Abstract

Patient selection

VeraTag assays for quantitative protein measurements

HER2 total assay (H2T) vs. HER3 total assay (H3T) and p95 vs. HER2 assay

Subsets of patients experiencing sub-opimal responses following treatment with trastuzumab

Methods

Background: Using IHC or FISH to select patients for trastuzumab-based therapy, only half of HER2-positive patients show evidence of response. In vitro data implicate HER2:HER3 heterodimers and p95/HER2 (p95) in HER2-positive cell lines, as mediators of resistance to trastuzumab at the receptor level. We have previously reported that central FISH- positive patients with low HER2 protein expression by VeraTag assay had significantly reduced response to trastuzumab compared to patients who had FISH-positive tumors with high HER2 protein expression (SABCS 2008). Adding quantitative measurements of p95 and HER3, we offer evidence for the existence of multiple subtypes of HER2-positive tumors that respond differently to trastuzumab.

Methods: Using the VeraTag assay, quantitative protein measurements of HER2, HER3, and p95 were made in FFPE specimens from a cohort of patients with metastatic breast cancer (MBC) and correlated with time to progression (TTP) and overall survival (OS) following treatment with trastuzumab using Kaplan-Meier (KM) and Cox proportional hazards regression analyses.

Results: Measurements of HER2 (H2T), HER3 (H3T) and p95 were made in FFPE tumor samples from 95 patients treated with trastuzumab for metastatic breast cancer. Within the group that over-expressed HER2 by the VeraTag assay (n=60), a group with high HER2 protein expression (median H2T >=12.95, HR=0.0004), median OS 29 vs. 40 mos, HR=2.0; p=0.047). Within the subgroup with moderate H2T over-expression (n=40), 2-variable Cox analyses demonstrated that p95 and H3T were independent predictors of TTP (p95 HR=2.3, p=0.0013; H3T HR=3.5; p=0.0037). For OS, p95 was significant and H3T showed a strong trend (p95 HR=2.5, p=0.029, H3T HR=2.2, p=0.032).

Conclusions: These data suggest the existence of multiple subgroups of HER2-positive patients expressing varying HER2, p95, and HER3 levels that experience different clinical outcomes following treatment with trastuzumab. Furthermore, the association of HER3 and p95 over-expression with poor response to trastuzumab in otherwise HER2-positive tumors suggests possible treatment approaches with combinations of targeted therapies.

Cohort characteristics

Subgroup for comparison

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