

Gene profiling predicts resistance to breast cancer drug Herceptin

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Using gene chips to profile tumors before treatment, researchers at Harvard and Yale Universities found markers that identified breast cancer subtypes resistant to Herceptin, the primary treatment for HER2-positive breast cancer. They say this advance could help further refine therapy for the 25 to 30 percent of breast cancer patients with this class of tumor.

In the February 15 issue of *Clinical Cancer Research*, the researchers found that HER2-positive tumors that did not respond to Herceptin expressed certain basal markers, growth factors and growth factor receptors. One of these, insulin-growth factor receptor 1 (IGF-1R), was associated with a Herceptin response rate that was half that of tumors that did not express IGF-1R.

They also discovered that resistant tumors continue to over-express the HER2 growth factor protein -- an important finding given that many scientists had thought that loss of HER2 was likely responsible for Herceptin resistance.

"Herceptin has revolutionized the care of HER2-positive breast cancer for many patients, but unfortunately, not for some. This work demonstrates that digging deeper into the molecular subtypes of these tumors helps us understand why some tumors are resistant and may point to ways to remedy that," said the study's lead author, Lyndsay Harris, M.D., associate professor and Director of the Breast Cancer Disease Unit at Yale University Medical Center.

If additional studies validate these findings, it may be possible to select those patients that will be resistant to Herceptin and treat them with additional drugs to restore Herceptin sensitivity, according to Harris. "Our goal is to see what the tumor tells us before any treatment starts and tailor therapy accordingly," she said.

To determine Herceptin sensitivity, investigators took a small tumor biopsy from 48 patients with newly diagnosed and operable stage II/III breast cancer. They examined the biopsy tissue using both single and multi-gene microarrays, looking for RNA that has been activated to produce proteins.

They then treated the women with a combination of Herceptin and the chemotherapy drug Navelbine weekly for 12 weeks. Although this is not the first study to test Herceptin use before surgery, it is the first to examine the use of Navelbine, a drug approved for lung cancer treatment, in combination with Herceptin to treat HER2-positive tumors. "We were motivated to use Navelbine because we found it has few side effects when used to treat metastatic breast cancer," said Harris, who conducted much of the research study at Harvard before moving to Yale.

After treatment, the tumors were surgically removed and gene chips were again used to examine RNA transcription -- making these investigators the first to use such a technique on Herceptin treated tumors. "This kind of profiling has been done to look at response to chemotherapy drugs, but not at Herceptin resistance," Harris said.

The researchers then divided tumors into groups depending on how well they responded to therapy, and examined the baseline and post-therapy RNA profiles to find genes that were more commonly expressed in Herceptin sensitive and Herceptin resistant tumors.

They first found that some single gene markers, such as HER2 and ER

(estrogen receptor), did not change in the majority of tumors. "That tells us that the cancer cells are still creating HER2 surface proteins even as Herceptin is being used, and that means HER2 loss does not appear to be a mechanism of resistance in early stage breast cancer," Harris said.

Then, using multigene chips, the researchers derived a bevy of transcribed genes that likely play a role in Herceptin resistance. Some, such as IGF-1R, were suspected, because this protein is frequently over-expressed in breast tumors, Harris says, but others were not. For example, non-responding tumors were more likely to express genes associated with basal-like breast cancer, which the researchers found to be surprising. "Most basal-like tumors are HER2-negative," Harris said.

Herceptin resistant tumors were also more likely to express a variety of growth factors, suggesting that "activation of parallel pathways may release tumors from dependence on HER2 proliferation and survival," she said.

Although the study was not designed to look at outcome, the researchers determined that 42 of 48 patients had a clinical response (16 complete responses and 26 partial responses) from the neoadjuvant treatment, and five patients experienced cardiotoxicity. After a median 2.6-year-follow-up, three of 48 patients relapsed and one died of her disease.

Source: American Association for Cancer Research

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