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Authors

Yin, J
Gascard, P
Last, B
et al.

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Abstract P5-18-04: HER2 overexpression in ductal carcinoma in situ: A biomarker for risk stratification and therapeutic implication

J Yin; P Gascard; B Last; M Singh; T Tlsty; JA Tjoe

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Abstract

Background:

After initial treatment for ductal carcinoma in situ (DCIS), a subsequent clinically significant event (SCSE) such as another diagnosis of DCIS, atypia or invasive breast cancer (IBC), will likely lead to further surgical/medical therapy. Pathologically, DCIS is treated on the basis of estrogen (ER) and progesterone receptor (PR) status with hormonal therapy (HT), ie, tamoxifen (TMX) or aromatase inhibitor, regardless of human epidermal growth factor receptor (HER2) overexpression. Although HER2 is a well-established prognostic marker for IBC, the role of HER2 in DCIS is less appreciated. Recent studies have documented the prognostic value of p16, COX-2 and Ki67 as prognostic biomarkers for locoregional invasive recurrences due to abrogated response to cellular stress (ARCS). Notably, a high-risk population of DCIS patients lacking ER expression but over-expressing HER2, p16 and COX-2 has been recently identified. In the present study, we compared expression levels of HER2 and the 3 ARCS markers in a large cohort of DCIS patients treated with contemporary standard of care and with >5-year follow-up to assess their association with cancer progression and predictive value for developing a SCSE.

Methods:

Formalin-fixed paraffin-embedded tissue sections from 99 patients diagnosed with primary DCIS(1999-2013) were stained forER, PR and HER2 expression by immunohistochemistry (IHC).If equivocal, HER2 amplification was assessed by Silver In Situ Hybridization. An additional slide was stained forp16, Ki67 and COX-2 using a novel multiplex IHC strategy. Quantification of the 3 ARCS markers' expression in both epithelial and stromal compartments was carried out using a software (Inform^{TM})-guided approach. For expression level comparison of the three markers between HER2+ and HER2- DCIS, Wilcoxon-Mann-Whitney test was used. Fisher's exact or Chi-square test was used for other data analysis.

Results:

Simultaneous increase in epithelial p16, COX-2 and Ki67 expression in DCIS lesions was associated with subsequent IBC progression. HER2+ DCIS was significantly associated with high grade (p=0.0014), comedo-necrosis subtype (p=0.0022) compared to HER2- lesions. Upregulation of stromal COX-2 and p16 was significantly (p=0.008) associated with progression to SCSE in HER2- DCIS. The majority (5/6, 83%) of HER2+ DCIS patients treated with HT developed a SCSE, while only 22% (6/27) of HER2- DCIS patients treated with HT developed a SCSE. COX-2 upregulation was significantly associated with resistance to HT in HER2+ DCIS patients.

Conclusion:

High expression of p16, COX-2 and Ki67 in DCIS lesions can serve as powerful predictive biomarkers for DCIS progression to IBC. Our preliminary data suggest that overexpression of stromal p16 and COX-2 may help predict SCSEs in HER2- DCIS. Additionally, assessment of HER2 expression in DCIS may allow identification of patients who would not benefit from traditional HT as HER2 overexpression may predict TMX resistance. Since our data suggest that TMX resistance in HER2+ DCIS may be linked to upregulation of COX-2, one may propose that COX-2 inhibitors in conjunction with TMX may minimize TMX resistance in HER2+ DCIS. These preliminary data will need to be reproduced in a larger cohort to solidify their significance.

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