CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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The Use of Immunotherapy in Metastatic Microsatellite-Stable Colorectal Cancer

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H&O What percentage of cases of metastatic colorectal cancer (CRC) fall into the microsatellite-stable (MSS) category?

CL Approximately 95% to 96% of patients with metastatic CRC fall into the MSS category. This percentage is slightly higher than the percentage in CRC as a whole, in which approximately 85% to 90% of patients fall into the MSS category. Unfortunately, immune checkpoint inhibition in CRC is indicated only in patients with microsatellite instability–high disease.

H&O What early strategies were used to try to get MSS CRC to respond to immunotherapy?

CL Numerous approaches were used that did not work, so we now know that single-agent immunotherapy and even combinations of immunotherapy are largely ineffective in MSS CRC. Combination treatments, such as chemotherapy plus immunotherapy and targeted therapy plus immunotherapy, also fail in most of these patients, although a small percentage of them do respond. Sometimes, the patients who respond to combination treatment even have durable responses, but they represent a very small portion of the pie.

The best-known example of a combination treatment that seemed highly promising at first in patients with metastatic MSS CRC was cobimetinib (Cotellic, Genentech) plus atezolizumab (Tecentriq, Genentech). An early phase 1 trial of this combination pointed to a signal of benefit. The phase 3 IMblaze 370 trial, however, did not show any improvement in overall survival with the combination.

H&O What more recent strategies have been attempted to make these cancers respond to immunotherapy?

CL LEAP-005 is an open-label phase 2 trial that is examining lenvatinib (Lenvima, Eisai) plus pembrolizumab (Keytruda, Merck) in patients with previously treated solid tumors. In results that Dr Carlos Gomez-Roca presented at the 2021 American Society of Clinical Oncology (ASCO) annual meeting, the overall response rate (ORR) among the 32 patients with CRC was 22%—a small but encouraging percentage. The study did not shed any light on how to identify the patients most likely to respond.

Also encouraging was the phase 1b REGONIVO trial from Japan, which examined regorafenib (Stivarga, Bayer HealthCare) plus nivolumab (Opdivo, Bristol Myers Squibb) in patients with advanced or metastatic tumors. Among 25 patients with CRC, the tumor response rate was 36% and progression-free survival was 7.9 months. Unfortunately, a similar phase 2 study of regorafenib plus nivolumab in a North American population, which Dr Marwan Fakih presented at the 2021 ASCO annual meeting, found an ORR of just 7% among 70 patients with MSS CRC. The ORR was notably higher among patients without liver metastases, however, at 22%.

More recently, Dr Fakih presented data from a phase 1 study of a novel combination immunotherapy regimen

at the 2022 European Society for Medical Oncology (ESMO) congress. For this study, researchers administered triplet therapy with regorafenib, ipilimumab (Yervoy, Bristol Myers Squibb), and nivolumab to 29 patients with chemotherapy-resistant, metastatic MSS CRC. After 20 months of follow-up, more than half of the 22 patients whose cancer had not yet spread to the liver were still alive. In contrast, median survival among the 7 patients whose disease had spread to the liver was just 7 months. Although this is a small study with limited follow-up, the results are encouraging, especially for patients who do not have liver metastases.

These findings confirm that patients who have CRC with liver metastases are especially difficult to treat. Sometimes, we will see a response to a treatment in patients with lung metastases, for example, but not in those with liver metastases. We believe that the liver creates an immunosuppressive tumor microenvironment, which makes it difficult for many treatments to work. If the T cells cannot be activated and recognize cancer in such an environment, treatment will not be effective. In addition, metastases to the lungs and lymph nodes tend to be less bulky than those to the liver. Some evidence suggests that the smaller a tumor is, the more likely it is to respond to immunotherapy.

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

CL We are still working to find the right combination of targeted therapy and immunotherapy. Here at the University of Colorado, we are recruiting patients for an ongoing phase 2 trial of cabozantinib (Cabometyx, Exelixis) and nivolumab in treatment-refractory metastatic MSS CRC (NCT04963283). The University of Colorado is also participating in an ongoing multi-institutional phase 2 study that is looking at cetuximab (Erbitux, Lilly) and pembrolizumab in combination with the anti-CD47 myeloid checkpoint inhibitor evorpacept, also known as ALX148, in treatment-refractory metastatic MSS CRC (NCT05167409). We are looking forward to the results of these studies to learn not only whether any patients are responding to the regimens but also, if so, which ones are responding.

One of the largest ongoing studies in metastatic CRC is SWOG 2107, which is specifically for patients with *BRAF* V600E–mutated disease (NCT05308446). This phase 2 multi-institutional study is looking at the addition of nivolumab to the targeted therapy regimen of encorafenib (Braftovi, Pfizer) and cetuximab, which has US Food and Drug Administration (FDA) approval for previously treated *BRAF* V600E–mutated metastatic CRC. This study is a good example of one that may determine whether immunotherapy can improve the performance of a targeted regimen.

Other upcoming studies are using chimeric antigen receptor (CAR) T-cell therapy in metastatic MSS CRC. Studies of CAR T-cell therapy in metastatic CRC have not shown good results to date, but future studies may produce better results.

H&O What should be the focus of future studies in metastatic MSS CRC?

CL We have a difficult road ahead, given how many studies have been negative. Can we learn more from these negative studies, however? Maybe we can go back and identify a specific subgroup of patients who can benefit from a certain approach. Just as we learned to use biomarker-directed therapy to chip away at very small populations with specific biomarkers, we hope to do the same with immunotherapy.

I would say we need to do 3 things. First, we need to go back and do basic research studies in the laboratory. Second, we need to be wary about over-extrapolating from small studies. Finally, we need to get smarter about choosing the population that will benefit from a certain approach.

Disclosures

Dr Lieu has received research funding from Merck and has served as an advisor to Natera.

Suggested Readings

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