

Could Pharmacogenomics Improve Efficacy and Safety of Trastuzumab?

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Trastuzumab (Herceptin™) is a humanized anti-ErbB2 monoclonal antibody that has been approved for the treatment in the adjuvant and the metastatic setting of breast cancer patients that either overexpress ErbB2, or demonstrate ErbB2 gene amplification [1]. An important serious adverse event associated with trastuzumab is the reduction of left heart ejection fraction resulting to congestive heart failure. The role of pharmacogenomics in breast cancer targeted treatment has been well recognized [2]. However, data on the role of pharmacogenomics on the efficacy and safety of trastuzumab are still scarce.

A number of single nucleotide polymorphisms (SNPs) have been reported in the extracellular, transmembrane and cytoplasmic regions of HER2. However, thus far, there is limited knowledge on SNPs that could affect the binding, efficacy or tolerability of trastuzumab. The most thoroughly investigated SNP at clinical level concerns Ile655Val (codon 655 GTC/valine to ATC/isoleucine in the transmembrane domain of the HER2 protein), that is a potentially functional SNP. Predictions based on *in silico* models have suggested that this SNP increases protein kinase activity. In addition, it has been suggested that the Val allele may constitute a risk factor for trastuzumab induced cardiotoxicity. A non-synonymous coding SNP rs4252633 has been identified in the extracellular domain of HER2 that is targeted by trastuzumab. However, the functional consequences of this SNP are not known.

Furthermore, antibody-dependent cell-mediated cytotoxicity via interactions with Fcγ receptors (FcγR) on leukocytes may contribute to the antitumor toxicity of trastuzumab. Single-nucleotide

polymorphisms (SNP) in FCGR3A and FCGR2A genes lead to amino acid substitutions at positions 158 and 131, respectively, and affect binding of antibodies to Fcγ R. A recent study found no correlation between Fcγ receptors IIIa and IIa and clinical outcome in trastuzumab treated patients with HER-2 non metastatic breast cancer [3]. The same conclusion was supported by another trial, that included patients treated with taxane plus trastuzumab chemotherapy for HER-2 positive metastatic breast cancer [4].

In conclusion, current literature suggests a possible role of pharmacogenomics on the efficacy and safety of trastuzumab. However, data are scarce, the clinical implications are not known yet and further research is needed.

References

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