New research challenges notion of using Herceptin only for HER2-positive breast cancer

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This image shows Max S. Wicha, M.D., University of Michigan Comprehensive Cancer Center. Credit: University of Michigan Comprehensive Cancer Center

New research from the University of Michigan Comprehensive Cancer Center finds that the protein HER2 plays a role even in breast cancers that would traditionally be categorized as HER2-negative – and that the drug Herceptin, which targets HER2, may have an even greater role for treating breast cancer and preventing its spread.

About 20 percent of women with breast cancer have tumors labeled HER2-positive. And since the drug Herceptin has come on the scene, it has had a tremendous impact on survival for these women, particularly when it is given in the adjuvant setting, after surgery to remove the primary cancer. The new findings have potential implications for an additional 65 percent of women with breast cancer.

A recent study based on new analyses of old data found some tumors were incorrectly categorized as HER2-positive and as a result those women received adjuvant Herceptin. It turns out, they benefited as much from the treatment as woman with actual HER2-positive cancer.

"We now provide a molecular explanation for the surprising finding that adjuvant Herceptin benefited some women with HER2-negative breast cancer. If this is confirmed in clinical trials, it could alter our approach to breast cancer treatment," says study author Max S. Wicha, M.D., distinguished professor of oncology and director of the U-M Comprehensive Cancer Center.

At this point, patients with HER2-negative breast cancer are not advised to take Herceptin.

The explanation is that HER2 is selectively expressed in the cancer stem cells of many HER2-negative breast tumors. Because the stem cells represent such a small number of cells in a tumor, the amount of HER2 is not high enough to meet the threshold for a HER2-positive cancer.

The researchers had previously shown HER2 plays an important role in cancer stem cells – the small number of cells in a tumor that fuel its growth and spread. These cells represent 1 percent to 5 percent of all the cells in a tumor. They are resistant to current chemotherapy and radiation treatments – but since they express HER2, they are effectively targeted by Herceptin.

Further, the researchers in this new study found that for tumors classified as HER2-negative, HER2 levels were higher in bone metastases compared to the primary breast tumor. Bone is the most frequent site to which breast cancer spreads.

The researchers administered Herceptin to mice with these bone lesions and found that it was most effective when given early, when tumors were small

or mere "micrometastases." In these cases, Herceptin almost completely blocked the tumors from growing. When the drug was given later, after tumors were established, it had little effect.

"We have shown that the bone microenvironment induces HER2 expression in these tumors. If Herceptin can target bone micrometastases, then administering it to patients before metastases develop could help reduce tumor recurrence," says study author Hasan Korkaya, Ph.D., research assistant professor of internal medicine at the U-M Medical School.

The implications of this finding are that we need cancer treatments that target the small number of cancer stem cells in addition to traditional chemotherapies that eliminate the bulk tumor cells. This means that merely looking at whether a tumor shrinks is not good enough to determine whether the treatment will have long term benefit.

"This work has very significant implications for how we have developed adjuvant therapies. The idea of using drugs that cause tumors to shrink, which has been the accepted paradigm for developing therapies, is flawed. Our work suggests that adjuvant therapies will need to target the cancer stem cell population. Eliminating cancer stem cells by effective adjuvant therapies should prevent tumor recurrence, ultimately resulting in more cures," Wicha says.

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