Trastuzumab May Have Role in HER2-Negative Breast Cancer Treatment

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A new study from cancer stem cell experts at the University of Michigan is challenging the notion that trastuzumab (Drug information on trastuzumab) (Herceptin) only works for HER2-positive breast cancer. Max S. Wicha, MD, professor of oncology and director of the University of Michigan Comprehensive Cancer Center and colleagues show a potentially wider role for the targeted therapy in preventing the spread of breast cancer. Breast cancer stem cells, the research shows, make up only a small minority of cells within a breast tumor but play an important role in driving tumor growth and evolution. These rare cells, Wicha and colleagues find, overexpress HER2 even in breast cancers that are not classified as HER2-positive.

“Our work shows that the HER2 protein is selectively expressed in and regulates the cancer stem cell population in tumors that are classified as HER2-negative, without an amplification of the HER2 gene,” said Wicha. “These [cancer stem] cells generally constitute only 1% to 5% of the total tumor cells and so if one looks at the entire tumor it appears to have low HER2 expression.”

Approximately 20% of women are diagnosed with tumors deemed HER2-positive, those that have an amplification of the HER2 gene. HER2-positive tumors are a relatively aggressive form of breast cancer, but since its first approval in 1998, trastuzumab has improved the survival for these patients. The drug is most frequently used in the adjuvant setting after surgical removal of the tumor.

The current findings, published in Cancer Research, suggest that an additional 65% of breast cancer patients may benefit from trastuzumab treatment. The study aimed to provide a biological explanation for a previously reported analysis of clinical data that controversially suggested women with HER2-negative breast cancer benefited from adjuvant trastuzumab therapy, explained Wicha. This study was contrary to previous clinical trial results which showed only breast cancer patients with amplification of the HER2 gene benefit from anti-HER2 therapy in addition to chemotherapy.

To address the controversial result, the current study used breast cancer cell lines, mouse xenograft models, as well as matched primary and metastatic tissue from patients to show that HER2 is selectively expressed in the cancer stem cell population in estrogen-receptor (ER) positive, HER2-negative luminal breast cancers. HER2 expression was found to increase in the luminal tumors in mouse bone xenograft models and in the bone metastases of breast cancer patients, but not in the primary tumor sample counterparts.
Rather than *HER2* amplification, the mechanism of increased protein levels of HER2 was a result of activation of the NF-κB (RANK)-ligand in the bone microenvironment. “We demonstrate that the HER2 expression in breast cancer stem cells is regulated by the microenvironment at metastatic sites such as the bone,” said Wicha. Treating the mouse models with trastuzumab in the adjuvant setting resulted in inhibition of growth of these HER2-negative breast cancers in the bone.

“These results may provide a biological explanation for the clinical trial results suggesting that the clinical benefits of adjuvant trastuzumab may extend to some patients whose breast cancers are classified as HER2-negative and currently don't receive trastuzumab,” said Wicha.

These new findings highlight the potential importance of the so-called cancer stem cell population when classifying a tumor based on a genetic aberration, which may have different networks of pathways that regulate their growth compared to bulk tumor cells. The results also point to the need for a potential reconsideration of how targeted therapies are developed and tested. “HER2 targeting agents may provide a model for this,” said Wicha whose cancer center is currently developing cancer stem cell–directed therapies.

**Trial Addresses Role of Trastuzumab in HER2-Negative Breast Cancer**

The current study suggests that trastuzumab may be a way to treat micrometastasis in these patients before full metastasis develops. A large, randomized phase III clinical trial, NSABP B47, is currently testing whether women with low HER2 expression can benefit from the combination adjuvant treatment of chemotherapy plus trastuzumab. The trial is currently accruing patients. “The development of this trial was controversial since some oncologists questioned the wisdom of giving trastuzumab to women whose breast cancer did not express HER2,” said Wicha. Whether HER2-negative/ER-positive luminal breast cancer patients could indeed benefit from trastuzumab therapy remains to be seen and will be partly determined by the ongoing trial. In the meantime, patients who are HER2-negative should not be given trastuzumab outside of a clinical trial.

This research suggests that the mechanism of tumor progression from micrometastasis to full metastatic tumors may be different from the growth of advanced, metastatic tumors. The shift from micro- to full metastatic growth may be mediated by cancer stem cells, although many more studies are needed to both characterize cancer stem cells and understand the shift from micrometastatic to full metastatic growth in breast as well as other tumor types.