Evaluation of the association of PIK3CA mutations and PTEN loss with efficacy of trastuzumab therapy in metastatic breast cancer.

Razis E, Bobos M, Kotoula V, Eleftheraki AG, Kalofonos HP, Pavlakis K, Papakostas P, Aravantinos G, Rigakos G, Efstratiou I, Petraki K, Bafaloukos D, Kostopoulos I, Pectasides D, Kalogeras KT, Skarlos D, Fountzilas G.

Source

First Department of Medical Oncology, Hygeia Hospital, Er. Stavrou & Kifissias Av, 151 23 Maroussi, Athens, Greece. e.razis@hygeia.gr

Abstract

Trastuzumab (T) is effective in metastatic breast cancer (MBC) with HER2 overexpression and/or amplification, but resistance to T develops in a significant number of HER2-positive patients. Understanding the mechanisms of resistance is critical to the care of these patients. Formalin-fixed paraffin-embedded tumor tissue samples were collected from 256 patients with T-treated MBC. Clinical information was collected retrospectively from the patients' medical records. Central review of HER2 status by fluorescent in situ hybridization (FISH) and/or immunohistochemistry (IHC) revealed that of the 227 eligible patients only 139 (61%) were truly HER2-positive. PTEN, ER, PgR, and Ki67 were evaluated by IHC, while PTEN status was evaluated by FISH as well. PIK3CA mutations were identified with single nucleotide polymorphism (SNP) genotyping. Median time to progression (TTP) was 14.4 months for the HER2-positive and 10.3 for the HER2-negative patients (log-rank, P = 0.22). Survival from the initiation of T (survivalT) was 50.4 months for the HER2-positive and 35.3 for the HER2-negative subgroups (P = 0.006). Higher risk of progression was associated with HER2-positive status and the presence of PIK3CA mutations (P = 0.014). PTEN loss, as determined by IHC, was associated with lower survivalT in the whole population (P = 0.029) and in the HER2-positive population (P = 0.017). PIK3CA mutations and/or PTEN loss status were evaluated together as a single parameter, to estimate the impact of activation of the PI3K/AKT molecular pathway, and it was significantly associated with both decreased TTP (P = 0.003 in the total population, P = 0.004 in HER2-positive patients) and survival (survivalT, P = 0.011 in total, P = 0.006 in HER2-positive). In this trastuzumab-treated breast cancer population, PIK3CA activating mutations were associated with shorter TTP and PTEN loss with decreased survival. The activation of the PI3K/AKT pathway from either defect was associated with both TTP and survival, indicating the adverse effect of this pathway's status on trastuzumab efficacy.