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Single dose of trastuzumab kick starts immune response in certain breast cancers

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A tumor's immune response to a single dose of the HER2 inhibitor trastuzumab predicted which patients with HER2-positive breast cancer would respond to the drug on a more long-term basis, according to the results of a study published recently in *Clinical Cancer Research*.

In addition, Vinay Varadan, PhD, assistant professor at Case Western Reserve University School of Medicine and member of the Case Comprehensive Cancer Center, and his colleagues found that women with the HER2-enriched subtype of HER2-positive breast cancer—a subtype that is estrogen and progesterone receptor negative—had the highest rate of immune response to treatment with trastuzumab, with significant increases in immune response after a single dose of the drug.

"Our study showed, for the first time, that the immune-cell-activating properties of trastuzumab are likely related to the subtypes of breast cancer," Varadan said. "Knowing this can inform future trials studying the usefulness of adding immunotherapy drugs to trastuzumab."

Only one-half of women with HER2-positive breast cancer treated with trastuzumab will have their tumor completely respond to therapy prior to undergoing surgery to remove the mass. Even when a second HER2-targeting drug, such as pertuzumab, is combined with trastuzumab, only 60% of women have a complete response. Therefore, there is a need to find ways to identify women who are the most likely to respond to this presurgical treatment.

Prior research showed that a patient's own immune system can play a role in determining whether the tumor will respond to therapy with trastuzumab. To look into this association further, Varadan and his colleagues used data from two clinical trials to measure the molecular makeup of breast tumors after treatment with a single dose of trastuzumab. They examined how and if the immune system interacted with the drug and if the immune-associated properties of trastuzumab were related to the subtype of HER2-positive breast cancer.

Women with the HER2-enriched subtype of disease had the highest rate of tumor response compared with other disease subtypes in patients taken from both clinical trials.

Based on these results, Varadan and colleagues used a molecular signature (Immune Index) to measure the amount of immune activity occurring within the tumor tissue. Again, the HER2-enriched subtype tumors had significant increases in immune activity after only one dose of trastuzumab compared with the other subtypes.

"We found that higher Immune Index evaluated after just one dose of trastuzumab predicted the tumor's response," Varadan said.

This response seems to be specific to trastuzumab. There was no association between immune activity and the subtype of breast cancer in patients who were given a single dose of another chemotherapy.

"Also, the predictive ability of the Immune Index test was not observed in patient tumors before any therapy was given, suggesting that just a single dose exposure may be a beneficial way to identify which patients are most likely to benefit from trastuzumab-based chemotherapy and, thus, do not need additional anti-HER2 treatment," Varadan said.

Finally, the researchers wanted to identify which types of immune cells

were associated with this brief exposure to trastuzumab. They found that signatures of T-cell activity—a key immune response—were consistently predictive of response after one dose of trastuzumab, suggesting that the immune system is likely playing a key role in enabling the therapeutic benefits of trastuzumab. Specifically, PD-1 expression, a marker of T-cells, was significantly increased in women with the HER2-enriched subtype of disease. This suggests that this subtype of breast cancer may benefit most from the addition of drugs that target PD-1.

"Given that the subtypes of HER2-positive disease and the immune signatures predict response to trastuzumab-based therapy, the next question is whether these signatures can also predict response to dual-HER2 targeted therapyVaradan said. "Additionally, we would like to understand why certain breast cancers have a strong immune response when treated with anti-HER2 therapy while others escape immune surveillance. We are poised to answer these questions using both lab-based research as well as an ongoing preoperative clinical trial—CASE14112—being conducted here at CWRU."

More information: V. Varadan et al. Immune Signatures Following Single Dose Trastuzumab Predict Pathologic Response to Preoperative Trastuzumab and Chemotherapy in HER2-Positive Early Breast Cancer, *Clinical Cancer Research* (2016). DOI: 10.1158/1078-0432.CCR-15-2021

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