Study identifies genes that may help predict response to BRAF inhibitors for advanced melanoma

June 1 2011

Genetic analysis of the tumors from patients with advanced melanoma can clue researchers in to how well patients will respond to a therapy that targets the growth-promoting protein called BRAF, a researcher from the Perelman School of Medicine at the University of Pennsylvania will report on Monday, June 6 at the annual meeting of the American Society of Clinical Oncology. Looking outside of the BRAF gene, the researchers found loss of the tumor suppressor gene PTEN also appears to be associated with patient response to GSK436, which could help guide researchers to even more personalized approaches to melanoma therapy.

The phase I clinical trial data highlight the role that genetic changes other than that in BRAF may play in a patient's resistance to BRAF inhibitors, a targeted therapy that has shown unprecedented efficacy among patients with metastatic disease.

"These findings are important because they suggest that performing genetic characterization of melanomas for genetic changes outside of BRAF could help predict the patients that may have worse responses to BRAF inhibitors," says Katherine Nathanson, MD, an associate professor of Medical Genetics in Penn's Abramson Cancer Center, who led the study. Armed with such information, a physician could prescribe a different drug or combination of drugs to target these advanced cancers. Guiding such decisions early can save time in the race to control

metastatic melanomas, which commonly kill patients within a year after they're identified.

An estimated 40 to 60 percent of all melanomas carry a mutated BRAF gene. Although patients with advanced melanoma are often resistant to chemotherapy, drugs that go after the overactive BRAF protein – which acts as a foot on a gas pedal promoting tumor growth -- have demonstrated promising results in Phase I and II trials. Research shows that as many as 80 percent of patients who take these drugs experience a clinical benefit. However, despite signs of initial success, months into receiving the therapy, the tumors of many patients receiving the BRAF inhibitor return and begin growing again.

"There has been a lot of focus on what happens with tumors as they develop resistance to BRAF inhibitors," Nathanson says. "We asked a different question: Are there mutations that help predict response to inhibitors before the patients begin drug treatment?"

Through a collaboration with GlaxoSmithKline, Nathanson's group obtained tumors from patients enrolled in a phase I trial of BRAF inhibitor GSK436. To date, the researchers have performed genomic profiling on the melanomas of 32 patients prior to beginning treatment with GSK436. "This unique sample set allowed us to systematically look at additional predictors for response to BRAF inhibitors," Nathanson says.

Her team found that patients with clear loss of PTEN genetically have a shorter period of progression free survival (4.2 months) on GSK436, as compared to those with normal PTEN (7.4 months). However, the numbers of patients are small and larger cohorts will be needed to confirm this preliminary finding. Mutations in several other genes believed to play a role in cancer, including MEK2 and CDK4, were also identified in two patients; however additional data are needed to clarify

the predictive value of such mutations to BRAF inhibitors. Exploratory analysis also was done looking at the copy number of genes known to be important in melanoma. The presence of additional copies of CDKN2A, which is associated with tumor suppression, was significantly associated with an improvement in outcome.

"Because BRAF inhibitors will likely receive FDA approval soon, it's important to understand what additional factors will predict the patients who will be most helped by the drugs," Nathanson says. "Understanding what additional genetic changes are present in melanomas taken directly from patients paves the way for the development of combination therapies."

Nathanson will present these findings in the BRAF: From Biology to Patients Clinical Science Symposium on Monday June 6 from 1:15 PM to 2:45 PM CST in McCormick Place E354b.

Provided by University of Pennsylvania School of Medicine