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Measurement of Domain-Specific HER2 (ERBB2) Expression May Classify Benefit From Trastuzumab in Breast Cancer.

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Abstract

BACKGROUND:

Studies have shown that antibodies targeting the intracellular (ICD) or extracellular domains (ECD) of human epidermal growth factor receptor 2 (HER2) are equivalent when traditional methods are used. We describe a new method to quantify ICD and ECD expression separately and assess the prognostic value of domain-specific HER2 results in patients who received adjuvant trastuzumab therapy.

METHODS:

We measured HER2 protein expression with quantitative immunofluorescence (QIF) in tissue microarrays (TMA) using two different antibodies targeting the ICD (CB11 and A0485) and ECD (SP3 and D8F12). We assessed the prognostic value of ICD and ECD expression in 180 patients from a clinical trial of adjuvant chemotherapy followed by trastuzumab (HeCOG 10/05). We performed an exploratory univariate domain-specific, disease-free survival (DFS) analysis and compared DFS functions with Kaplan-Meier estimates. All statistical tests were two-sided.

RESULTS:

HER2 ICD expression by QIF showed slightly higher sensitivity to predict ERBB2 (HER2) gene amplification than ECD expression, which was more specific and had higher positive predictive value. In the HeCOG 10/05 trial specimens, 15% of cases showed discordant results for ICD and ECD expression. High ECD was statistically associated with longer DFS (log-rank P = .049, HR = 0.31, 95% CI = 0.144 to 0.997), while ICD status was not. Among patients with low ECD, there was no difference in DFS by ICD status. However, when ICD was high, high ECD was statistically associated with longer DFS (log-rank P = .027, HR = 0.23, 95% CI = 0.037 to 0.82) compared with low ECD.

CONCLUSION:

Quantitative measurements of HER2 ICD and ECD expression in breast cancer suggest a subclassification of HER2-positive tumors. Trastuzumab-treated patients with high ECD showed better DFS than patients with low ECD. This suggests differential benefit from trastuzumab therapy based on HER2 ECD expression.