Wider sampling of tumor tissues may guide drug choice, improve outcomes

November 15 2017

cfDNA analysis using a commercial assay from Guardant Health to explore the variations within each patient. Credit: Guardant Health

A new study focused on describing genetic variations within a primary tumor, differences between the primary and a metastatic branch of that tumor, and additional diversity found in tumor DNA in the blood stream

could help physicians make better treatment choices for patients with gastric and esophageal adenocarcinoma.

Many current approaches to genome-guided therapy, often referred to as "precision medicine," have produced imprecise results. This is particularly the case for gastric and esophageal adenocarcinoma (GEA), which are common cancers. They can be difficult to control and are often detected and diagnosed late. They frequently recur after surgery, and those recurrences are generally incurable. GEAs lead to more than 700,000 deaths a year globally.

"The extensive genetic variation of these cancers from patient to patient has recently become better understood," said the study's senior author, Daniel Catenacci, MD, assistant professor of medicine and associate director of gastrointestinal oncology at the University of Chicago. "Our study was designed to quantify the level of variation within each patient's cancer at baseline, prior to receiving any treatment."

"How a patient's cancer develops resistance to targeted therapies over time has been studied in a number of cancers, including GEA," said co-senior author Adam Bass, MD, a physician-scientist at the Dana-Farber Cancer Institute and an associate member of the Broad Institute's Cancer Program. "The unusual genetic instability of GEA tumors enables them to evolve and diversify even prior to receiving therapy. As a result, various regions of the cancer can have unique features, even within the same anatomical site."

"This poses a serious challenge to the current dogma of genetically testing one tumor site and trying to match it to a targeted therapy," Catenacci said. "Given the high discrepancy of genetic findings between a primary tumor and metastatic sites within the same patient, our study suggests we should concentrate on metastatic sites that represent the majority of the tumor burden. That's ultimately where problems arise in

our patients."

For this multi-institutional study—"Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma," published in the journal *Cancer Discovery*—Catenacci, Bass and colleagues explored the genetic differences between a primary tumor and its metastatic offspring. They evaluated four independent cohorts of patients with metastatic GEA.

- In the first cohort, researchers led by Jeeyun Lee, MD, from Sungkyunkwan University School of Medicine in Seoul, performed whole exome sequencing on samples from paired synchronous primary and metastatic tumors. Five of the 11 patients (45 percent) had "discrepant pathogenic alterations" in the metastasis that were not present in the primary tumor. An average of 42 percent of mutations and 63 percent of gene amplifications differed between primary and metastatic sites. This confirmed the growing sense that tumor profiling based on only the primary tumor could lead to suboptimal or mistargeted therapy.
- The second cohort, based at Dana-Farber Cancer Institute and the University of Pittsburgh, included 26 GEA patients. The researchers took multiple samples from primary tumors, regional lymph nodes and distant metastases. Again, they found "striking heterogeneity" within the primary tumors as well as significant differences between primary and metastatic tumors.
- In the third cohort—11 new patients from Dana-Farber—the researchers also evaluated cell-free DNA (cfDNA). These are small DNA fragments found circulating in blood. The use of cfDNA, which is much less invasive and costly than a biopsy, revealed the presence of several altered cancer-related genes. These were not always concordant with genomic aberrations found in the primary tumors. "The discrepancies we found when

comparing cfDNA results to primary tumor results suggested that other sites in the body possibly harbored different genetic makeup than the primary tumor, with potential clinically relevant implications on therapeutic decisions," Bass said.

- The fourth cohort—an ongoing trial known as PANGEA, Personalized ANtibodies for GastroEsophageal Adenocarcinoma designed by Catenacci and based at the University of Chicago Medicine—included 28 patients. One focus of this trial was genetic analysis of biopsies of both the primary tumor and metastatic tumors, plus cfDNA analysis using a commercial assay from Guardant Health. This analysis was designed to explore the variations within each patient. Basing treatment decisions on the metastatic lesions and the cfDNA, rather than the primary tumor, led to medication changes in 32 percent of cases (9 out of 28). The cfDNA results were 87.5 percent concordant with results from the metastatic lesions.

"To our knowledge," the authors wrote, "our study is the first to explore cfDNA systematically as a means to identify therapeutic targets not detectable from standard tissue-based testing in untreated metastatic disease." These treatment changes, the authors suspect, likely led to clinical benefit.

"In cancer, it's usually the metastases to the lung, liver or brain that kill the patient, but it's hard to get tissue safely from these areas," said Rick Lanman, MD, Guardant Health's chief medical officer. "This study shows that we can use ctDNA in the bloodstream to identify patients who acquire these targetable alterations in the metastases. A tissue biopsy of a primary GEA tumor does not always tell the whole story, while a simple blood test may provide a more complete representation of metastatic disease without requiring multiple, invasive biopsies."

One example is a patient named Guillermo, treated in cohort 4 in the

PANGEA study, for stage 4 stomach cancer that had spread to his bones and liver. The biopsy of his primary tumor pointed to treatment with anti-HER2 therapy (Herceptin), but tissue from the metastatic biopsy, as well as cfDNA analysis, was negative for HER2 and positive for anti-epidermal growth factor receptor (EGFR) therapy (ABT-806). So, they switched his treatment per study protocol. That made the difference. Guillermo, once headed for hospice, is alive and well almost two years since diagnosis, "which I consider incredible," said Catenacci.

"Even if we get it right initially by targeting the profile representing the bulk of the disease burden, we still face treatment resistance over time. So, we reconsider our drug choice up to three times in the trial," Catenacci said. "This strategy of 'keeping up with the tumor' may be better than matching drugs based solely on the primary tumor analysis and then, when this fails, proceeding blindly to the next therapy, as is the current approach."

"These results, from different cohorts obtained from a large collaborative effort of a number of medical centers and using various molecular profiling assays, all point to the common problem of baseline tumor genetic diversity within GEA patients as a contributing reason for the failure of several targeted therapy trials," Bass said.

The initial precision medicine strategy, based on biomarker assessment from primary tumors, "has had disappointing results to date in GEA," the authors conclude. Large clinical trials testing therapies in patients who test positive for the standard biomarkers have generally "all failed to improve outcomes."

"These provocative results challenge current guidelines and practice," the authors conclude. Current tissue sampling practices "do not effectively guide precision medicine in this disease. Routine profiling of metastatic lesions and/or cfDNA should be systematically evaluated."

More information: Eirini Pectasides et al, Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-17-0395