless of stage, should undergo testing for microsatellite instability, as microsatellite instability has not only diagnostic but prognostic and therapeutic implications.[2] It is estimated that approximately 15% to 20% of colorectal carcinomas are high microsatellite-instability (MSI-H), with 3.5% to 5% of stage IV tumors being classified as MSI-H.[3] This suggests that MSI-H tumors have a lower propensity to metastasize than MSI-stable (MSI-S) tumors and indicates a more favorable prognosis. Only a small proportion of MSI-H tumors are owing to a germline mutation in the setting of Lynch syndrome; the remainder of MSI-H tumors are due to somatic inactivation of mismatch repair (MMR) genes *PMS2*, *MLH-1*, or *MSH-2/6*.[4] Regardless of whether the mutation is somatic or germline, studies have shown that patients with MSI-H tumors do not gain a survival benefit from fluorouracil-based therapy as compared with patients with MSI-S tumors.[5] Conversely, treatment with immune checkpoint inhibitors targeting programmed cell death 1 and cytotoxic T-lymphocyte antigen 4 results in improved overall survival in patients with metastatic MSI-H colorectal cancer. Therefore, pembrolizumab and nivolumab, 2 anti− programmed cell death 1 agents, were granted accelerated United States Food and Drug Administration (FDA) approval in 2017 in the setting of metastatic MSI-H colorectal cancer.[6] More recently, on June 29, 2020, the FDA approved first-line immunotherapy for patients with MSI-H metastatic colorectal cancer based on the phase III KEYNOTE-177 study.[7] However, their role in early stage or non-metastatic resectable colon cancer is yet to be determined.

Case Report

A 52-year-old male with no significant past medical history presented to the emergency room with abdominal pain and an enlarging palpable abdominal mass. He had no obstructive symptoms and reported having normal bowel movements prior to admission without unintentional weight loss or other constitutional symptoms. A computed tomography of the abdomen and pelvis revealed a large abdominal mass measuring 13 × 11 × 9 cm

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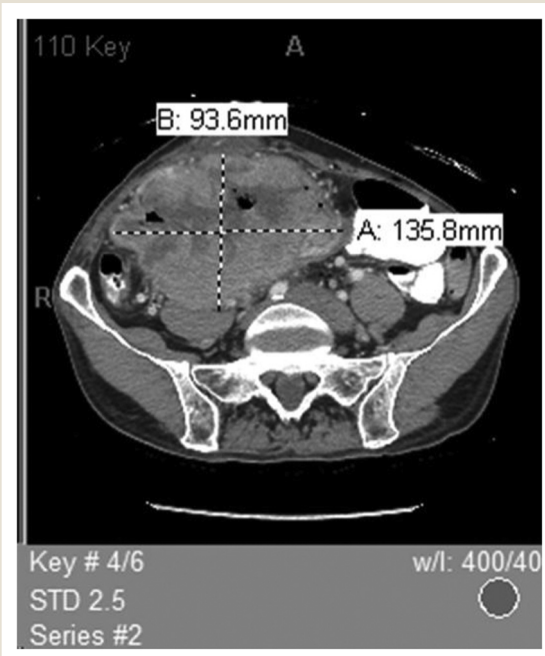
Figure 1 Initial Computed Tomography of the Abdomen/Pelvis Revealed a 9 × 13 cm Colon Mass



originating from the proximal transverse colon without associated adenopathy or evidence of obstruction (Figure 1). There was concern for invasion into the anterior abdominal wall with mass effect on the right ureter with mild right hydronephrosis. There were scattered prominent mesenteric lymph nodes, the largest of which measured 9 × 10 mm. The patient was also noted to have a microcytic anemia, with a hemoglobin of 9.1 g/dL, a mean corpuscular volume of 70, and thrombocytosis with platelet count of 856 × 10^3/cm^3. His carcinoembryonic antigen level was normal at 0.7 ng/mL (reference range, < 7.0 ng/mL). The remainder of his laboratory results were unremarkable.

He underwent colonoscopy, which revealed an obstructing ulcerating mass near the hepatic flexure and proximal transverse colon. Pathology revealed well-differentiated adenocarcinoma. Immunohistochemical analysis of MMR proteins indicated abnormal expression of MMR proteins and loss of the MMR proteins hMLH-1 and PMS2.

He was evaluated for colorectal surgery; however, the surgeon felt that the large tumor size with radiographic appearance of invasion into the anterior abdominal wall would make upfront surgical resection possible, though technically difficult, although possible. Therefore, based on data presented at the European Society for Medical Oncology (ESMO) 2018 conference, the decision was made to proceed with neoadjuvant immunotherapy followed by resection.[8]

He was started on ipilimumab 1 mg/kg on day 1 and nivolumab 240 mg days 1, 15, and 29 every 6 weeks and tolerated therapy without difficulty. Restaging scans performed after 1 cycle of therapy showed improvement in the size of the large transverse colon mass, which measured 7.3 × 6.2 cm from an initial maximum measurement of 13 × 11 × 9 cm. Restaging scans after the second cycle showed further improvement in the size of his mass to 4.1 × 4.5 cm (Figure 2). Additionally, the previously noted mildly enlarged mesenteric lymph nodes also decreased in size, the largest of which decreased from 9 × 10 mm to 7 × 9 mm. He was then treated on days 1 and 15 of cycle 3, and further therapy was held in preparation for surgery.

He underwent open extended right hemicolectomy with partial omentectomy. Intraoperatively, there were no findings of remaining tumor and no evidence of metastatic disease. Final pathology revealed lymphohistiocytic granulomatous inflammation with no evidence of malignancy. The proximal ileal and distal colonic margins were negative for dysplasia/malignancy. The appendix was benign. Seventy-seven lymph nodes were sampled, and all were negative for metastatic carcinoma, yielding a final pathologic stage of ypT0 ypN0, reflective of a complete pathologic response. A post-treatment carcinoembryonic antigen remains normal at 0.2 ng/mL (reference range, < 7.0 ng/mL).

Discussion

Standard-of-care initial treatment for nonmetastatic, resectable colorectal cancer is colectomy with en bloc removal of regional lymph nodes. For unresectable, non-metastatic disease, treatment has, until recently, included neoadjuvant systemic chemotherapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPEOX (capecitabine and oxaliplatin) followed by colectomy based on response to therapy. Based on National Comprehensive Cancer Network guidelines, neoadjuvant immunotherapy can be

Figure 2 Repeat Computed Tomography of the Abdomen/Pelvis after 2 Cycles of Nivolumab/Ipilimumab Revealed Improvement in the Size of the Colon Mass to 4.1 × 4.5 cm

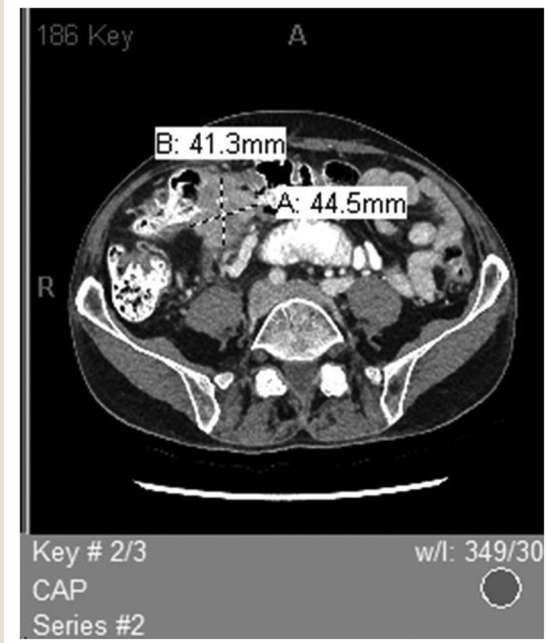


Table 1 Colorectal Cancer Trials Utilizing Immunotherapy With FDA-approved Uses[10-12]

	Trial	Intervention/Treatment	Disease	Line of Therapy
1	KEYNOTE-164	Pembrolizumab	Recurrent or metastatic	≥1 prior therapy
2	KEYNOTE-177	Pembrolizumab	Recurrent or metastatic CRC	Front-line therapy
3	CHECKMATE-142	Nivolumab and nivolumab + ipilimumab	Recurrent or metastatic CRC	≥1 prior therapy

Abbreviations: CRC = colorectal cancer; FDA = United States Food and Drug Administration.

considered for patients with MSI-H colorectal cancer who are too frail or otherwise poor candidates for intensive therapy.[2]

Although immunotherapy has been extensively studied in colorectal cancer, its role to date is primarily in the metastatic setting. It is widely recognized that immune checkpoint inhibitors have increased activity in MSI-H or MMR-deficient tumors in both colorectal cancer other solid tumors.[8] The active and currently enrolling Adjuvant Trial of Deficient Mismatch Repair in Colon Cancer (ATOMIC trial) randomized patients with stage III colon cancer with dMMR tumors following surgery to standard chemotherapy alone or in combination with immunotherapy.[9] This study will help determine the role of immunotherapy in the nonmetastatic, adjuvant setting. Similarly, the role of immunotherapy in the first-line metastatic setting was unknown until recently when the results of the KEYNOTE-177 study were released, leading to the FDA approval of pembrolizumab for unresectable or metastatic MMR-deficient or MSI-H colorectal cancer.[7] However, what has not yet been thoroughly studied or established is the role of immunotherapy in the neoadjuvant setting in a patient with resectable disease who would otherwise be a chemotherapy candidate. The results of key published trials using immunotherapy in colorectal cancer are summarized in Table 1.

The first trial to examine neoadjuvant immunotherapy in colorectal cancer was the NICHE trial, with data presented at the 2018 ESMO conference. There were 19 patients originally enrolled in the phase II NICHE trial, all of whom had resectable, early-stage colon cancer; both MMR-deficient and MMR-proficient tumors were included. Patients were treated with ipilimumab at 1 mg/kg on day 1 and nivolumab at 3 mg/kg on days 1 and 15 with a maximum interval of 6 weeks between colonoscopy and surgery. The data presented at ESMO in 2018 included 14 of the initial 19 patients, with a breakdown including 7 MMR-deficient tumors and 8 MMR-proficient tumors (1 patient had 2 tumors, accounting for the discrepancy).[13]

A major pathologic response, defined as < 5% residual vital tumor, was observed in 100% of the MMR-deficient patients (7/7 tumors), 4 (57%) with a complete pathologic response. Conversely, there were no observed major pathologic responses in the MMR-proficient group. The authors proposed that primary tumors are more likely to have T-cell infiltration than metastatic tumors and may account for the improved response rates to immunotherapy seen in the neoadjuvant setting when compared to the metastatic setting.[14] More recently, Chalabi et al published an update in *Nature Medicine* that looked at 40 patients with nonmetastatic, resectable colorectal cancer — including 21 dMMR and 20 pMMR tumors — who were treated with neoadjuvant immunotherapy. A total of 35 patients were included in the final analysis, with a breakdown of 20 dMMR and 15 pMMR tumors. Again, patients with dMMR tumors had an excellent response, with a pathologic response observed in 20 of 20 tumors. In that subset, 12 of 20 tumors had a complete pathologic response, and 19 of 20 tumors had a major pathologic response, defined as 10% residual viable tumor. Interestingly and in contrast to the data presented in 2018, in patients with pMMR tumors, a pathologic response was noted in 4 of 15 patients. In those with a pathologic response, 3 had a major pathologic response, and 1 had a partial response.[14]

The NICHE trial authors cite mutational burden differences and subsequently a higher neoantigen burden in dMMR tumors in comparison with pMMR tumors as one explanation for why dMMR tumors respond better to immunotherapy than their pMMR counterparts. Owing to the higher antigen burden, it is theorized that dMMR tumors also have a higher number of intratumor T-cells, thereby making them more likely to respond to immunotherapy. This theory also applies when comparing primary versus metastatic tumors — specifically, primary tumors appear to have higher T-cell infiltration than their metastatic counterparts in both pMMR and dMMR tumor types. This is also seen in other cancers such as melanoma and lung cancer, whereby neoadjuvant treatment of nonmetastatic tumors with immunotherapy leads to deep, prolonged pathologic responses as well as higher response rates felt to be, at least in part, owing to increased T-cell infiltration when compared with metastatic tumors.[14]

Conclusion

In summary, our patient was successfully treated with 3 cycles of neoadjuvant ipilimumab and nivolumab without any adverse side effects, with an excellent radiographic response and a complete pathologic response. Our case clearly illustrates the benefit of neoadjuvant immunotherapy in the setting of MSI-H colorectal cancer with a resectable tumor, and further studies should be considered to evaluate the role of neoadjuvant therapy in MSI-H tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

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