A liquid biopsy test can identify patients who may respond to immune checkpoint blockade

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A new liquid biopsy test could detect microsatellite instability (MSI) and tumor mutational burden (TMB), indicating that it could help determine which patients are likely to respond to immune checkpoint inhibitors, according to results published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

In May 2017, the U.S. Food and Drug Administration (FDA) approved the immune checkpoint inhibitor pembrolizumab (Keytruda) for patients with unresectable or metastatic tumors that tested high for MSI (MSI-H or MSI-high) or mismatch repair deficiency (dMMR). This marked the FDA's first "site-agnostic" drug approval.

However, detecting MSI-H and dMMR status is often challenging, explained the study's lead author, Andrew Georgiadis, MS, scientist at Personal Genome Diagnostics in Baltimore. Currently, MSI is detected using tissue m biopsies and technologies such as PCR-based amplification or next-generation sequencing. These processes are complicated and have sensitivity limitations, and certain tumor samples lack enough tissue for accurate testing, he added.

"A liquid biopsy test assessing MSI could reach a larger subset of patients, such as those where tissue is limited or where there are safety concerns around additional surgical intervention," Georgiadis said.

In this study, researchers sought to evaluate the sensitivity and specificity of a liquid biopsy approach developed by Personal Genome Diagnostics. They developed a 98 kb pan-cancer 58-gene panel, then employed a multifactorial error-correction method and a novel peak-finding algorithm to identify MSI frameshift alleles in cell-free DNA (cfDNA). The study was based on 61 patients with advanced cancer and 163 plasma samples from healthy individuals.

The authors explained that MSI can be detected by measuring the length of altered microsatellite sequences in tumor DNA as compared with normal DNA. In this study, the researchers flagged certain sequence data for error correction, then subjected the data to a peak-finding algorithm that identified instability in the loci. If 20 percent or more of the loci were determined to have MSI, the samples were classified as MSI-high.

For TMB, next-generation sequencing data were processed, and variants were identified using the VariantDx software. The researchers set five mutations in the targeted plasma panel as the threshold for identifying tumors as having exceptionally high mutational burden.

For MSI, the test produced a specificity of greater than 99 percent, and a sensitivity of 78 percent. For TMB, the test produced a specificity of greater than 99 percent, and a sensitivity of 67 percent.

The researchers also obtained plasma from 29 patients with metastatic cancers, including colorectal, ampullary, small intestine, endometrial, gastric, and thyroid. Among these, archival tissue-based analysis classified 23 cases as MSI-high and six cases as microsatellite stable. The VariantDx test detected high MSI in 18 of the 23 MSI-high patients (78.3 percent), and correctly identified the six microsatellite stable cases.

The researchers found that direct detection of MSI in baseline cfDNA was associated with progression-free survival of patients who were being treated with immune checkpoint blockade. Improvements in overall survival were not statistically significant.

"Our data also demonstrate that liquid biopsy analysis of MSI and TMB may be more predictive of immunotherapy response than archival tissue, given that it is both a real-time and global measurement and resolves the inherent sampling bias of tissue biopsy," Georgiadis said.

Fellow author Dung Le, MD, associate professor of oncology at the Sidney Kimmel Cancer Center at Johns Hopkins, said that if results of this study are further validated and the test becomes commercially available, more patients could benefit from immune checkpoint inhibitors.

"A majority of patients with advanced incurable cancers who have an

MSI-high tumor should be given the option to be treated with immunotherapy," she said. "If the tests become more accessible, less expensive, and require fewer resources such as tissue acquisition and pathology resources, more patients could be tested."

The authors noted that this study was limited to a small population of cancer patients. Further research, conducted across a broader range of tumor types, will be necessary to confirm the study results.

More information: Andrew Georgiadis et al. Noninvasive Detection of Microsatellite Instability and High Tumor Mutation Burden in Cancer Patients Treated with PD-1 Blockade, *Clinical Cancer Research* (2019). DOI: 10.1158/1078-0432.CCR-19-1372

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