血液検査は組織生検に対する非侵襲的な代替法である（Abstract LBA11501）

リキッドバイオプシーは進行固形がんの治療方針決定に役立つ可能性がある

Liquid biopsy may help guide treatment decisions for advanced solid tumors

進行がん患者15,000人超のリキッドバイオプシーの解析の結果、循環腫瘍DNAにおけるゲノム変異は、対応する腫瘍組織において認められるものとほぼ一致していることが示された。これらの結果から、患者の血液内に流出した腫瘍DNAの解析は、組織生検がジェノタイプ判定には不十分、または安全に施行できない場合、非常に有益で低侵襲の代替法となり得ることが示唆された。さらにこの検査は、臨床上の方針決定に重要となり得る、経時的に進展するがんの変化をモニターする機会となる。このスタディ結果は2016年American Society of Clinical Oncology年次集会で発表された。

Full Text

A large-scale genomic analysis finds that patterns of genetic changes detected in blood samples (liquid biopsy) closely mirror those identified in traditional tumor biopsy. With blood samples from more than 15,000 patients and 50 different tumor types, this is one of the largest cancer genomics studies ever conducted.

The study was presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting.

"These findings suggest that analysis of shed tumor DNA in patient blood, also known as a liquid biopsy, can be a highly informative, minimally-invasive alternative when a tissue biopsy is insufficient for genotyping or cannot be obtained safely," said study presenter Philip Mack, PhD, Professor and Director of Molecular Pharmacology at the University of California Davis Comprehensive Cancer Center. "Moreover, this test, known as Guardant360, provides an unparalleled opportunity to monitor changes in the cancer as it evolves over time, which can be critical when patients and physicians are discussing treatment options for continued tumor control."

Currently, doctors largely rely on tumor biopsies to assess whether tumors have certain genetic mutations that can be targeted by available cancer drugs. Tumor biopsy involves a surgical procedure, however, and patients are not always healthy enough to undergo it, and frequent repeated tests are not always feasible.

Tumor cells also shed small pieces of their genetic material or DNA into the bloodstream. This so-called circulating tumor DNA (ctDNA) can be collected from the blood and analyzed in the lab to help inform treatment decisions for individual patients, similar to tumor biopsy. According to the authors, this is the largest study to use ctDNA analysis to select the appropriate targeted treatments for individual patients.

This study included 15,191 patients with advanced lung cancer (37%), breast cancer (14%), colorectal cancer (10%), and other cancers (39%). Each patient provided one or more blood samples for analysis of ctDNA.

This study assessed the accuracy of liquid biopsies, as compared to tumor samples, in two ways. First, it compared the patterns of genomic changes in ctDNA to those found in 398 patients with available results of genetic testing of the tumor tissue. When ctDNA was positive for key abnormalities in *EGFR*, *BRAF*, *KRAS*, *ALK*, *RET*, and *ROS1* that drive tumor growth, the same mutations were reported in tissue 94-100% of the time. Most ctDNA alterations were found at very low levels. Half occurred at a frequency below 0.4% of the total DNA in circulation. The accuracy of the liquid biopsy assay remained high even at these low levels.

The authors also assessed consistency in the frequencies of specific changes in ctDNA against previously published data from genomic analyses of tumor tissue, including data from The Cancer Genome Atlas. The findings suggest that liquid biopsy provides an accurate snapshot of the genomic landscape of the tumor.

Across multiple cancer genes and different classes of alterations correlations typically ranged from 0.92-0.99. However, one general exception was found in which ctDNA findings were often not seen in tumor biopsies: detection of new genomic alterations associated with resistance to targeted cancer drugs, such as the EGFR T790M resistance mutations in patients on *EGFR* inhibitor therapy. The authors hypothesize that these alterations were absent in the tissue-based population data because those patients had yet to receive treatment.

Based on the genetic changes the blood test revealed, the researchers provided the study participants' physicians with lists of possible treatment options, including FDA-approved drugs and/or clinical trials. Overall, ctDNA testing revealed a possible treatment option for nearly two-thirds of patients tested (63.6%), which included FDA-approved drugs as well as eligibility for clinical trials.

Clinical utility was evident among lung cancer patients. In 362 lung cancer cases, tissue was insufficient for testing or partially tested in 63%. Among these cases, the ctDNA test identified key genetic mutations at frequencies consistent with their prevalence in the published literature, providing these patients with their only source of an actionable target.

A liquid biopsy can be used periodically to monitor disease progression, response to therapy, and development of treatment resistance. If a repeat test suggests that the cancer is getting worse or becoming resistant to treatment, doctors may be able to adjust the patient's treatment plan.

Periodic liquid biopsy, which requires a simple blood draw, may be preferable to repeat tissue biopsy in terms of patient safety and convenience. In addition, because genetic changes in ctDNA often occur before signs of tumor growth are apparent on a scan, liquid biopsy can help doctors adjust treatment sooner.
Liquid biopsy has another important advantage over tissue biopsy. The genetic changes that drive tumor growth often differ in different parts of the tumor. Because tissue biopsy removes only small pieces of the tumor, key mutations can be missed, depending on what area of the tumor is sampled. Analysis of ctDNA provides information on all the different genetic changes that may be present in the tumor.

Although ctDNA mutations were detected in 83% of the blood samples in this study, not all patients had sufficient ctDNA for the test. For example, the researchers found that the ability to detect ctDNA is lower for patients with glioblastoma, presumably because the blood-brain barrier makes it more difficult for ctDNA from a brain tumor to enter the circulation.

They are addressing this by increasing the sensitivity of the assay to detect mutations at extremely low levels of ctDNA, which will not only make the test more sensitive for all solid cancer types in advanced stages, but also in applying this technology to cancers in earlier stages.

"The fact that genomic mutations vary not only patient to patient but also change over time has been a constant challenge in cancer treatment, especially in the precision medicine era," said Sumanta Kumar Pal, MD, ASCO expert in developmental therapeutics. "Having a good, reliable option beyond a tumor biopsy could have a major impact on our ability to select the right therapy for the right patient."

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