High circulating concentrations of HER2 extracellular domain (ECD) exhibits a poor prognostic impact on metastatic breast cancer patients

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BACKGROUND: Overexpression of HER2, usually as a result of HER2 gene amplification, occurs in up to 20% of newly diagnosed breast cancers and is associated with aggressive disease and markedly decreased survival.The HER-2/neu oncoprotein is composed of three domains: the internal tyrosine portion responsible for intracellular signaling, the transmembrane and the external domain (ECD) which can be cleaved from the cell surface by matrix metalloproteases and then released into blood where it can be detected by ELISA without any significant cross-reactivity with other members of the HER receptor family. Increased levels of HER2 ECD (≥15ng/mL) can be detected in 30%-90% of patients with metastatic breast cancer (MBC) and high serum concentrations of HER2 ECD have been associated with HER2 overexpression, increased tumor burden.

HYPOTHESIS: As an easily accessible tumor marker, HER2 ECD could offer additional useful prognostic or predictive information beyond what is available with currently approved histologic methods of HER2 tumor tissue diagnosis.

METHODS: Two hundred and seven metastatic breast cancer patients from March 2009 to July 2011 were involved in this prospective study at Zhejiang Cancer Hospital. Serum HER2 ECD levels were measured by ELISA. Tissue HER2 was determined by IHC and FISH in tumor samples, respectively.

RESULTS: The level of serum HER2 ECD was at least more than 15 ng/ml in 31.4% (65/207) metastatic breast cancer patients, 39.1% (43/110) in HER2-positive patients and 23.4% (22/94) in HER2-negative cases, respectively, *P*=0.017. We also found that high serum HER2 ECD levels (≥15 ng/ml) were significantly associated with elevated serum CEA (52.1% v 21.5%, OR 3.978, 95%CI 2.138-7.401, *P*=0.000), CA125 (48.5% v 23.5%, OR 3.064, 95%CI 1.650-5.691, *P*=0.000), CA153 (53.2% v 17.1%, OR 5.48, 95%CI 2.897-10.366, *P*=0.000), LDH (53.3% v 23.1%, OR 3.798, 95%CI 2.011-7.173, *P*=0.000) and AKP (51.2% v 26.5%, OR 2.911, 95%CI 1.442-5.879, *P*=0.002), respectively. For the effect of HER2 ECD on the site of relapse, still there were statistically significant correlation between increased serum HER2 ECD levels and liver involvement (42.7% v 24.0%, OR 2.358, 95%CI 1.294-4.297, *P*=0.005), brain metastasis (50.0% v 26.7%, OR 2.744, 95%CI 1.397-5.391, *P*=0.003) and visceral involved (37.9% v 14.8%, OR 3.511, 95%CI 1.548-7.961, *P*=0.002), respectively. While serum HER2 ECD levels were not related to age, BMI, tumor size, lymph node involvement and hormone receptors status, respectively (*P*>0.05). This study suggested that monitoring the circulating levels of the HER2 ECD in patients with metastatic breast cancer provides a real-time assessment of tumor burden and indicates poor prognosis, and may provide important information for reassessment of HER2 in HER2-negative metastatic breast cancer.