Biomarker may predict who'll benefit from targeted therapy for HER2-negative breast cancer

17 September 2015

A multicenter team led by Case Western Reserve has demonstrated that brief exposure to a targeted therapy can tell doctors which HER2-negative patients will respond—and which should switch to another kind of treatment.

If confirmed in clinical trials, the discovery would provide physicians invaluable information regarding the effectiveness of bevacizumab, known commercially as Avastin. Such early results would spare patients weeks of the medication's sometimes severe side effects, and also allow them to pursue options with greater chances for success. The findings appear in this month's *International Journal of Cancer*.

"What all this means is that we have identified a signature that tells us which patients are likely to respond to bevacizumab and chemotherapy," said Principal Investigator and senior author Lyndsay Harris, MD, Professor of Medicine at Case Western Reserve, "and we can identify those patients within 15 days of the very first dose they receive."

The research is another compelling example of the concept of "personalized medicine." Given that few medications are equally effective in all patients, scientists now are seeking ways to determine which medication works best with whom—and which bring no or even negative results. In this instance, Harris and a team of scientists and physicians from Case Western Reserve University, Brown University, Yale University, and Philips Research North America came together to determine whether a way could be found to tell early whether bevacizumab might work—or whether the medication's significant toxicity would cause much harm without commensurate success in stemming breast cancer.

Bevacizumab emerged in the early 2000s as a therapeutic agent known for inhibiting blood vessel formation that nourishes tumors. Based on early reports of improved efficacy of this agent in advanced disease, the Food and Drug Administration approved bevacizumab in February 2008 for use in metastatic HER2-negative breast cancers. However, longer term follow up in clinical trials did not show improvements in overall survival as compared to other chemotherapy drugs, and thus the FDA retracted approval of bevacizumab for breast cancer in 2011.

Despite this setback, ongoing experience with bevacizumab revealed that some breast cancer patients achieved significant survival benefit from bevacizumab even if others did not. What the researchers needed were biomarkers that could show which patients would benefit most from bevacizumab to justify the toxicity in those patients and avoid it in those who would not benefit from the drug.

Previous studies revealed no predictable biomarkers for HER2-negative breast cancer chemotherapy, so Harris, also Director of the Breast Cancer Program, University Hospitals Seidman Cancer Center, led fellow researchers in a study of the molecular responses within these breast tumors after an initial dose of bevacizumab.

Researchers assessed tumor tissue from HER2-negative breast cancer patients at baseline before therapy began. Then patients received a single dose of bevacizumab to "perturb" the tumor. Ten to 14 days later, tumor tissue was collected again to examine what molecular changes occurred with bevacizumab treatment. What investigators found was a decrease in TGF-beta signaling activity, a process that affects cell proliferation, occurs exclusively in tumors that achieve a

complete response—that is no tumor left at surgery. This finding is associated with a more than 90 percent cure rate for that patient and is likely due to decreases in hypoxia, a state of low oxygen, in the tumor cells that makes them more sensitive to treatment.

Furthermore, this decrease in TGF-beta activity in responders was only seen when tumors were perturbed by bevacizumab and not observed by other targeted therapies, making this a specific biomarker signature for HER2-negative breast cancer treated with bevacizumab.

"The novelty of the study is that for the first time, we show an advantage for a brief-exposure framework to identify molecular and pathologic biomarkers that provide an early readout of the way a HER2-negative tumor responds to a targeted therapeutic agent," said lead author Vinay Varadan, PhD, Assistant Professor of General Medicine and a member of the, Case Comprehensive Cancer Center. "We are among the first groups in the world to show that this approach, which perturbs the tumor with one dose of therapy, allows us to see the changes induced by the therapy that predict how the tumor will respond to the remaining cycles of chemotherapy."

Even though bevacizumab is not currently used to treat breast cancer in the United States, the drug is widely used for that purpose in Europe. The potential may be there for bevacizumab making a comeback in the United States, but more importantly, the drug is used for treating other cancers, such as colon cancer. The brief-exposure framework used in this study could work to identify biomarkers for bevacizumab in other cancers—or other chemotherapy agents for that matter—to determine their effectiveness in cancer treatment for individual patients.

"Our finding is not so much about the single drug," Harris said. "What matters most is we can identify biomarkers to help us select therapy properly. In our study, we have found this signature to be specifically useful in response to bevacizumab, but it may be useful in predicting response to other anti-angiogenic agents as well and should be tested."

Provided by Case Western Reserve University