3 Molecular Mechanisms of Cardiovascular Damage Induced by Anti-HER-2 Therapies

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Introduction

In order to overcome the increased risk of cardiovascular toxicity associated with classic chemotherapeutics, since the last two decades, newer biological drugs have been designed to "target" specific proteins involved in cancer proliferation. Unfortunately, these proteins are also important for the maintenance of cardiovascular homeostasis. Endothelial damage is a common feature not only of anti-VEGF agents (bevacizumab, sunitinib, sorafenib) but also of anti-Her-2 drugs [1, 2]. The humanized anti-ErbB2 antibody trastuzumab is the prototypical biological drug first introduced in antineoplastic protocols for the treatment of ErbB2+ breast cancer. ErbB2 is a transmembrane glycoprotein receptor overexpressed in several breast cancers, which also plays a major role in the heart in cell growth, including myocyte growth, and inhibition of apoptosis [3–7]. When administered alone, the risk of significant cardiotoxicity by anti-Her-2 drugs appears to be low, but in clinical trials, 25% of patients treated with trastuzumab developed systolic dysfunction, especially when administered with or shortly after doxorubicin [2, 8–10].

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Cardiac Toxicity of Anti-ErbB2 Inhibitors

Inhibition of the axis neuregulin 1/ErbB2 signaling has been considered the key cardiotoxic effect of anti-ErbB2 drugs [11, 12]. Briefly, adult cardiac microvascular endothelial cells can release neuregulin 1 (NRG1, especially the NRG1b isoform) [13] following to various stimuli, including mechanical strain. NRG1 acts on cardiac myocytes in a paracrine manner, triggering ErbB4/ErbB4 homodimerization and ErbB4/ErbB2 heterodimerization to induce protective pathways in response to stress [11, 12]. Importantly, the ErbB2 pathway regulates cell survival and function and can even impact mammalian heart regeneration [14] and can be stimulated when the heart faces adverse hemodynamics or other stress, such as ANT therapies (Fig. 3.1) [11, 15]. It has been hypothesized that anti-ErbB2 drugs can induce myocyte damage and,

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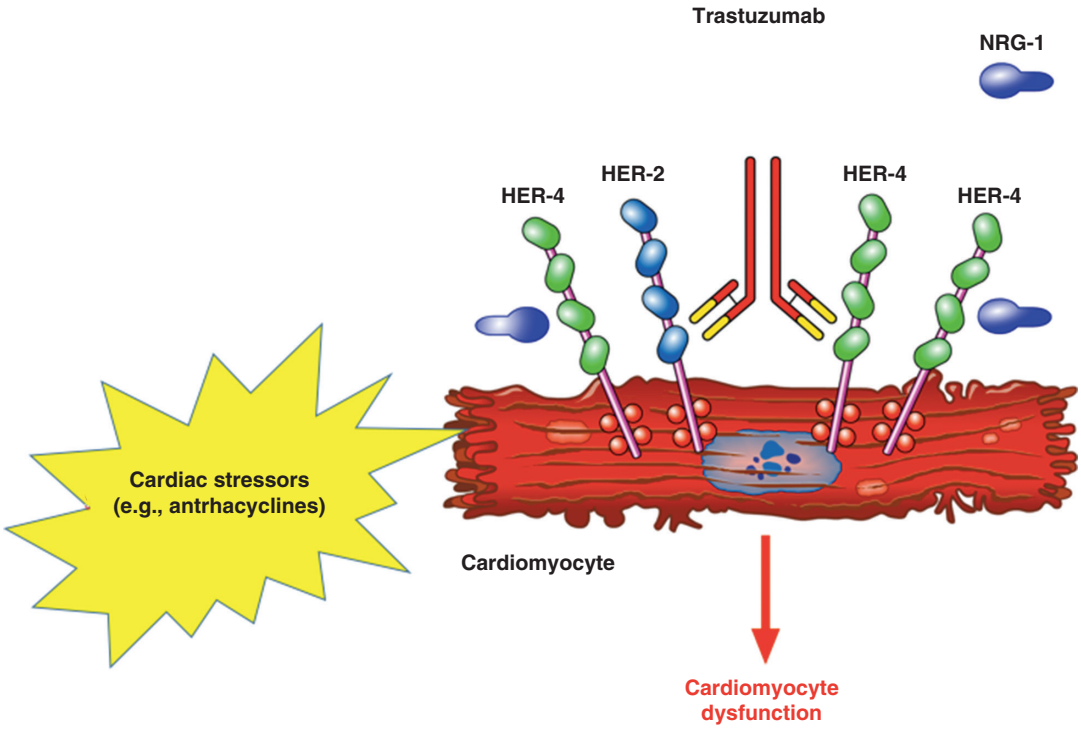

Fig. 3.1 Cardiomyocyte damage induced by trastuzumab. Cardiac stressors, such as pressure or volume overload but also anthracyclines, are able to upregulate Her-2 on cardiomyocyte, rendering these cells more susceptible to following exposure to trastuzumab

eventually, HF by deranging the NRG1/ErbB4/ErbB2 pathway in the myocardium. This event is more likely to occur upon cardiomyocyte exposure to other stressors, such as hypertension or doxorubicin [11, 16, 17]. Such concept seems to be corroborated by seminal papers that showed LV dilation in ErbB2 cardiac KO mice, with enhanced susceptibility to cardiomyocyte damage from anthracyclines [18, 19]. On the opposite, ErbB2-overexpressor hearts exhibited reduced levels of ROS in mitochondria, with lower ROS levels and less cell death in neonatal myocytes isolated from ErbB2(tg) hearts after administration of anthracyclines. This was due to higher levels of glutathione peroxidase 1 (GPx1) protein and activity, coupled to an increase of two known GPx activators, c-Abl and Arg, suggesting novel mechanisms by which ErbB2 blockers can damage heart structure and function [20].

Additional studies on NRG1/ErbB4/ErbB2 have moved from cancer and HF to heart disease from any cause, paving the way to novel therapeutic implications. For instance, in mice subjected to pressure overload, both mRNA and protein levels of ErbB4 and ErbB2 were significantly diminished with the progression of the disease from hypertrophy to decompensated HF [7, 11, 21]. Consistently, human failing myocardia exhibited lower ErbB2 and ErbB4 receptor expression and activation/phosphorylation, when compared to organ donors [22]. Interestingly, levels of ErbB4 and ErbB2 could be restored back to normal by implanting LV assist device and unloading the heart [22, 23]. In an apparent contrast with these results, there was enhanced phosphorylation of ErbB4 and ErbB2 in dogs with HF induced by tachypacing [24]. Dysregulation of the intracellular downstream effectors of ErbB4 and ErbB2, ERK1/2, and Akt was also observed, suggesting deranged NRG1/ErbB4/ErbB2 pathway. Importantly, most studies show enhanced expression of NRG1 in HF compared to control conditions [11, 22, 24]. This evidence points out that in the pathophysiology of

HF, a major player is deregulation of the NRG1/ErbB4/ErbB2 signaling. In particular, anti-ERbB2 drugs can bring to cardiac dysfunction; and, in spite of normal or enhanced levels of NRG1, ErbB4/ErbB2 is downregulated and/or uncoupled from intracellular signaling, possibly exacerbating LV decompensation [11]. In addition, recent studies show that catecholamines, which usually increase in the setting of heart dysfunction and with administration of doxorubicin [11, 25, 26], can enhance ErbB2 expression in cardiomyocytes, thus making these cells more vulnerable to the effects of trastuzumab, bringing to cardiotoxicity [27].

Vascular Toxicity of Anti-ErbB2 Inhibitors

ErbB2 inhibition was also demonstrated to cause damage to vascular function through a reduction in NO bioavailability and an increase in ROS production [28, 29]. Indeed, cardiac endothelium produces the growth factor NRG1, which activates the Her-2/Her-4 complex, thus activating cascades of ERK–MAPK and PI3K–Akt signaling pathways, promoting cell survival [13]. Importantly, NRG1 modulates angiogenesis and NOS-dependent desensitization of adrenergic stimulation [30]. Trastuzumab treatment acts on Her-2, inhibiting survival signals and bringing to mitochondrial dysfunction and depletion of energy supplies. In addition, stress factors, such as hypertension or previous anthracycline administration, increase the production of reactive oxygen species (ROS) [31].

Under normal conditions, cells restrict this event by overexpressing Her-2, thus leading to the activation of the cell survival pathways. Her-2 blockade does not allow the activation of these pathways, thus creating a state of enhanced oxidative stress leading to apoptosis [3–6, 8, 30, 32–35].

Importantly, an inverse correlation between circulating levels of neuregulin 1 and level of coronary artery disease has been observed [36]. In addition, low NRG1 synthesis impairs cardiac recovery after an ischemic insult, and impairment in NRG1/HER axis was found in experimental diabetic cardiomyopathy [37, 38]. Intriguingly, patients with coronary artery disease and those with diabetes mellitus also have a higher risk of doxorubicin-induced cardiomyopathy, and neuregulin administration ameliorates heart function after anthracycline-induced myocardial injury [39]. Hence, there may be elements of neuregulin-related endothelial–myocardial coupling even in mechanisms of toxicity from classic cardiotoxic drugs such as anthracyclines. Accordingly, it can be postulated that patients with higher activity/stimulation of the NRG1/HER signaling pathway are more susceptible to trastuzumab cardiotoxicity. This would explain the increased incidence of cardiotoxicity in patients treated with trastuzumab in close temporal proximity to anthracyclines. The fact that subjects with concomitant cardiovascular risk factors or disease have an increased higher risk suggests that this pathway is particularly important and any further reduction from baseline can be detrimental. Experimental work has shown that lack of ErbB2 induces the development of dilated cardiomyopathy and impaired adaptation response to after load increase [18]. Further studies will need to demonstrate correlations between ErbB2 regulation of cardiac function and microvascular density [40].

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