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HER2 and TOP2A in high-risk early breast cancer patients treated with adjuvant epirubicin-based dose-dense sequential chemotherapy.

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Source

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Abstract

BACKGROUND:

HER2 and TOP2A parameters (gene status, mRNA and protein expression) have individually been associated with the outcome of patients treated with anthracyclines. The aim of this study was to comprehensively evaluate the prognostic/predictive significance of the above parameters in early, high-risk breast cancer patients treated with epirubicin-based, dose-dense sequential adjuvant chemotherapy.

METHODS:

In a series of 352 breast carcinoma tissues from patients that had been post-operatively treated with epirubicin-CMF with or without paclitaxel, we assessed HER2 and TOP2A gene status (chromogenic in situ hybridization), mRNA expression (quantitative reverse transcription PCR), as well as HER2 and TopoIIa protein expression (immunohistochemistry).

RESULTS:

HER2 and TOP2A amplification did not share the same effects on their downstream molecules, with consistent patterns observed in HER2 mRNA and protein expression according to HER2 amplification (all parameters strongly inter-related, p values < 0.001), but inconsistent patterns in the case of TOP2A. TOP2A gene amplification (7% of all cases) was not related to TOP2A mRNA and TopoIIa protein expression, while TOP2A mRNA and TopoIIa protein were strongly related to each other (p < 0.001). Hence, TOP2A amplified tumors did not correspond to tumors with high TOP2A mRNA or TopoIIa protein expression, while the latter were characterized by high Ki67 scores (p = 0.003 and p < 0.001, respectively). Multivariate analysis adjusted for nodal involvement, hormone receptor status, Ki67 score and HER2/TOP2A parameters revealed HER2/TOP2A co-amplification (21.2% of HER2 amplified tumors) as an independent favorable prognostic factor for DFS (HR = 0.13, 95% CI: 0.02-0.96, p = 0.046); in contrast, increased HER2/TOP2A mRNA co-expression was identified as an independent adverse prognostic factor for both DFS (HR = 2.41, 95% CI: 1.31-4.42, p = 0.005) and OS (HR = 2.83, 95% CI: 1.42-5.63, p = 0.003), while high TOP2A mRNA expression was an independent adverse prognostic factor for OS (HR = 2.06, 95% CI: 1.23-3.46, p = 0.006). None of the parameters tested was associated with response to paclitaxel.

CONCLUSIONS:

This study confirms the favorable prognostic value of HER2/TOP2A co-amplification and the adverse prognostic value of high TOP2A mRNA expression extending it to the adjuvant treatment setting in early high-risk breast cancer. The strong adverse prognostic impact of high HER2/TOP2A mRNA co-expression needs further validation in studies designed to evaluate markers predictive for anthracyclines.

TRIAL REGISTRATION:

Australian New Zealand Clinical Trials Registry ACTRN12611000506998.