Analysis of blood samples could help monitor response of colorectal cancer patients to BRAF inhibitors

November 9 2015

For patients with colorectal cancer enrolled in a phase I clinical trial, response to the combination treatment being tested and disease progression were accurately tracked by quantifying levels of the BRAF V600E genetic mutation in circulating cell-free DNA obtained from patient blood samples, according to data presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Nov. 5–9.

"BRAF V600E mutations occur in less than 10 percent of patients with colorectal cancer, but these cancers do not respond well to monotherapy with the BRAF inhibitor vemurafenib," said Van Morris, MD, an assistant professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston. "The goal of this phase I clinical trial was to evaluate the combination of vemurafenib, cetuximab, and irinotecan in patients with BRAF-mutated metastatic colorectal cancer. As part of the trial, we analyzed circulating cell-free DNA in plasma obtained from blood samples collected from patients over the course of the trial to monitor dynamic changes in the frequency of BRAF V600E.

"BRAF V600E mutations were present in circulating cell-free DNA from all 12 patients in the study for whom serial plasma samples were available, and the direction of change in the ratio of BRAF V600E to BRAF wild-type [no BRAF mutation present] appeared to correlate with

whether or not a tumor responded to treatment," Morris continued. "Declines in the ratio preceded detection of a radiographic response and increases, following an initial response, were observed before a radiographic progression.

"These results generate optimism that circulating cell-free DNA can be used as a sensitive and specific marker to monitor response to treatment in patients with colorectal cancer who are treated on clinical trials, which would be less risky and more convenient to patients relative to analyzing traditional tumor biopsies," Morris added.

Morris and colleagues analyzed serial plasma samples from 12 patients using digital droplet PCR to quantify the ratio of BRAF V600E to BRAF wild-type. Samples were obtained prior to starting treatment and then every two weeks, including and following disease progression and/or coming off the clinic trial. The median number of samples per patient was 9.5.

Decreases in the ratio of BRAF V600E to BRAF wild-type were greatest in patients who had a partial response, as assessed by RECIST 1.1 criteria. The ratio decreased from baseline by a median of 98 percent for the six patients who had a partial response and by a median of 33 percent for the six patients with stable disease.

For all nine patients who had disease progression, the ratio of BRAF V600E to BRAF wild-type was increasing at the time of progression.

Morris explained that circulating cell-free DNA from pretreatment and postprogression plasma samples were also analyzed by next-generation sequencing to look for potential genetic alterations underlying disease progression, and that this revealed a number of interesting mutations that will inform future research into novel treatments for metastatic BRAF-mutant colorectal cancer.

According to Morris, the major limitation of the current study is that it involved only small numbers of patients. Therefore, additional studies incorporating larger numbers of patients are needed to validate these findings, he said.

Provided by American Association for Cancer Research