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Determining the role of IGF-IR and VEGFR-2 in the development of resistance to trastuzumab in breast cancer

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Introduction: Overexpression of HER2 is identified in approximately 20-30% of invasive breast carcinomas and indicates poor prognosis. Trastuzumab (Herceptin®) has shown activity both as a single agent and in combination with chemotherapy in HER2-overexpressing breast cancers. Nevertheless, 70% of patients with HER2-positive breast cancers develop intrinsic or secondary resistance to trastuzumab. This resistance has been associated with the activation of an alternative signalling pathway such as the insulin-like growth factor (IGF) or vascular endothelial growth factor (VEGF) pathway. The cells shed from the primary tumor (circulating epithelial tumor cells, CETCs) are the origin of later metastasis formation. We therefore investigated the expression of IGF-IR and VEGFR-2 on the CETCs in addition to HER2 amplification in breast cancer patients to identify patients who might benefit from a combined targeted therapy against HER2 and IGF-IR or VEGFR-2.

Methods: CETCs were determined from blood of 40 breast cancer patients with different stage of disease. The number of vital CETCs and the expression of IGF-IR or VEGFR-2 were investigated using the maintrac® approach. FISH was used for analysis of HER2 amplification in CETCs.

Results: CETCs could be detected in all breast cancer patients. The number of CETCs ranged from 4 to 163 in 100 µl of cell suspension. IGF-IR and VEGFR-2 expression on the surface of CETCs were detected in all patients. HER2 status may differ during course of treatment. 26% of patients with a negative HER2 status in the primary tumor had HER2 positive CETCs. In contrast, only 6% of patients changed their HER2 status from positive tissue to negative CETCs. A statistically high correlation was found between the percentage of IGF-IR positive and HER2 positive CETCs. Additionally, the expression of IGF-IR and VEGFR-2 on the CETCs was strongly correlated. However, no statistically significant relationship was observed between VEGFR-2 positive and HER2 positive CETCs.

Conclusion: Our results demonstrate a parallel expression of IGF-IR and HER2 amplification in CETCs and to a lesser extent VEGFR-2 expression. IGF-IR may be involved in the development of resistance to trastuzumab in contrast to VEGFR-2 and may be an important potential therapeutic target in HER2 positive breast cancers. Combining targeting of IGF-IR and HER2 may be a rational approach to improve response to trastuzumab in the sub-group of CETCs that express both, HER2 and IGF-IR.