

Interaction between Specialties: Dilated Cardiomyopathy and HER2-Positive Breast Cancer

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Abstract

Basic research may result in unexpected benefit in terms of progress in the understanding of mechanisms responsible for different diseases and their potential treatment alternatives. This is seen, for instance, when a specific situation, defined in clinical practice, may be translated into laboratory findings which suggest a new therapy for an unrelated disease, representing the inverse of the more usual bench-to-bedside path. During the past few years, the use of the monoclonal antibody trastuzumab, in the adjuvant and therapeutic context, has become of fundamental importance in the treatment of breast cancer with amplification/overexpression of HER2, resulting in significant increase in survival rates. The observation that trastuzumab also induces cardiotoxicity, and the identification of mechanisms involved in this side effect, have allowed the investigation of these factors as a therapeutic alternative for dilated cardiomyopathy, in a highly interesting fashion.

The ErbB receptor family

The family of receptors of epidermal growth factors (EGFR) or ErbB belongs to the subclass 1 of the receptor tyrosine kinase superfamily, and includes four components:

- 1) ErbB1 – EGFR, HER1
- 2) ErbB2 - HER 2/neu
- 3) ErbB3 - HER 3
- 4) ErbB4 - HER4

These receptors have an extracellular domain (which includes the binding region), a transmembrane domain and a cytoplasmic tyrosine kinase domain. Ligand binding to the extracellular domain of EGFR, HER3 and HER4 results in the formation of homo and heterodimers, with preferential recruitment of HER2 as part of the dimer¹. As a result, the intrinsic kinase domain is activated and specific tyrosine residues in the cytoplasm are phosphorylated, which leads to the activation of intracellular signals inducing cell growth,

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proliferation, differentiation and migration¹⁻⁴.

Neuregulins comprise a group of proteins that selectively stimulate the heterodimerization of HER2 and HER3, or HER4, and whose function has been shown to be important for normal cardiovascular function⁵. Neuregulins are released from the endocardial surface and endothelial cells, exerting a paracrine effect on cardiomyocytes which is important for development and maintenance of functional and structural integrity of the heart⁶⁻⁹.

ErbB receptors and cancer

The whole receptor family, and more specifically EGFR and HER2, are involved with the carcinogenic process. Generally, tumors with modifications in these receptors are more aggressive, with worst clinical outcome¹⁰. Several types of modifications, such as gene amplification, overexpression of receptors or their ligands, or loss of negative regulation control, are identified in tumors³.

HER2 amplification is seen in 25% to 30% of breast cancer cases, and is associated to reduced disease-free and overall survival^{11,12}. This overexpression is observed both in the primary tumor and in metastases, suggesting a potential benefit of the anti-HER2 therapy for this pathology.

Trastuzumab

Trastuzumab is a humanized monoclonal antibody specific for the extracellular region of HER2. Its mechanism of action has not been fully characterized, but involves the occurrence of antibody-dependent cell-mediated cytotoxicity (ADCC), inhibition of HER2 cleavage, inhibition of PI3K and angiogenesis, and arrest of cells in G1¹³.

The use of trastuzumab as adjuvant treatment reduces in around 50% the risk of relapse, resulting in a significant increase in disease-free survival and around a 1/3 reduction in mortality rates^{14,15}. In a neoadjuvant context, in which the chemotherapy precedes surgery, the addition of trastuzumab determined a pathological complete response rate of 66.7%, which was significantly higher than the 25% rate observed in patients treated with exclusive chemotherapy¹⁶. Trastuzumab results in significant clinical improvement in cases of metastatic disease, with an increase of 8.5 months in overall survival when associated to docetaxel chemotherapy, as compared to exclusive chemotherapy (median survival of 31.2 months with trastuzumab-docetaxel versus 22.7 months with docetaxel alone)¹⁷.

Clinical trials have shown that treatment with trastuzumab alone, in sequence or combined with chemotherapy may result in damage to the heart, with reduction in the contractile function of the left ventricle. The effect is usually reversible with cessation of the treatment. There are no reports on damage to myocardial cells, as seen for instance as an effect of anthracycline on the cardiac muscle.

Among 3.5% and 17.3% of the patients included in clinical trials with the monoclonal antibody associated to chemotherapy presented asymptomatic reduction in left ventricle ejection fraction, leading to the need to interrupt the treatment with trastuzumab^{15,18-21}. Symptomatic heart failure was observed in 2.5% to 5.1% of the cases, with severe myocardial failure (New York Heart Association - NYHA III/IV) and death between 0% and 4.1%^{15,18-20}. This variability may be related to existing conditions of cardiac overload, including blood hypertension and coronary ischemic disease, as well as to the type of chemotherapy used. The cardiac dysfunction induced by trastuzumab is in most cases attenuated or reversed by interruption of the treatment. Mean time for recovery is around one and a half month, independent of the cardiac support provided. It is interesting to observe that, in case of improvement of heart function and proven efficacy of trastuzumab, patients may be treated again with the drug. In these cases, the ejection fraction must be monitored and inhibitors of enzima de conversão should be used with prophylactic intent²².

Cardiac dysfunction induced by trastuzumab seems to be due mainly to the inhibition of ErbB2 signaling in cardiomyocytes, associated to modifications in the expression of BCL-X proteins and ATP depletion, with the consequent contractile dysfunction, but with no modifications in cellular structure²³. In this situation, cardiac dysfunction is not related to myocardial lesion, and its effects are functional but not morphological.

The inhibition of the ErbB2 intracellular pathway induced by trastuzumab prevents cardiomyocytes from responding to signals of cardiac overload, interfering with the pathways of cytokines gp130 and neuregulin and with the mechanisms responsible for myocardial viability, which results in cardiac dysfunction²⁴ (Figure 1).

ErbB receptors and cardiac function

In animal models and in humans, a direct relationship between myocardial function and ErbB levels is observed^{25,26}. Situations of myocardial dysfunction are followed by low levels of ErbB, which are increased when conventional therapies result in improved cardiac function²⁶. Animal models with reduced expression of the ErbB2 gene present dilated cardiomyopathy, similar to dilated cardiomyopathy seen in humans²⁷. The animals are viable at birth, but in adult life develop a severe cardiomyopathy which causes death by heart failure. A decrease in the expression of the ErbB2/ErbB4 pathway is also observed during the transition from a situation of myocardial hypertrophy due to pressure overload to dilation with myocardial failure²⁵. The use of trastuzumab, which inhibits the HER2 intracellular signaling, is also related to a deficit in myocardial function, similar to

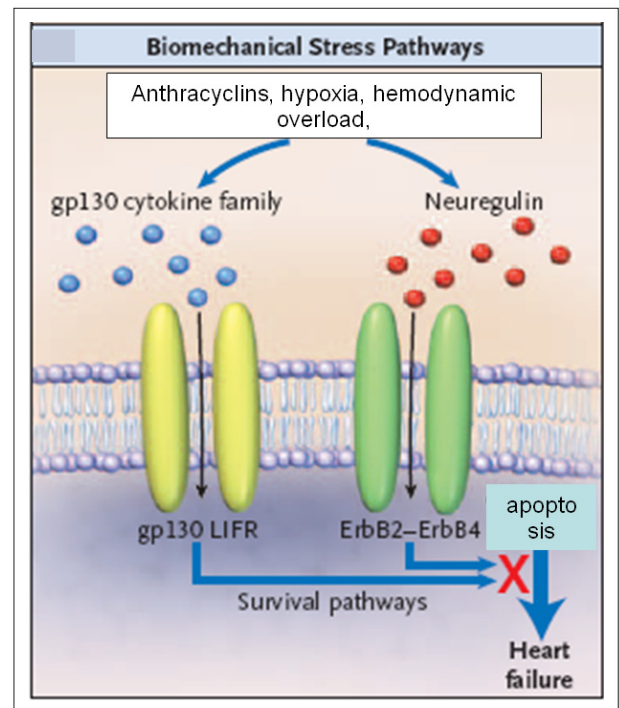


Figure 1 - Proposed mechanism for induction of cardiac toxicity by trastuzumab. Pathways involved with the survival/hypertrophy of myocardial cells are usually activated in response to myocardial damage induced by the use of anthracyclines, hypoxia or hemodynamic overload. Inhibition of ErbB2 by trastuzumab results in blockage of this pathway and, consequently, induction of apoptosis, leading to heart failure. From: Chien, KR²⁴.

dilated cardiomyopathy²¹ (Figure 2).

Through the activation of ErbB2 and ErbB4, neuregulin induces hypertrophy in adult cardiomyocytes and proliferation of embryo cardiomyocytes, which represents a protection against apoptosis⁹. The intracellular signaling pathways of ErbB2 and ErbB4 involve the activation of the serin/threonine kinase Akt, which phosphorylates and inactivates proteins important for apoptosis, preventing thus the occurrence of this process²⁸⁻³⁰ (Figure 3). The anti-apoptotic effect exerted by Akt depends probably on the intensity of Akt activation and needs the participation of other factors, such as IGLF-1 and cardiotrophin-1³¹. In adult cardiomyocytes, neuregulin induces the organization of sarcomeres, protects against myofibrillar disarray and inhibits apoptosis^{6,9,32,33}. This "cardiotonic" effect of neuregulin had not yet been investigated in the context of reversal of cardiac dysfunction.

A preclinical study by Liu et al³⁴ showed that neuregulin is capable of reversing the cardiomyopathy induced by infarction (ligation of the anterior descending coronary artery), drug (doxorubicin) or myocarditis due to infection with the virus Coxsackie B3. A peptide composed of 61 aminoacid residues, corresponding to the EGF-like domain in neuregulin, was capable of activating the ErbB signaling pathway. Treatment with neuregulin during the period between one week and two months after the induction of heart failure in this animal model resulted in improvement in parameters such as the dimensions of cardiac chambers and systolic function, with

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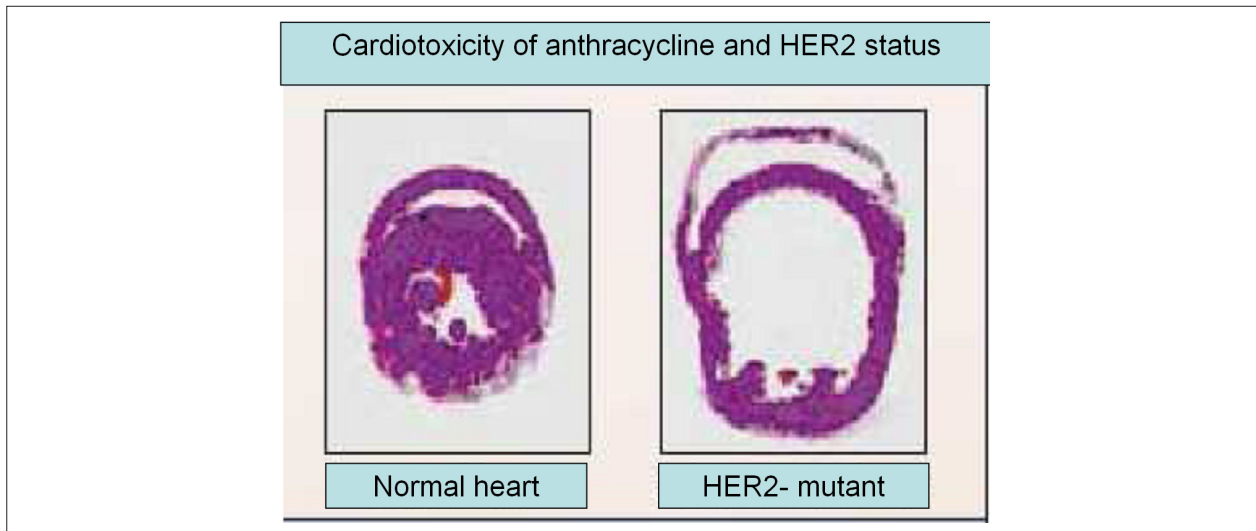


Figure 2 - Development of cardiac dilation induced by anthracyclines in mice with a mutated ErbB gene. Cross-sectional slices of the heart of mice with the normal or mutated ErbB2, showing that loss of ErbB2 function is related to cardiotoxicity, with significant cardiac dilation after cardiac stress (in this case, represented by anthracycline). From: Chien, KR²⁴.

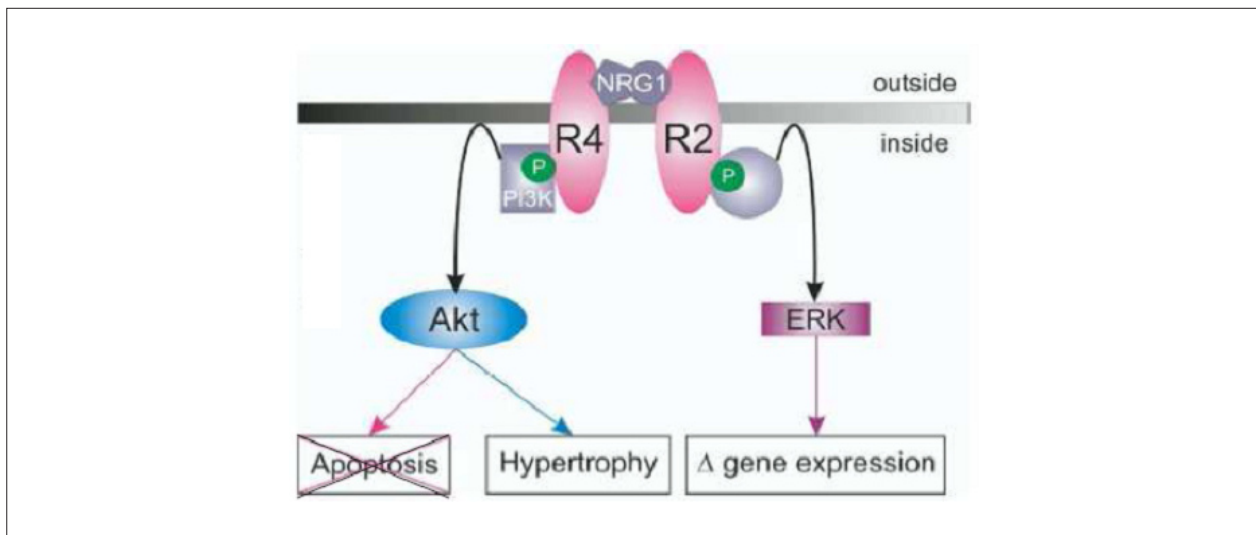


Figure 3 - Activity of ErbB on cardiomyocytes. Neuregulin (NRG1) induces dimerization of ErbB2 (R2) and ErbB4 (R4), activating the intracellular pathway of protein transduction which results in inhibition of apoptosis, hypertrophy of myocardial cells and activation of gene transcription factors mediated by ERK. From: Freedman and Ginsburg⁵.

increased survival rates. A gain in myocardial function and survival rates was also observed in animals treated with captopril, and the simultaneous use of this drug and neuregulin showed an additive effect, suggesting different mechanisms for these two drugs. Sarcomere organization was shown to be blocked by Erk-Mek inhibitor but not by PI3 kinase inhibitor, showing that the Erk pathway is involved with the improvement of myocardial function, hypertrophy and inhibition of apoptosis.

The activation of the ErbB2/ErbB4 pathway by neuregulin improved cardiac function and survival rates in animals with cardiomyopathy induced by infarction, drugs or myocarditis. The response was not immediately apparent,

but the parameters were modified a few days after beginning of the treatment and were maintained for around 60 to 80 days after its interruption. This effect mirrors inversely the results of the treatment of metastatic breast cancer with trastuzumab, in which the effects are maintained for around 6 to 8 weeks after interruption of treatment. The maintenance of improved myocardial function and survival even after two months after the induction of cardiac damage suggests that neuregulin may be used in the treatment of chronic dilated cardiomyopathy.

The therapeutic effects related to ErbB2 activation (sarcomere organization, maintenance of cell integrity, cell adhesion, suppression of apoptosis and increased

angiogenesis) are different from those of any other agent currently used for treating myocardial dysfunction, and suggest that this pathway is an interesting alternative for the therapy of heart failure.

This example illustrates a non-conventional situation in which a side effect, observed during the conventional treatment of a disease, may open new possibilities for the therapy of a disease representing another specialty. Although the constant attention to incorporate laboratory information into clinical practice is of great importance, situations such as the one presented in this work, in which the usual laboratory-clinical practice path is inverted, must not be neglected.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

Clinical Update

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