

In situ quantitative measurement of HER2mRNA predicts benefit from trastuzumab-containing chemotherapy in a cohort of metastatic breast cancer patients.

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Abstract

BACKGROUND:

We sought to determine the predictive value of in situ mRNA measurement compared to traditional methods on a cohort of trastuzumab-treated metastatic breast cancer patients.

METHODS:

A tissue microarray composed of 149, classified as HER2-positive, metastatic breast cancers treated with various trastuzumab-containing chemotherapy regimens was constructed. HER2 intracellular domain(ICD), HER2 extracellular domain(ECD) and HER2 mRNA were assessed using AQUA. For HER2 protein evaluation, CB11 was used to measure ICD and SP3 to measure ECD of the HER2 receptor. In addition, HER2 mRNA status was assessed using RNAscope assay ERB2 probe. Kaplan - Meier estimates were used for depicting time-to-event endpoints. Multivariate Cox regression models with backward elimination were used to assess the performance of markers as predictors of TTP and OS, after adjusting for important covariates.

RESULTS:

HER2 mRNA was correlated with ICD HER2, as measured by CB11 HER2, with ECD HER2 as measured by SP3 (Pearson's Correlation Coefficient, $r=0.66$ and 0.51 respectively) and with FISH HER2 (Spearman's Correlation Coefficient, $r=0.75$). All markers, HER2 mRNA, ICD HER2 and ECD HER2, along with FISH HER2, were found prognostic for OS (Log-rank $p=0.007$, 0.005 , 0.009 and 0.043 respectively), and except for FISH HER2, they were also prognostic for TTP (Log-rank $p=0.036$, 0.068 and 0.066 respectively) in this trastuzumab- treated cohort. Multivariate analysis showed that in the presence of pre-specified set of prognostic factors, among all biomarkers only ECD HER2, as measured by SP3, is strong prognostic factor for both TTP (HR= 0.54 , 95% CI: $0.31-0.93$, $p=0.027$) and OS (HR= 0.39 , 95%CI: $0.22-0.70$, $p=0.002$).

CONCLUSIONS:

The expression of HER2 ICD and ECD as well as HER2 mRNA levels was significantly associated with TTP and OS in this trastuzumab-treated metastatic cohort. In situ assessment of HER2 mRNA has the potential to identify breast cancer patients who derive benefit from Trastuzumab treatment.