COMMENTARY

What is the Mechanism of Progression with Trastuzumab Treatment - Escape or Resistance?

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Abstract

Human epidermal growth factor receptor (HER) 2 overexpression, observed in 20-25 percent of invasive breast cancers, is well known to be associated with a more aggressive phenotype and poor prognosis, with resistance to certain chemotherapeutic agents. The majority of patients with metastatic breast cancer who initially respond to trastuzumab, demonstrate disease progression within 1 year of treatment initiation. Furthermore, lack of response in some patients and relapse during the course of therapy, continue to challenge researchers and clinicians. A better understanding of the fundamental mechanisms of trastuzumab action is required so that new therapies directed at HER2 can be developed. We present here findings for mechanisms, both of Trastuzumab action and clinical resistance or escape.

Keywords: Breast cancer - anti-HER2 treatment - trastuzumab - lapatinib

Asian Pacific J Cancer Prev, **13 (11)**, 5915-5916

Introduction

Human epidermal growth factor receptor (HER) 2 overexpression is observed in 20-25 percent of invasive breast cancers. It is well known that HER2 overexpression is associated with more aggressive phenotype and poor prognosis with resistance to certain chemotherapeutic agents (Ross et al., 2009). Anti-HER2 humanized monoclonal antibody (Trastuzumab) plus chemotherapy is a standard approach for metastatic breast cancer patients with visceral crisis (Slamon et al., 2001; Marty et al., 2005). The majority of patients with metastatic breast cancer who initially respond to trastuzumab, however, demonstrate disease progression within 1 year of treatment initiation (Slamon et al., 2001). However, lack of response in some patients and relapse during the course of therapy, continue to challenge researchers and clinicians towards a better understanding of the fundamental mechanisms of trastuzumab action. Due to the the new therapies directed at HER2 are being developed; we present here the mechanisms, both of Trastuzumab action and clinical resistance or escape mechanism.

HER2 is a member of the ErbB (Epidermal Growth Factor Receptor) family of receptor tyrosine kinases, which includes EGFR (ErbB1, HER1), ErbB3 (HER), and ErbB4 (HER4) (Bailey et al., 2011). A variety of anti-HER2 resistance mechanisms were defined until now in the literature. The main known mechanisms resistance to anti-HER2 treatments were; signaling downstream of the alternative growth factor receptors (such as, EGFR, ErbB3, p95ErbB2, and IGF-1R), compensation of the receptor blockade by overexpression of alternative HER ligands and receptors, loss of downstream controllers (PTEN; Phosphatase and tensin homolog), activation of PI3K-Akt and mitogen activated protein kinase (MAPK) pathway and host-related factors (Tortora, 2011).

As signaling downstream of the alternative growth factor receptors implicated in trastuzumab resistance (such as, EGFR, ErbB3, p95ErbB2, and IGF-1R), several strategies are being tested to block the ability of alternative growth factor receptors to signal. Like overexpression of HER2; HER1 and HER3 overexpression is associated with poor prognosis in patients with breast cancer (Tovey et al., 2004). One approach to achieve signal blockage, which has recently achieved considerable success, is the use of monoclonal antibodies that prevent ErbB2 heterodimerization with EGFR or ErbB3. A new class of agents targeting HER2, inhibits dimerization with other receptors in its family, and is known as HER dimerization inhibitors. Pertuzumab in combination with Trastuzumab has been seen to have a higher efficacy in pre-clinical models (Nahta et al., 2004). Pertuzumab is the first drug in this class that effectively was succesfully used in neoadjuvant and metastatic setting. Pertuzumab, a recombinant humanized monoclonal antibody binding to the HER2 dimerization domain, prevents dimerization

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of HER2 with other HER receptors (HER3, HER1, and HER4) especially with HER3 (Adams et al., 2006). In neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere) study Gianni L. reported that adding pertuzumab to docetaxel plus trastuzumab had a significantly improved pathological complete response (pCR) rate compared with those given trastuzumab plus docetaxel (45.8% vs 29.0%; p=0.0141) (Gianni et al., 2011). In another recently published study, the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study, Baselga J. and colleagues reported that in patients with HER2-positive metastatic breast cancer receiving first-line therapy, adding pertuzumab to docetaxel-trastuzumab combination significantly improved progression-free survival (PFS) compared to docetaxel plus trastuzumab (18.5 monts vs 12.4 months; p<0.001) (Baselga et al., 2011).

The addition of lapatinib (oral inhibitor of the tyrosine kinase activity of EGFR and HER2) to trastuzumab enhanced immune-mediated trastuzumab-dependent cytotoxicity (Montemurro et al., 2007). Recently, Baselga J. and colleagues reported that pCR rate was significantly higher in combination trastuzumab and lapatinib group for HER2-positive early breast cancer in Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Study (Baselga et al., 2012). In another study, the addition of lapatinib to trastuzumab prolonged PFS with HER2 positive metastatic breast cancer who had documented progression on at least one trastuzumab containing regimen in the metastatic setting (Wu et al., 2011). On these grounds, recent published data support that dual inhibition better than single treatment for HER2-positive breast cancer, thus trastuzumab escape is the most possible contributing mechanism under trastuzumab resistance.

In conclusion, as pathways contribute to the trastuzumab escape are well-known, dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer.

Acknowledgements

The authors declare that they have no conflict of interest.

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