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Letter to Editor

Pro1170 Ala Polymorphism in HER2-neu: A Potential Risk Factor of Trastuzumab-Related Cardiotoxicity in the Breast Cancer women Patients

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Abstract

Genetic alterations of the proto-oncogene human epidermal growth factor receptor (HER-2/neu) have been shown to induce malignant transformation and metastasis. its over-expression have been frequently implicated in the carcinogenesis and prognosis in a variety of solid tumours, especially breast cancer patients classified as 'HER-2-positive' would be still resistant to the anti-HER-2 therapy. Various mechanisms of drug resistance have been illustrated and the alteration of HER-2 was considered as a crucial mechanism. Notably, the alterations of HER-2 play an important role in drug resistance, therefore the alteration of HER-2, as a potential mechanism of resistance to trastuzumab such as the HER-2 mutations (Pro1170 Ala polymorphism) associated with trastuzumab-related cardiotoxicity. HER-2 related activating mutations could potentially offer more therapeutic opportunities to decrease the cardiac toxicity caused by anti-tumor treatment in breast cancer.

Keywords: *HER-2; Breast Cancer; Cardiotoxicity; Resistance*

I am very enthusiastic about the research article by Sasha E Stanton, Maureen M Ward "Pro1170 Ala polymorphism in HER2-neu is associated with risk of trastuzumab cardiotoxicity". In BMC Cancer (2015) 15:267 [1] DOI 10.1186/s12885-015-1298-6). The article reported that SNP variations in the ErbB2 gene can alter the protein sequence of the HER2-neu protein. while HER2-neu amino acid sequence to determine particular polymorphisms, which were associated with increased trastuzumab cardiotoxicity. I really support the author's point of the views The Her2/neu Pro1170 Ala polymorphism can be used to identify a subset of patients who are at increased risk of cardiotoxicity from trastuzumab therapy.

Variations in single nucleotide polymorphisms (SNPs) were associated with enhanced drug efficacy and toxicity in cancer therapy [2]; such as the monoclonal antibody trastuzumab has provided a critical directed therapy that has dramatically improved the prognosis of breast cancer patients whose tumor over presses the HER2-neu receptor; and which also cause trastuzumab cardiotoxicity. the major toxicity is cardiomyopathy with asymptomatic left ventricular ejection fraction (LVEF) decline and developing signs of congestive heart failure [3].

Compared with anthracyclines-reduced cardiotoxicity, trastuzumab related cardiac dysfunction showed no structural changes [4]. As well as trastuzumab toxicity is not dose dependent and is reversible; The mechanism of trastuzumab cardiotoxicity is unknown. HER2/neu has been shown to be essential in cardiac myocytes in animal models [5-7].

As we know, HER-2 (ErbB2 in rodents) is a membrane tyrosine kinase receptor belonging to the EGFR family, which also includes HER-1, HER-3, and HER-4, in normal tissues, ligand-stimulated EGFR, HER-3, and HER-4 form homodimers or combine with HER-2 in

heterodimers, and elicit a number of physiological cellular responses. Many studies showed that HER-2 is over expressed in the BC and instead capable of undergoing ligand-independent homodimerization and intracellular signal transduction; This activated signaling pathways promoting proliferation and survival of tumor cells. As a result, BC with amplified HER-2 carries a poorer prognosis [8,9].

Single nucleotide polymorphisms (SNPs) are normal variations in a gene sequence which can influence a drug's efficacy or toxicity. The best studied is the polymorphism of HER2-neu. one study showed HER-2/neu Ile655Val polymorphism may contribute to a higher risk of breast cancer [10]; and the following studies also confirmed that patients with HER2 positive breast cancer, the Ile 655 Val polymorphism was found to be associated with a 1.5-fold increase in HER2-neu expression and a worse outcome [11]; other studies suggested that that V/V or V/I genotype have a twofold increased risk compared with I/I genotype among women who were both younger than 45 years of age and reported a positive family history of breast cancer [12]. However, some conflicting results emerged, revealing that HER-2 I655V polymorphism may be a biomarker for breast cancer susceptibility among older women [13]. Furthermore, a rare HER-2 variant Ile654Val is also associated with an increased familial breast cancer risk [14]. Compared with the Ile 655 Val polymorphism, the Pro1170 Ala polymorphism has been less well studied. One study evaluating breast cancer and the Pro1170 Ala polymorphism that we could find, suggested that the Pro1170 Ala polymorphism did not increase breast cancer risk [15]. But the Her2/neu polymorphism Pro 1170 Ala is associated with increased risk of cardiotoxicity in patients with HER2-neu positive breast cancer treated with trastuzumab. Amino acid codon 1170 is located at the carboxydomain of the Her2-neu receptor which is not part of the trastuzumab binding site. The carboxydomain contains tyrosine residues that are phosphorylation sites for the kinase [15]. How this could alter downstream signaling and lead to increased trastuzumab associated cardiotoxicity is unclear. Breast cancer is the most common type of cancer among women as well as the first cause of cancer-specific mortality for women worldwide. as the population as a whole increases and cancer therapies improve, the numbers of elderly patients with cancer tare rising. More than half of patients newly diagnosed with cancer are aged 65 years or older; meanwhile, more and more cancer survivors were over age 65; This is especially the case with breast cancer (BC): according to the latest statistics, around half of BC are diagnosed in women aged 65 years or more [16] there is already quite a large experience with the implement of the HER-2 targeting antibody, trastuzumab, in the geriatric population with HER-2 expressing tumors [17,18]. Cardiotoxicity has been, and will remain, the main safety issue of this treatment [19].

In summary, The Pro1170 Ala SNP Her2/neu single nucleotide polymorphisms, may be useful in conjunction with other biomarkers such as micro RNA and troponin levels [20], stratify patients into those who might benefit from early institution of cardiac medications so that clinical management could be tailored to avoid or minimize the risk of cardiotoxicity.

Conflict of Interest

The author reports no relationship that could as a conflict of interest.

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