CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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The Role of CTLA-4 Inhibition in Immunotherapy for MSI-H/dMMR Metastatic Colorectal Cancer

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H&O When is immunotherapy used in microsatellite instability–high/mismatch repair–deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC)?

CW Immunotherapy is used for patients with mCRC whose tumors test positive for dMMR by immunohistochemistry staining or MSI-H biomarker polymerase chain reaction (PCR) testing. Knowing the MSI-H or dMMR status of any newly diagnosed CRC, regardless of stage, is crucial. A positive test result for MSI-H/dMMR not only affects treatment options but also necessitates screening for Lynch syndrome through genetic testing or further biomarker testing.

Immunotherapy was first used in patients with MSI-H/dMMR mCRC who had chemorefractory disease, and it is now used in patients with untreated disease. In the phase 2 study that led to the US Food and Drug Administration approval of the programmed death inhibitor (PD-1) pembrolizumab (Keytruda, Merck) for the treatment of refractory dMMR mCRC, 41 patients who had dMMR or mismatch repair–proficient (pMMR) mCRC received pembrolizumab.[1] The researchers found that the immune-related response rate was 40% in the patients with dMMR tumors and 0% in those with pMMR tumors, and that the immune-related progression-free survival (PFS) rate was 78% in the patients with dMMR tumors and 11% in the those with pMMR tumors. The most important studies in patients with untreated disease are CheckMate 142 and KEYNOTE-177.[2,3]

The phase 2 CheckMate 142 study led to the approval of nivolumab (Opdivo, Bristol Myers Squibb), another PD-1 inhibitor, with or without the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol Myers Squibb) in patients with MSI-H/dMMR mCRC that had progressed following treatment with chemotherapy. This study also included a cohort of patients who had received no prior treatment in the metastatic setting. In the cohort that received first-line therapy, the patients who received nivolumab plus low-dose ipilimumab had a response rate of 69% and a disease control rate of 84%, respectively, with a 13% complete response rate.

In the phase 2 KEYNOTE-177 study, a total of 307 patients with untreated MSI-H mCRC were randomly assigned to the PD-1 inhibitor pembrolizumab or chemotherapy. The study showed that the median PFS was longer in the pembrolizumab group than in the chemotherapy group, at 16.5 vs 8.2 months, respectively. In addition, pembrolizumab was better tolerated than chemotherapy, with fewer patients experiencing a grade 3 or higher adverse event. On the basis of this study, immunotherapy is now offered in the first-line setting for eligible patients with the MSI-H biomarker.

The ongoing phase 3 CheckMate-8HW study is examining the use of nivolumab/ipilimumab vs chemotherapy alone vs nivolumab alone in the first-line setting for mCRC.[4] In results that were presented at the 2024 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, PFS was significantly longer with

nivolumab/ipilimumab than with chemotherapy and was better tolerated. On the basis of all these results, we prefer to use immunotherapy rather than chemotherapy in the first-line setting.

H&O What is the preferred immunotherapy regimen at this point?

CW We do not have results from a head-to-head comparison of single-agent PD-1 inhibition vs a combination of PD-1 inhibition plus CTLA-4 inhibition, such as nivolumab vs nivolumab/ipilimumab. We are still awaiting results from the nivolumab/ipilimumab arm and the nivolumab-alone arm of the CheckMate-8HW study. In the absence of evidence that the doublet yields superior outcomes, we base our choice largely on toxicity concerns. Many clinicians will choose to use a single agent, such as pembrolizumab or nivolumab, because each of these agents has shown a good response rate, and a single agent may lead to fewer immune-related toxicities than combination therapy does. When a patient has a high tumor burden and is highly symptomatic, however, combination treatment with nivolumab/ipilimumab may be preferred to monotherapy in an effort to maximize the response. We hope to find that the addition of ipilimumab can improve the response rate and overall survival rate.

The results of the NICHE-2 study have also led to the question of whether combination immunotherapy might replace surgery in certain cases if the response is good enough.

H&O What is the status of immunotherapy in nonmetastatic CRC?

CW Given the excellent responses we have been seeing in the first-line metastatic setting, we are now considering how to advance this success to earlier-stage cancers.

A notable study from Memorial Sloan Kettering looked at dostarlimab (Jemperli, GSK) in patients with nonmetastatic rectal cancer.[5] This study is important because the treatment of localized rectal cancer typically involves chemotherapy and chemoradiation and often also involves surgery, which can lead to life-altering sequelae such as the need for a permanent ostomy bag. In the study, 12 patients with MSI-H rectal cancer received the PD-1 inhibitor dostarlimab for 6 months. All 12 patients had a complete response to treatment, negating the need for surgery and chemoradiation. This study is still ongoing, and we await the survival data.

Other ongoing studies are investigating the use of immunotherapy in locally advanced colon cancer. In the phase 2 NICHE-2 study, 115 patients with nonmetastatic locally advanced, previously untreated dMMR colon cancer were treated with neoadjuvant nivolumab plus ipilimumab.[6] All but 2 of the patients underwent timely surgery, supporting the safety of this immunotherapy combination. Among the 111 patients included in the efficacy analysis, 95% had a major pathologic response and 68% had a pathologic complete response. No patients discontinued treatment because of adverse events. Additional studies in the neoadjuvant setting include NEOPRISM-CRC and IMHOTEP,[7,8] both with pembrolizumab in MSI-H/dMMR CRC, and a study of dostarlimab in MSI-H/dMMR rectal cancer.[9]

In the adjuvant setting, the ongoing ATOMIC study is looking at the use of chemotherapy alone vs chemotherapy plus the PD-L1 inhibitor atezolizumab (Tecentriq, Genentech) in patients with stage III MSI-H colon cancer (NCT02912559).

H&O What questions remain to be answered?

CW One question is how long to administer immunotherapy. In the metastatic setting, some studies suggest 2 years if the patient responds well, but we wonder if that duration could be shortened to reduce immune-related toxicities.

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We also have unanswered questions about biomarkers that could help guide treatment duration and whether *BRAF* mutations affect responsiveness to immunotherapy, especially because not all patients with MSI-H disease respond equally well. The ongoing SEAMARK study is evaluating whether adding BRAF inhibitors to immunotherapy might help these patients.[10]

Disclosures

Dr Wu has served on the advisory boards of Seagen, Exelixis, Pfizer, Merck, and Natera.

References

1. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.

2. André T, Shiu KK, Kim TW, et al; KEYNOTE-177 Investigators. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218.

3. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. *J Clin Oncol*. 2022;40(2):161-170.

4. Andre T, Elez E, Van Cutsem E, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): first results of the CheckMate 8HW study [ASCO GI abstract LBA768]. *J Clin Oncol*. 2024;42(3)(suppl).

5. Cercek A, Sinopoli JC, Shia J, et al. Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer [ASCO abstract LBA3512]. *J Clin Oncol*. 2024;43(17)(suppl).

6. Chalabi M, Verschoor YL, Tan PB, et al. Neoadjuvant immunotherapy in locally advanced mismatch repair-deficient colon cancer. *N Engl J Med*. 2024;390(21):1949-1958.

7. Shiu KK, Jiang Y, Saunders M, et al. NEOPRISM-CRC: Neoadjuvant pembrolizumab stratified to tumour mutation burden for high risk stage 2 or stage 3 deficient-MMR/MSI-high colorectal cancer [ASCO abstract LBA3504]. *J Clin Oncol*. 2024;42(17)(suppl).

8. de la Fouchardiere C, Zaanan A, Cohen R, et al. IMHOTEP Phase II trial of neoadjuvant pembrolizumab in dMMR/MSI tumors: results of the colorectal cancer cohort [ESMO abstract 504O]. *Ann Oncol*. 2024;35(2)(suppl).

9. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med*. 2022;386(25):2363-2376.

10. Kopetz S, Bekaii-Saab TS, Yoshino T, et al. SEAMARK: randomized phase 2 study of pembrolizumab + encorafenib + cetuximab vs pembrolizumab alone for first-line treatment of BRAF V600E–mutant microsatellite instability–high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) [ASCO GI abstract TPS268]. *J Clin Oncol*. 2023;41(4)(suppl).