Medical Xpress

High levels of immune cells in tumors may ID breast cancer pts most likely benefit from trastuzumab

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Women with HER2-positive breast cancer who had the highest levels of immune cells in their tumors gained the most benefit from presurgery treatment with chemotherapy and trastuzumab, according to results presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10-14.

"We have previously shown that high levels of tumor-infiltrating lymphocytes [immune cells in a tumor] are predictive of response to trastuzumab and chemotherapy administered after surgery for early-stage, HER2-positive breast cancer using samples from patients enrolled on the randomized, adjuvant phase III clinical trial called the FinHER study," said Sherene Loi, M.D., Ph.D., medical oncologist and head of the Translational Breast Cancer Genomics Lab at the Peter MacCallum Cancer Centre in Melbourne, Australia. "Our new data further support the positive relationship between tumor-infiltrating lymphocytes and better outcomes with trastuzumab therapy, this time in a cohort of patients with newly diagnosed HER2-positive breast cancer who received the therapy before surgery.

"It seems, therefore, that levels of tumor-infiltrating lymphocytes may be a good biomarker of response to trastuzumab in primary breast cancer, something that researchers have been looking for with little success for some time," added Loi.

Loi and colleagues evaluated breast tumor samples from 156 patients with operable or locally advanced HER2-positive breast cancer enrolled in the GeparQuattro trial. All these participants received chemotherapy and trastuzumab prior to surgery as part of the trial, which showed that women who received the combination were more likely to have a pathologic complete response; that is, they were more likely to have no residual invasive cancer detectable in the breast tissue and lymph nodes removed during surgery.

Loi and colleagues found that for every 10 percent increase in the levels of tumor-infiltrating lymphocytes there was a 16 percent increase in the number of patients who had a pathologic complete response.

"These data indicate that a patient's immune system influences outcome and trastuzumab response," said Loi. "What we don't know is why some patients have tumor-infiltrating lymphocytes in their breast tumor at diagnosis and others do not. Currently, we are actively investigating this and trying to understand why there is a positive relationship between tumor-infiltrating lymphocytes and better outcomes with trastuzumab therapy."

To address the second point, the researchers analyzed breast tumor samples from patients enrolled in the FinHER study, in which patients with HER2-positive primary breast cancer were randomly assigned to trastuzumab or no trastuzumab with their postsurgery chemotherapy agents. Loi and colleagues found evidence that trastuzumab modulates the immune microenvironment, probably by relieving tumor-mediated immunosuppression through multiple immune-related factors, including one called PD-1.

They also found in a mouse model of HER2-positive breast cancer that combining trastuzumab with either an agent that blocks PD-1 or an agent that blocks a protein to which PD-1 binds, PD-L1, resulted in greater

tumor regression compared with trastuzumab alone. "Thus, we suggest that adding an inhibitor that can block factors that suppress patient antitumor immune responses to trastuzumab therapy could potentially improve clinical outcomes," said Loi.

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Presenter: Sherene Loi, M.D., Ph.D.

Title: Tumor infiltrating lymphocytes (TILs) indicate trastuzumab benefit in early-stage HER2-positive breast cancer (HER2+ BC)

BACKGROUND: We have previously shown that TILs are predictive of benefit to trastuzumab and chemotherapy in HER2+ BC in the FinHER study, an adjuvant, phase III study in early-stage BC, where HER2+ patients were randomized to 9 weeks of trastuzumab or no trastuzumab in addition to chemotherapy (Loi et al, ASCO 2012). We sought to further confirm this positive association as well as to understand the composition of TILs.
METHODS: The association between TILs and response to trastuzumab with chemotherapy (epirubicin/cyclophosphamide with docetaxel with or without capecitabine) was evaluated in 156 HER2+ patients from the neoadjuvant GeparQuattro trial. The primary correlative endpoint was the association between TILs (quantified using the same method as previously published) with pathological complete response rates (pCR), adjusted for clinicopathological characteristics. To understand the composition of TILs, correlations between TILs and gene expression levels of 13 pre-defined immune markers were evaluated from 202 HER2+ samples from the FinHER study. These represented T and B cell infiltration (CD3D, IGKC), Th1 (IFNG, CD8A), chemoattractants (CXCL9, CXCL13), immunosuppression (VEGFA, FOXP3, IDO1) and T-cell checkpoint receptors and ligands (PD-1, PD-L1, CTLA-4, CD80). Prognostic associations and interactions with trastuzumab were studied

in Cox regression models for distant-disease free survival (DDFS). Preclinical mice models of HER2 mammary cancer were used to investigate combination therapies.
RESULTS: In the GeparQuattro trial data, each 10% increment in TILs was associated with higher rates of pCR (adjusted OR:1.14 95%CI:1.01-1.29;P=0.037) after neoadjuvant trastuzumab and chemotherapy supporting the findings from the FinHER study. Gene expression analyses using the FinHER samples revealed IDO1 and CXCL13 were most highly correlated with TILs (R=0.58 and 0.51;p