CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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The Emerging Role of Immunotherapy-Based Strategies in Nonmetastatic Colorectal Cancer

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H&O What makes immunotherapy an appealing option for patients with nonmetastatic colorectal cancer (CRC)?

MC Immunotherapy has become important because it is more effective than chemotherapy in many tumor types and is also much better tolerated than most chemotherapy regimens. That combination of greater effectiveness and less toxicity is like hitting the jackpot. When it comes to mismatch repair–deficient (dMMR) CRC, immunotherapy also has the benefit of shortening the duration of treatment. In the NICHE-2 study, we saw tremendous, deep, quick responses after just 2 cycles of immunotherapy in patients with dMMR colon cancer.[1]

H&O When should the MMR status be determined?

MC We should learn the MMR status of all patients with CRC. This is especially important when systemic therapy is being considered for patients, ideally before surgery, and is a must if patients are to receive neoadjuvant therapy. Such testing is still not done in every instance, but we should be doing it reflexively.

H&O Could you describe the research that led to the NICHE-2 study?

MC We knew that in metastatic CRC, patients responded to immunotherapy only if they had dMMR tumors. The response rate in these highly pretreated patients was approximately 35%, and no responses occurred in patients with MMR-proficient (pMMR) tumors.

On the basis of preclinical data and other data in CRC and melanoma, we hypothesized that earlier-stage tumors might be more likely to respond to immunotherapy. That was the impetus for the NICHE study, which enrolled more than 60 patients with nonmetastatic, resectable colon cancer, including 32 patients with dMMR tumors and 30 patients with pMMR tumors.[2,3] All patients received neoadjuvant treatment with a single dose of the anti–cytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab (Yervoy, Bristol Myers Squibb) at 1 mg/kg and 2 doses of the anti–programmed death 1 agent nivolumab (Opdivo, Bristol Myers Squibb) at 3 mg/kg. Patients with pMMR tumors were also randomized to receive neoadjuvant celecoxib. In the final clinical analysis of this study, the pathologic response rate was 100% in the patients with dMMR colon cancer and 30% in those with pMMR colon cancer.[3] In other words, there is a chance that patients with pMMR colon cancer will respond to just 2 cycles of neoadjuvant immunotherapy if they are treated before the disease becomes metastatic. Many of these tumors disappeared within 4 weeks of treatment. We wanted to validate the pathologic response data and know how treatment affected disease-free survival, which is why we launched the NICHE-2 trial.

H&O Could you describe the design of the NICHE-2 study?

MC The design of NICHE-2 was the same as that for NICHE, except that NICHE-2 enrolled more than 100 patients with dMMR tumors. We kept the dose of ipilimumab low because it causes much more toxicity at higher doses. We were especially concerned about the possibility of colitis because the patients would be undergoing bowel surgery within 6 weeks of study registration. After surgery, treatment was dictated by the pathology findings.

> The response rates to neoadjuvant immunotherapy are very high in patients with mismatch repair–deficient tumors.

H&O Could you describe the results of the NICHE-2 study?

MC In our most recent results, which were published in the *New England Journal of Medicine*, we reported on 111 evaluable patients from a total of 115 patients.[1] All but one of those 111 patients had a pathologic response, which was complete or near-complete in 95% of the cases. The exact tumor regression could not be determined in one other patient, for a pathologic response rate of 98%. In a near-complete pathologic response, no more than 10% of residual viable tumor is left. A pathologic complete response occurred in 68% of patients. These responses occurred within 5 1/2 weeks of the first immunotherapy treatment, so they represented very quick, very deep responses in almost all the patients. In the only patient without a pathologic response, 60% of the tumor was left. After a median follow-up of 26 months, we did not see any recurrences.

Although we do not have head-to-head comparisons between neoadjuvant immunotherapy and neoadjuvant chemotherapy in these patients, recently published trials—including the phase 3 FOxTROT study[4] and the OPTICAL study[5]—have shown a pathologic response rate of just 7% in patients with dMMR tumors after neoadjuvant therapy. The difference between a pathologic response rate of 98% and one of 7% is huge.

We are looking forward to presenting our 3-year disease-free survival data, which we hope to have ready in time for this year's European Society for Medical Oncology (ESMO) World Congress. The pathologic response rate is not a validated endpoint for CRC because neoadjuvant therapy is not yet standard for colon cancer. There are, however, indications from our study and from FOxTROT that pathologic responses (to chemotherapy, in the case of FOxTROT) are associated with survival. The 3-year disease-free survival rate is the most accepted surrogate endpoint for overall survival in CRC.

H&O Could you describe the adverse events that were seen in the NICHE-2 study?

MC We saw very limited grade 3 and 4 adverse events, which occurred in fewer than 5% of patients. Some of these were based on laboratory test results, were asymptomatic, and resolved without treatment. We did have 1 patient with grade 3 myositis and 1 patient with grade 2 myositis; these were the only patients in whom we delayed surgery beyond the predefined 6 weeks. Both patients who experienced myositis had their surgery.

Grade 1 and 2 adverse events included thyroid dysfunction, diarrhea, and colitis, all of which resolved after treatment ended. All these adverse events were less frequent in this study than in studies in which treatment lasted longer. We also saw the expected infusion reactions.

H&O Is there a role for circulating tumor DNA in assessing response to immunotherapy?

MC We are currently analyzing circulating tumor DNA for the entire study population, and we hope to be able to present those data along with the 3-year disease-free survival data. We have an established way of determining whether organ preservation is possible in rectal cancer. We traditionally have not considered organ preservation in colon cancer because we have not had a treatment that is sufficiently efficacious to make that possible, but organ preservation may become possible for patients with dMMR colon cancer. Circulating tumor DNA may be able to help us establish whether a patient has had a complete or near-complete pathologic response, and whether we can avoid or extend the time to surgery. It is very difficult to assess response before the surgery with our standard ways of assessing response.

H&O How would you characterize the current status of immunotherapy in nonmetastatic CRC?

MC The status in the United States is different from

the status in Europe. In the United States, the National Comprehensive Cancer Network guidelines advocate the use of neoadjuvant dual immunotherapy for patients with locally advanced/T4 dMMR colon cancer on the basis of results of the NICHE-2 trial. That is also the case for patients with dMMR rectal cancer, on the basis of research by Cercek and colleagues.[6] The US Food and Drug Administration has not approved this regimen for these uses, however, so that is a next step. In Europe, by contrast, neoadjuvant dual immunotherapy is not a standard of care for these patients. It does not have European Medicines Agency approval, and we are unable to use it outside clinical trials.

H&O What should be the role of chemotherapy in treatment regimens for nonmetastatic CRC?

MC We have seen immunotherapy replace chemotherapy as first-line treatment in metastatic dMMR CRC. According to the data we have so far on rectal cancer and colon cancer, immunotherapy is also a better option than chemotherapy for nonmetastatic dMMR disease. We still need to establish immunotherapy as a standard of care, however. I hope that the 3-year disease-free survival data from NICHE-2 will help us to do that. Additional data on immunotherapy as neoadjuvant and adjuvant therapy are also expected. The more data we have showing that immunotherapy is superior to chemotherapy, the more clearly we will be able to say that immunotherapy is the treatment of choice.

H&O Which patients with nonmetastatic CRC are eligible to avoid surgery?

MC This question is easy to answer for rectal cancer. According to research by Cercek and colleagues, patients with dMMR rectal cancer have a rate of clinical complete response to immunotherapy of 100%.[6] This can be confirmed with magnetic resonance imaging, a digital rectal examination, or endoscopy, so these patients have the option of avoiding surgery.

We do not have all the data we need regarding colon cancer; we still need to improve our methods of assessing response so that we know which patients can safely avoid surgery. Updated data from NICHE-2 and other studies should help us answer these questions. We are currently conducting a study in which we are giving patients with initially unresectable dMMR CRCs the option of undergoing surgery or continuing with immunotherapy (NCT05131919). We hope to have data from this study sometime in the next year.

On the other hand, a complete response does not automatically mean that organ preservation is possible. For example, a left-sided colon tumor might respond very well to immunotherapy but exhibit obstructive fibrosis. As a result, the decision must be tailored to the patient.

H&O What other ongoing studies are looking at the use of immunotherapy in nonmetastatic CRC?

MC As mentioned earlier, we are continuing to look at the effect of neoadjuvant immunotherapy on patients in the NICHE platform with pMMR tumors. We are continuing to follow patients in the NICHE-2 study, and we are also conducting the NICHE-3 study in patients with dMMR tumors.[7]

The phase 3 ATOMIC study is looking at adjuvant chemotherapy with or without atezolizumab (Tecentriq, Genentech) in patients with stage III dMMR colon cancer (NCT02912559).

The phase 2 NEOPRISM trial, which is being conducted in the United Kingdom, is looking at the use of neoadjuvant pembrolizumab (Keytruda, Merck) in patients with stage II or III dMMR CRC (NCT05197322). We just saw the first data from this study at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, in which pembrolizumab was highly efficacious and safe at a median follow-up of 6 months.[8] The extension of the phase 2 study of 6 months of dostarlimab (Jemperli, GSK) in stage II or III rectal cancer, by Cercek and colleagues, is also ongoing, and an update was presented at the 2024 ASCO Annual Meeting.[9] The regimens are very different in all of these studies. For example, in NICHE, patients receive just 2 cycles of neoadjuvant therapy and undergo surgery within 6 to 8 weeks. In the study of Cercek and colleagues, patients receive 6 months of treatment with the potential for no surgery. In the NEOPRISM study, patients receive 3 cycles of neoadjuvant treatment with pembrolizumab. These differences in treatment make it difficult to compare the pathologic responses. In addition, we need to coordinate the ways of assessing pathologic responses in the case of surgery. Despite these shortcomings, what we have seen so far is that the response rates to neoadjuvant immunotherapy are very high in patients with dMMR tumors.

H&O What questions remain to be answered?

MC One big question is whether we need dual checkpoint inhibition, as in the NICHE study, or whether we can use monotherapy, as in the study of Cercek and colleagues. If we used monotherapy for 2 cycles, would we see the same responses that we did with dual checkpoint inhibition? We have seen that in NEOPRISM, 3 cycles

of monotherapy led to pathologic complete responses in 59% of patients 3 to 4 months after the start of treatment, with a major pathologic response rate of approximately 72% and a nonresponse rate of 7%. We have not yet conducted a monotherapy cohort in the NICHE platform, but that might follow soon. Another question is whether we can achieve the same rate of clinical complete responses at 3 months of treatment that we see with 6 months because we know that immunotherapy keeps working after treatment stops.

An equally important question is whether adjuvant immunotherapy is as good as neoadjuvant immunotherapy, which we have seen is not the case in melanoma. The only study looking at this question is the ATOMIC study, which will not be able to answer this question because it includes chemotherapy. It will, however, be interesting to see how well chemotherapy plus immunotherapy works in comparison with chemotherapy alone.

Disclosures

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