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Brief Communications

Pathological Tumor Response Following Immune Checkpoint Blockade for Deficient Mismatch Repair Advanced Colorectal Cancer

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Abstract

Immune checkpoint inhibition (CPI) for metastatic colorectal cancer (mCRC) with deficient mismatch repair (dMMR) demonstrates high clinical activity that appears durable, but the impact of CPI on pathological tumor response is unknown. In this retrospective analysis, our objective was to assess pathological response and clinical outcomes in dMMR mCRC patients treated with CPI prior to surgical resection of primary and/or metastatic tumor. Among 121 advanced dMMR mCRC patients treated with CPI at 2 institutions between November 2016 and December 2018, 14 underwent surgery. Pathologic complete response was noted in the resected specimens of 13 patients despite the presence of residual tumor on preoperative imaging in 12 of those patients. With median follow-up of 9 months, no patients have had disease relapse or progression. For this small retrospective study, the data suggest that residual radiographic tumor may not require systematic resection following response to anti-PD1–based therapy. However, larger prospective studies are warranted.

The efficacy of checkpoint inhibition (CPI) for the treatment of metastatic colorectal cancer (mCRC) with microsatellite instability or deficient mismatch repair (dMMR) has been demonstrated (1-3); however, the pathological status of residual radiographic lesions after CPI has not been reported. To investigate the rates of complete pathologic response (pCR) in the metastatic setting, this retrospective study assessed the outcomes of patients who underwent surgical resection for mCRC after CPI.

One hundred twenty-one patients with initially unresectable stage III-IV CRC and dMMR by immunohistochemistry or microsatellite instability by polymerase chain reaction were treated with anti-PD1 with or without CTLA4 inhibitor at the University of Texas MD Anderson Cancer Center (Houston, TX, USA) or Saint-Antoine Hospital (Paris, France) between November 2016 and December 2018. Ethical approval was obtained from the institutional review board at MD Anderson Cancer Center. All patients at Saint-Antoine Hospital signed a written consent for the analysis of their tumor samples. Of the patients, 14 underwent surgical resection after immunotherapy (stage IV = 13; unresectable stage III = 1); 28.6% were female. Median age was 40 years (range = 30-70 years). The etiology for dMMR was confirmed as Lynch syndrome in 8 patients, sporadic in 3, and Lynch-like in 3. Histological grade included poorly (n = 4), moderately (n = 7), and well-differentiated (n = 3) primary tumors. Of the patients, 57.1% received 1 line of chemotherapy prior to CPI, and 35.7% received 2 or more lines. Of the 14 who underwent surgical resection, 6 were treated with nivolumab and ipilimumab, and 8 received single-agent pembrolizumab or nivolumab. Eleven surgeries were done with curative intent. Three surgeries were done for palliation of symptoms that developed while on treatment despite clinical response: 1 for rectal stump leak, 1 for colovesical fistula, and 1 for bowel obstruction. Clinical characteristics are summarized in Table 1.

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Table 1. Patient characteristics and clinical outcomes[a]

Patient number	Location of primary tumor in the colon	Stage of colon cancer	Age at diagnosis, y	Sex	Deficient mismatch repair protein (by IHC)	Etiology (Lynch or sporadic)	Immuno-therapy	No. of cycles before surgery	Surgery	Intent of surgery	Pathology postresection	Best overall radiographic response
1	Transverse	IV	33	M	MSH2	Lynch	Pembro	3	Right hemicolectomy	Curative	Near pCR	SD
2	Right	IV	48	F	MLH1/PMS2	Lynch	Pembro	4	Right hemicolectomy	Palliative	pCR	SD
3	Right	III	70	F	MLH1/PMS2	Sporadic	Nivo	8	Right hemicolectomy	Curative	pCR	SD
4	Left	IV	45	M	MSH2/MSH6	Lynch-like	Nivo	14	Rectal stump resection and hepatic metastasectomy	Curative and palliative	pCR	PR
5	Right	IV	30	M	MSH2/MSH6	Lynch	Nivo	56	Peritoneal metastasectomy	Curative	pCR	PR
6	Left	IV	55	M	MSH6	Lynch	Nivo + Ipi	27	Pelvic mass metastasectomy	Palliative	pCR	PR
7	Right	IV	67	F	MLH1	Sporadic	Pembro	35	Peritoneal metastasectomy	Curative	pCR	PR
8	Left	IV	45	F	MLH1	Lynch	Pembro	16	Hepatic metastasectomy	Curative	pCR	PR
9	Right	IV	38	M	MSH2	Lynch	Nivo + Ipi	54	Right hemicolectomy	Curative	pCR	CR
10	Right	IV	37	M	MSH2/MSH6	Lynch	Nivo + Ipi	24	Ileocolectomy and peritoneal metastasectomy	Curative	pCR	SD
11	Left	IV	37	M	MLH1/PMS2	Lynch	Nivo+ Ipil	12	Laparoscopic jejunostomy	Palliative	pCR	SD
12	Left	IV	39	M	MLH1	Lynch-like	Nivo + Ipi	24	Liver metastasectomy	Curative	pCR	PR
13	Right	IV	31	M	MLH1	Lynch-like	Pembro	15	Liver metastasectomy	Curative	pCR	PR
14	Left	IV	59	M	MSH2/MSH6	Sporadic	Nivo + Ipi	24	Sigmoidectomy	Curative	pCR	PR

[a]CR = complete response; F = female; IHC = immunohistochemistry; ipi = ipilimumab; M = male; nivo = nivolumab; pCR = pathologic complete response; PD = progressive disease; pembro = pembrolizumab; PR = partial response; SD = stable disease.

The median time from CPI introduction to surgery was 12 months (range = 2–28 months). Best overall radiographic response prior to surgery was complete response in 1, partial response in 8, and stable disease in 5 (Supplementary Figure 1, available online). Representative cases are shown in Figure 1. Of the patients, 13 achieved pCR, and 1 achieved near pCR despite the presence of residual lesions on preoperative imaging in 12 of those patients. Complete pathologic response was defined as the absence of residual cancer cells in the surgical specimen and near-complete pathological response as less than 5% cancer cells in the surgical specimen. The pCR postresection specimens consisted primarily of acellular mucin pools (n = 7), necrosis (n = 3), fibrosis (n = 1), or a combination of these. The median follow-up from surgery was 9 months (range = 3-32 months) with 6 patients being followed longer than 1 year. Median follow-up from initiation of CPI was 22 months (range = 14.5-40 months). No patients progressed or expired following surgical resection as of August 2019.

This retrospective analysis has demonstrated that high rates of pCR can be achieved with CPI in pretreated dMMR mCRC patients. Interestingly, despite the high rate of pCR, 13 of 14 patients had residual disease on imaging. The discordance between radiographical and histological findings could be due to immune cell infiltration into the tumor as has been observed in analyses of resected melanoma and non-small cell lung cancer tumors after neoadjuvant immunotherapy (4,5), or a combination of mucin and necrosis as we have primarily seen on the specimens in this study. This observation suggests that the decision to cease therapy in dMMR patients who have demonstrated clinical benefit from CPI should not be based on resolution of all radiographic disease. For example, in the study by Le et al. (3), 7 of the 18 patients with dMMR metastatic cancer treated with pembrolizumab had radiographically residual disease at the time of pembrolizumab cessation and remained progression free at a median follow-up of 7.6 months. These data highlight the important role CPI can play in enhancing the frequency of potentially curative surgery for stage IV tumors (6) and in general the curative potential of anti-PD1 ± anti-CTL4–based therapy in dMMR mCRC.

Attainment of pCR with neoadjuvant chemotherapies has been associated with improvement disease-free survival and overall survival in many early-stage cancers (7–9). In a clinical trial of 23 high-risk resectable melanoma treated with neoadjuvant CPI, a trend toward improved relapse-free survival and overall survival was demonstrated in those who achieved pCR compared with those who did not (7). Preliminary results from a phase II clinical trial evaluating nivolumab and ipilimumab in resectable dMMR CRC showed near pCR or pCR in all 7 treated patients (10). By extension, achievement of pCR in the metastatic setting may also be associated with better clinical outcomes.

It is unclear what is the optimal duration of preoperative CPI. The optimal duration of preoperative CPI is unclear. Median duration for this cohort of patients was 12 months, but complete pathological response was noted in 1 patient even after 3 months. The shortest duration—2 months—resulted in near pCR. Small neoadjuvant immunotherapy studies in melanoma, non-small cell lung, and urothelial cancers have given between 2 and 4 preoperative doses of immunotherapy with high rates of complete or major pathological response as high as 73%, 45%, and 42%, respectively (4,5,11). Larger prospective studies are needed to further investigate

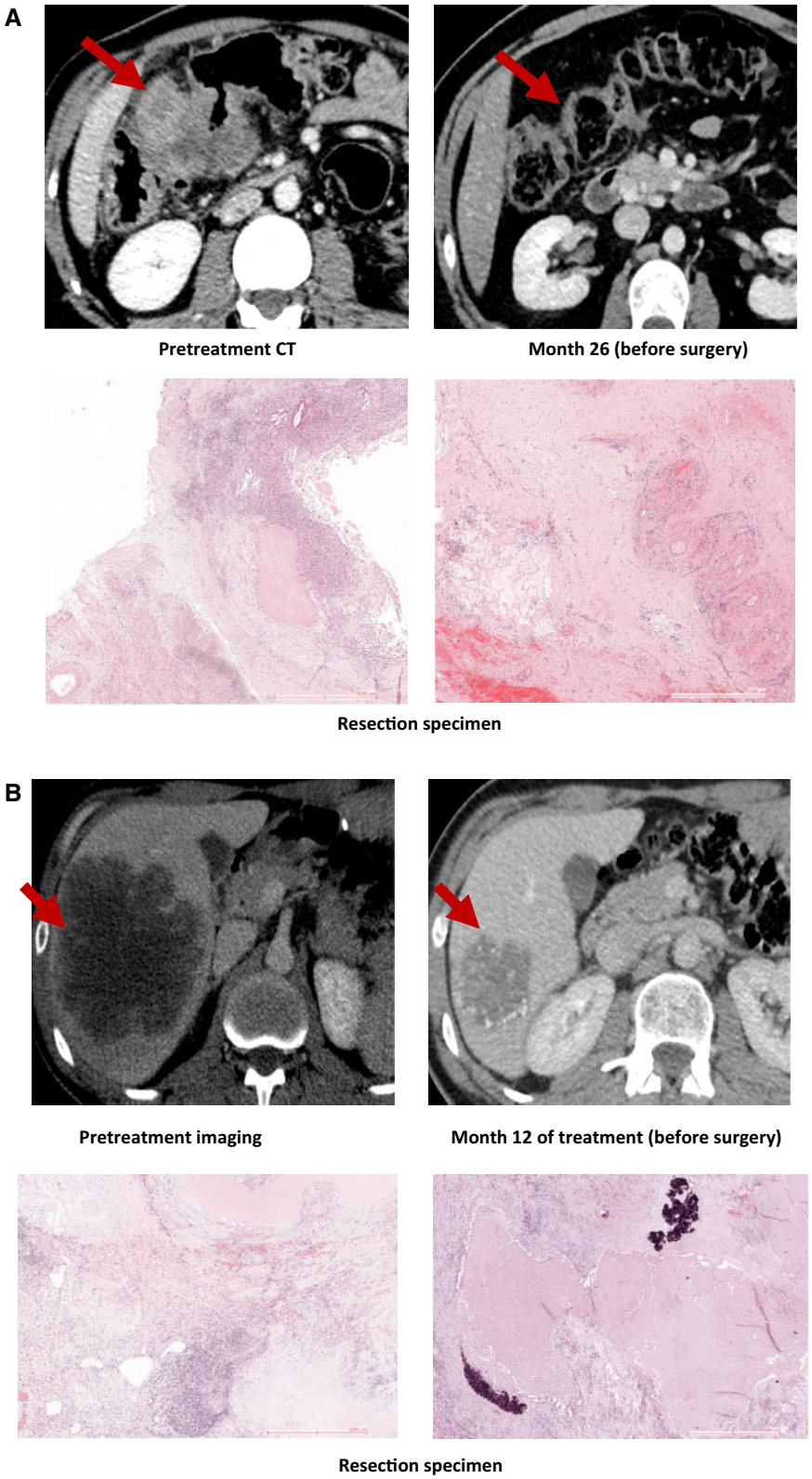

Figure 1. Patterns of radiologic and pathological response to preoperative nivolumab ± ipilimumab. **A)** The upper row shows computed tomographic (CT) imaging of the abdomen of patient 9 before and after nivolumab + ipilimumab. A scan performed before surgery shows complete radiographic resolution of colonic tumor (**arrow**) seen in the pretreatment scan. The lower row shows representative sections of tumor specimens obtained from patient 9's right hemicolectomy following 26 months of CPI. **Left:** In the stenosis zone, the muscularis propria bundles are interrupted by a fibroelastic tissue containing areas of eosinophilic necrosis, as well as a polymorph inflammatory infiltrate including cholesterol clefts surrounded by giant resorptive cells (x25 magnification). **Right:** The fibrous scar contained many vessels, sometimes with thrombosis. Acellular mucin was also visible. **B)** The upper row shows computed tomographic imaging of the abdomen of patient 12 before and after nivolumab + ipilimumab. A scan performed before surgery shows partial response of metastatic liver lesion seen in the pretreatment scan (**arrow**). The lower row shows representative sections of tumor specimens obtained from patient 12's liver metastasectomy done after 12 months of ICKi. **Left:** This mass consisted of large areas of necrosis, surrounded by foamy histiocyte nests, as well as giant resorptive cells, and fibro-hyaline fibrosis rich in inflammatory elements arranged in lymphoid nodules. Acellular mucin was also visible. No residual tumoral cell was observed (x25 magnification). **Right:** The necrosis, of infarct-like type, contained cholesterol clefts, as well as calcifications (x25 magnification).

optimal treatment duration, which may vary according to disease type (12) and volume of tumor.

The results of this study support the curative potential of CPI and suggest that residual radiographic tumor may not require resection following response to these inhibitors. The pCR rate observed in this population suggests that the need to perform certain high-risk surgical resections may be obviated. The pCR rate also has implications for the use of CPI in the neoadjuvant setting for dMMR CRCs and warrants further prospective study.

Limitations of this study include small sample size, which is the result of a limited number of patients going to surgical resection after receiving CPI for unresectable colon cancer. Additionally, this study is retrospective in nature and thus limited by the inherent biases in the selection of which patients underwent surgical resection. Further prospective studies are needed to validate the data generated by this analysis.

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