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Human epidermal growth factor antagonists and cardiotoxicity—A short review of the problem and preventative measures

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ABSTRACT

The Human Epidermal growth factor Receptor 2 (HER2) is a potent mediator of cellular growth and proliferation. It plays an important role in cardiac development and maintaining the physiologic function of an adult heart. Amplification of the HER2 gene, and the corresponding overexpression of the HER2 receptor, occurs in roughly 20% of breast tumors and is associated with a poor outcome. Molecular targeting of the HER2 receptor with the humanized monoclonal antibody, Trastuzumab has improved disease-free and overall survival in patients with both metastatic and early HER2-positive breast cancer. Although trastuzumab is devoid of the classical toxicities associated with chemotherapy, one of the major concerns noted is the occurrence of symptomatic and asymptomatic cardiotoxicity (decline in left-ventricular-ejection-fraction (LVEF). Additionally, newer HER2 therapies such as Lapatinib, Pertuzumab and Ado-trastuzumab (TDM1) are either approved or are being evaluated in clinical trials for cancer therapy. Targeted therapies against HER2 have led to revolutionary strides in breast cancer research and treatment.

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With the concern of cardiotoxicity caused by these agents, new treatment strategies for preventing cardiac side effects need to be developed. In this review, we discuss the proposed mechanisms of HER 2 antagonist-induced cardiotoxicity and the ways to prevent it.

1. Introduction

Amplification of the HER2 gene and/or overexpression of its protein product occurs in approximately 20% of breast cancers and is associated with poorer prognosis (Slamon et al., 2001). To improve survival in patients with HER2 positive (HER2+) breast cancer, research has focused on developing therapies directed to the HER 2 receptor and its pathway. Trastuzumab is a humanized monoclonal antibody, the first targeted therapy against HER2 pathway and its use changed the natural history of HER2 positive breast cancer resulting in its approval by Food and Drug Administration (FDA) in 1998. In 2005, landmark adjuvant studies demonstrated that adjuvant trastuzumab either following, or in combination with chemotherapy reduced the risk of relapse by approximately 50% and the risk of death by 33% for women with HER2 positive early breast cancer (Piccart-Gebhart et al., 2005; Romond et al., 2005). Although there was hope that targeted cancer therapeutics would spare patients of the morbidity associated with cancer therapy, patients treated with trastuzumab were found to be at increased risk of cardiotoxicity, worsened when treated with concomitant or sequential anthracycline chemotherapy (Slamon et al., 2001; Bowles et al., 2012). Additionally newer HER2 therapies such as Lapatinib, Pertuzumab and Ado-trastuzumab (T-DM1) are either approved or are being evaluated in clinical trials for cancer therapy. Their potential role in cardiotoxicity is currently being investigated. This review aims to briefly outline the pathogenesis of cardiac dysfunction associated with the use of the anti-HER2 agents; and management and prevention of cardiotoxicity.

1.1. HER2/Erb B2 pathway

HER2 is a member of the HER/ErbB group of protein kinase superfamily, which encodes a 185 kDa transmembrane protein with tyrosine kinase activity involved in the regulation of proliferation and survival of epithelial cells. The HER family includes four receptors; HER1 (also known as epidermal growth factor receptor (EGFR)), HER2 (neu, C-erbB2), HER3 (Erb3) and HER4 (Erb B4). As of date at least 12 ligands to HER receptors have been identified including an epidermal growth factor and neuregulins (or heregulins) (Yarden and Sliwkowski, 2001). HER2 is considered an orphan receptor as it has no known ligand whereas HER3 receptor has very little enzymatic kinase activity and mainly functions as a ligand-activated dimer partner for the other family members. The other three HER receptors have known ligands and form either homodimers or heterodimers upon ligand binding (Citri and Yarden, 2003).

The HER receptors are type 1 transmembrane proteins that contain three functional domains: an extracellular domain of ligand binding, a transmembrane domain, and an intracellular tyrosine kinase domain (Fig. 1). Four subdomains have been identified in the extracellular domain; subdomain I (L1), subdomain II (CR1), subdomain III (L2) and subdomain IV (CR2) (Citri and Yarden, 2003). Crystal structures of ligand bound HER1 and HER3 receptors suggest that without ligand binding, domain II interacts with domain IV, exhibiting a "closed" form of receptor; upon ligand binding to domains I and III, the HER1 and HER3 receptors are transformed to an "open" form, freeing domain II from IV to mediate receptor dimerization (Yarden and Sliwkowski, 2001; Citri and Yarden, 2003; Citri, 2006). HER2 receptor however exhibits a fixed conformation that resembles a ligand activated state, suggesting the HER2 receptor is "primed" to form dimers with the other HER receptors (Citri, 2006). Receptor dimerization is an essential first step to propagate an intracellular signal and occurs through homodimerization (between two HER2 molecules) or heterodimerization (between HER2 and other ErbB receptors). Dimerization of the HER receptors leads to activation of the receptor tyrosine kinase domain and autophosphorylation. This is the first step of a cascade of downstream signaling events, which involve several important pathways mainly the Ras/Raf/mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, both of which lead to cell growth, division, angiogenesis, survival and migration (Babar et al., 2014) [Fig. 1].

1.2. Therapies targeting the HER2 pathway

Two major classes of anti-HER2 therapies are currently in clinical practice or are being tested in clinical trials: monoclonal antibodies (MoAbs) and Tyrosine kinase inhibitors (TKIs).The monoclonal antibodies include trastuzumab, pertuzumab, Ado Trastuzumab Emtansine (T-DM1) and investigational agents such as MM111 and Ertumaxomab. The Tyrosine kinase inhibitors include Lapatinib and Neratinib (HKI 272). Other HER2 targeted therapies which are still investigational are Heat shock protein 90 inhibitors (Hsp90), Erb hcAb (Erbicin human compact antibody) and HER2 targeted vaccines [Fig. 1].

1.3. Mechanism of cardiotoxicity with anti-HER2 therapy

HER2 is an important mediator of unregulated cell growth and cell survival and is involved in the embryogenesis of the heart (Erickson et al., 1997). The embryonic/neonatal myocardium expresses HER2, HER3 and HER4, whereas the adult myocardium expresses HER2 and HER4 but not HER3 (Sawyer et al., 2002; Zhao et al., 1998; Strasser et al., 2001).

1.3.1. Role of neuregulin in cardiotoxicity

The action of trastuzumab on blocking the enhanced proliferation and decreased apoptosis of HER2 cells is mainly due to the activation of the transcription nuclear factor-kβ (NF-kβ). The activation of Akt and NF-kβ pathways is also involved in cardiac cells under stress (Strasser et al., 2001). During cellular stress such as hypoxia and oxidative stress, a protein called neuregulin, is released by the endothelial cells located in the coronary microvasculature and endocardium. There are four types of neuregulins. Neuregulin1 (NRG-1) proteins belong to the epidermal growth factor family and binds directly to HER3 and HER4, while recruiting HER2 as a co-receptor. The binding to HER3 and HER4 receptors causes dimerization of the HER2 receptors and activation of cell survival pathways. The survival pathways inhibit cellular apoptosis by increasing cellular transcription factors, reduce reactive oxygen species (ROS) from mitochondrial respiration via activation of protein kinase B and stimulate production of endothelial nitric oxide synthase (eNOS) which produces cardio protective molecules, nitric