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Invited Commentary | Oncology

Microsatellite Stable Colorectal Liver Metastases—Understanding the Mechanisms of Immune Resistance

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The use of immunotherapy in the form of immune checkpoint inhibitors (ICIs) has transformed the treatment of cancers that are presumed to be immunogenic and are commonly characterized by a high tumor mutation burden (TMB), which conceivably is associated with the expression of neoantigens on the surface of cancers cells as targets for cytotoxic T cells. High TMB can be associated with exogenous carcinogens, such as smoking (eg, non–small cell lung cancer) and ultraviolet light (eg, melanoma), but also with endogenous cellular factors, such as inherited or acquired deficiencies in DNA repair mechanisms, as in mismatch-repair deficient (dMMR), microsatellite instable (MSI-H) colorectal cancer (CRC). Although MSI-H dMMR CRC has long been known to respond well to ICIs in a later-line setting, the phase 3 KEYNOTE-177 trial[1] established single-agent treatment as a new standard of care in the first-line setting of these cancers by demonstrating superior progression-free survival and prolonged duration of response compared with chemotherapy. In addition, combinations of ICIs, such as nivolumab plus ipilimumab, have also shown remarkable activity in MSI-H dMMR CRC.

Unfortunately, approximately 95% of metastatic CRCs are classified as mismatch repair proficient (pMMR), microsatellite stable (MSS) and do not exhibit an immunogenic phenotype. Multiple strategies have been explored to make these cancers respond to immunotherapy by combining ICIs with various agents meant to augment an immune response to MSS pMMR CRCs. Some examples include the use of fluoropyrimidine alone or with bevacizumab as maintenance treatment after induction polychemotherapy in metastatic CRC, atezolizumab plus cobimetinib, or durvalumab and tremelimumab in previously treated advanced CRC.[2-4] These strategies disappointingly have not demonstrated convincing activity.

A promising immunotherapy approach in MSS, pMMR CRC seemed to emerge with the combination of a programmed cell death receptor 1 antibody with a multikinase inhibitor with anti–vascular endothelial growth factor activity in further studies. The REGONIVO (Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer) trial evaluated the treatment effect of regorafenib and nivolumab in patients with metastatic MSS CRC who experienced disease progression while receiving standard chemotherapy.[5] Specifically, patients with liver metastases had a lower response rate (8.3%) than those with lung metastases without any liver involvement (63.6%), suggesting a preferential response in patients without hepatic metastases.[5] Since the REGONIVO trial, additional data from the LEAP-005 (LEnvatinib And Pembrolizumab) study emerged,[6] which evaluated the efficacy and safety of lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors.[6] Within the CRC cohort, including 32 patients, the objective response rate was 22% with manageable toxic effects.[6] This cohort has been expanded to 100 patients, and it is still unknown whether this combination will show any clinical benefit in patients with liver metastases.

The study by Wang and colleagues[7] provides further evidence for the differential response to multikinase inhibitor plus ICI combination based on the location of metastases. Patients with lung and lymph node metastases were much more likely to respond than patients with liver metastases, a consistent phenomenon across clinical studies. Specifically, a significant difference in response rates was observed in patients without liver metastases (8 of 41 patients [9.5%]) compared with no response in those patients with liver metastases (0 of 54 patients).[7] The authors did not observe any

association between TMB and response rate. On multivariate analysis incorporating age, sex, primary tumor location, Eastern Cooperative Oncology Group status, metastatic site, variant status (*APC*, *RAS*, *BRAFV600E*, and *TP53*), and TMB, the presence of liver metastases at the time of treatment remained the most significant factor associated with worse progression-free survival (hazard ratio, 7.00; 95% CI, 3.18-15.42; $P < .001$).[7]

Discrepancies in response rates based on the site of metastatic lesions have been observed in various other tumors. For instance, in a previous study,[8] treatment with interleukin-2 (720 000 IU/kg intravenously) showed an overall response of 20% in patients with metastatic renal cell cancer or melanoma. Except for 1 patient with liver metastases who had a complete response, all other responders had lung or lymph node metastases.[8] Similar lower efficacy of checkpoint blockade has been found in patients with liver metastases from various primary tumors, including melanoma, non–small cell lung cancer, urothelial cancer, or renal cell cancer.[9]

Because liver metastases commonly represent the most clinically important site of disease in metastatic CRC, the development of active immunotherapy options in this setting is of utmost importance. It appears that the hepatic microenvironment is immunosuppressive for yet unknown biological reasons, which need to be elucidated. Because CRC liver metastases are routinely targeted for curative resection after neoadjuvant therapy, they provide a unique clinical model to identify pathways of immune resistance and explore the role of the tumor microenvironment and develop novel immune combination therapies. This strategy could finally expand treatment options for MSS, pMMR CRC into the world of immunotherapy.

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REFERENCES

1. 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. doi:10.1056/NEJMoa2017699

2. Manfredi S, Turpin A, Malka D, et al. Maintenance treatment with fluoropyrimidine plus bevacizumab versus fluoropyrimidine alone after induction chemotherapy for metastatic colorectal cancer: the BEVAMAINT-PRODIGE 71- (FFCD 1710) phase III study. *Dig Liver Dis*. 2020;52(10):1143-1147. doi:10.1016/j.dld.2020.06.034

3. Abdel-Misih SR, Bloomston M. Liver anatomy. *Surg Clin North Am*. 2010;90(4):643-653. doi:10.1016/j.suc.2010.04.017

4. Chen EX, Jonker DJ, Loree JM, et al. Effect of combined immune checkpoint inhibition vs best supportive care alone in patients with advanced colorectal cancer: the Canadian Cancer Trials Group CO.26 Study. *JAMA Oncol*. 2020;6(6):831-838. doi:10.1001/jamaoncol.2020.0910

5. Fukuoka S, Hara H, Takahashi N, et al. Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). *J Clin Oncol*. 2020;38(18):2053-2061. doi:10.1200/JCO.19.03296

6. Gomez-Roca C, Yanez E, IM SA, et al. LEAP-005: a phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—results from the colorectal cancer cohort. *J Clin Oncol*. 2021;39(3)(suppl):94. doi:10.1200/JCO.2021.39.3_suppl.94

7. Wang C, Sandhu J, Ouyang C, Ye J, Lee PP, Fakih M. Clinical response to immunotherapy targeting programmed cell death receptor 1/programmed cell death ligand 1 in patients with treatment-resistant microsatellite stable colorectal cancer with and without liver metastases. *JAMA Netw Open*. 2021;4(8):e2118416. doi:10.1001/jamanetworkopen.2021.18416

8. Rosenberg SA, Yang JC, Topalian SL, et al. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA*. 1994;271(12):907-913. doi:10.1001/jama.1994.03510360033032

9. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med*. 2021;27(1):152-164. doi:10.1038/s41591-020-1131-x