Researchers narrow the search for biomarkers of drug resistance in head and neck cancer patients

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Researchers from Fox Chase Cancer Center will present data at the 49th Annual Meeting of the American Society of Clinical Oncology on Saturday, June 1, which shows the discovery of potential biomarkers that may be used to identify patients with head and neck cancer whose tumors are unlikely to respond to treatment by the targeted therapy cetuximab—a type of monoclonal antibody. The FDA approved the drug, in combination with radiation or as a second-line drug after chemotherapy had failed, in 2006. In 2011, the drug was approved as a first-line treatment for metastatic disease, in combination with chemotherapy.

"Targeted therapies should optimally be used in patients who are selected for sensitivity or the absence of sensitivity, and we've been handicapped by not knowing the resistance in head and neck cancers," says Barbara Burtness, MD, chief of head and neck medical oncology at Fox Chase and chair of the Eastern Cooperative Oncology Group (ECOG), a National Cancer Institute-funded team of researchers who organize and carry out clinical trials.

Before cetuximab, head and neck cancer patients' only options were conventional platinum-based chemotherapy and radiation, says Burtness. But since tumors in different people may have different biologies, not all patients respond to same treatment in the same ways. Those whose tumors do not respond to cetuximab suffer the drug's side effects

without gaining benefits. Biomarkers can help providers match appropriate treatments to disease. They may also provide inroads toward re-sensitizing tumors to treatment by cetuximab.

She and researchers from the ECOG head and neck committee have been studying the biology of cetuximab-resistant and non-resistant tumors in search of telltale molecular signatures, or biomarkers, that might indicate if a disease will respond to the drug. The researchers have zeroed in on two potential biomarkers.

Cetuximab targets the epidermal growth factor receptor (EGFR) in a cancerous cell. When EGFR is activated, it sends signals through the cell using several pathways. Burtness and her team suspected that abnormalities in one of those pathways may be connected to cetuximab resistance. Their search for related molecules led them to a protein called PTEN and a gene called PIK3CA. They hypothesized that cells which either don't express PTEN or have a mutation in the PIK3CA gene are more likely to be unresponsive to cetuximab.

To test the biomarkers, they used tumor samples from a small phase III randomized trial that compared chemotherapy with cetuximab to chemotherapy alone for patients with head and neck cancer. That study showed that cetuximab improved responses in patients with metastatic/recurrent head and neck cancer who were receiving chemotherapy. A subsequent larger European study called EXTREME, showed that cetuximab conferred a significant survival benefit to these patients. Those studies did not identify which patients were most likely to respond to the drug.

Burtness first used tumor samples from Fox Chase Cancer Center to develop tools designed to show if a test sample had the mutation or lacked PTEN. Then, she and her collaborators analyzed 67 samples for PTEN and found 23 (34 percent) did not express the protein. The

researchers studied the PIK3CA gene in 52 separate samples and found mutations in two samples (four percent). When the researchers grouped together samples that either did not express PTEN or had the PIK3CA mutation, they did not identify a significant difference in overall survival or progression-free survival, compared to the rest of the sample population.

However, the analyses suggest that for patients who expressed PTEN and lacked the PIK3CA mutation, cetuximab increased progression-free survival and overall survival each by more than a month, compared to patients lacking PTEN or with the mutation.

Burtness says these results are promising, but they're still early. "It's a small sample, and clearly more work needs to be done on larger sample sets," she says. "But we do think that this combination biomarker—the signature of PTEN loss and/or PIK3CA mutation—might point the way to those patients who are resistant to cetuximab."

A critical biomarker may also help researchers better understand the biology of tumors that don't respond to treatment with the drug. That knowledge could point to the use of other treatments, either new or existing, to re-sensitize a tumor to cetuximab.

"If you find a molecule that can be targeted that seems to produce resistance, it would make sense to look at cetuximab in combination with something that turns off the abnormality in the chemical pathway," says Burtness.

Provided by Fox Chase Cancer Center