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Topoisomerase II alpha gene amplification is a favorable prognostic factor in patients with HER2-positive metastatic breast cancer treated with trastuzumab.

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Source

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Abstract

ABSTRACT:

BACKGROUND:

The vast majority of patients with HER2-positive metastatic breast cancer (MBC) treated with trastuzumab eventually develop resistance to this agent. There is an unmet need therefore, for identifying biological markers with possible prognostic/predictive value in such patients. The aim of this study was to investigate the prognostic role of topoisomerase II alpha gene (TOP2A) amplification and protein (TopoIIa) expression in patients treated with trastuzumab-containing regimens.

METHODS:

Formalin-fixed paraffin-embedded tumor tissue samples were retrospectively collected from 225 eligible patients treated with trastuzumab. Protein expression of ER, PgR, Ki67, PTEN, HER2 and TopoIIa were centrally assessed by immunohistochemistry. HER2 and TOP2A gene amplification was evaluated by fluorescence in situ hybridization. PIK3CA mutations were identified by single nucleotide polymorphism genotyping. Survival was evaluated from the initiation of trastuzumab as 1st line treatment to the date of last follow-up or death.

RESULTS:

Among the 225 samples analyzed, only 137 (61%) were found to be HER2-positive. TOP2A was amplified in 41% and deleted in 16% of such tumors. TOP2A gene amplification was more frequent in ER-negative tumors. TopoIIa protein expression was observed in the majority (65%) of the samples and was associated with ER-positive status, high Ki67 expression, presence of PTEN protein and PIK3CA mutations. Median follow-up for patients treated in the 1st line was 51 months. Survival was more prolonged with trastuzumab-containing treatment in HER2-positive patients (50 months, log-rank, p=0.007). TOP2A non-amplified or deleted tumors were associated with increased risk for death compared to TOP2A amplified tumors (HR=2.16, Wald's p=0.010 and HR=2.67, p=0.009, respectively). In multivariate analysis, a significant interaction of TOP2A with anthracycline treatment (either in the adjuvant or the 1st line setting) was observed for survival (Wald's p=0.015). Among the TOP2A amplified subgroup, anthracycline-treated patients were associated with decreased risk for death.

CONCLUSIONS:

TOP2A gene amplification was shown to be a favorable prognostic marker in HER2-positive MBC

patients treated with trastuzumab, such an effect however, appears to rather be related to treatment with anthracyclines (predictive marker for benefit from anthracyclines). The results of the present retrospective study warrant validation in larger cohorts of patients treated in the context of randomized trials.