FOCUS ON RESEARCH

Herceptin and the Heart — A Molecular Modifier of Cardiac Failure

Kenneth R. Chien, M.D., Ph.D.

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Translation, translation, translation. Around the halls of academic medicine, translation is the mantra of the moment. In the literary world, translation is the process of interpreting an extant body of written work and converting it into a new language. In the scientific world, translation is the application of fundamental discoveries in basic science to clinical medicine, with the goal of developing new treatments for debilitating diseases.

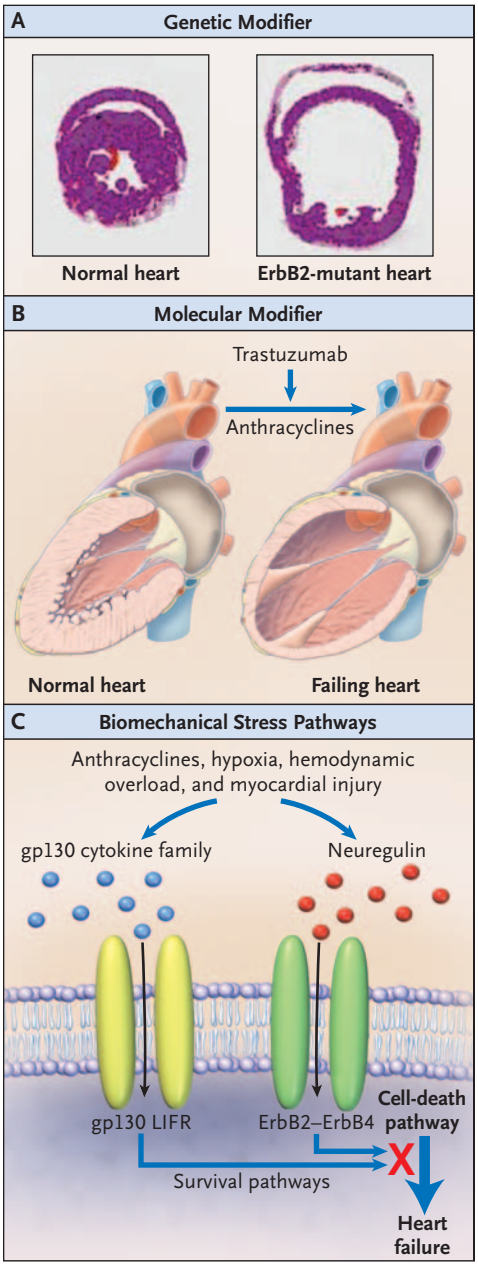
In this arena, the development of a humanized monoclonal antibody against the HER2 protein (trastuzumab, or Herceptin) as adjuvant therapy for early HER2-positive breast cancer ranks as one of the most satisfying and powerful examples of translational medicine to date. The development of this antibody built on the discovery of the amplification of the *HER2/neu* (*ErbB2*) gene as a pivotal modifier in a subgroup of breast cancers. A series of large-scale studies have conclusively shown that trastuzumab can substantially reduce the risk of recurrence and early death in women with HER2-positive breast cancer.

Heart failure, a serious side effect of trastuzumab, occurs in 1 percent to 4 percent of patients treated with the antibody, and 10 percent of patients have a decrease in cardiac function. The incidence of cardiotoxic effects of trastuzumab appears to increase with exposure to anthracyclines, which mediate cardiac failure in a direct, dose-dependent manner. In short, it seems as if trastuzumab both reduces the risk of recurrence of breast cancer and increases the susceptibility to heart failure. A longstanding question is whether it is possible to delineate the biologic pathways that link trastuzumab to the onset of cardiotoxic effects, so as to reveal approaches to the design of drugs that would dissociate the beneficial effects from the adverse ones.

Studies of mutant mouse models have documented a pivotal role of the *erbB2* gene in the embryonic and postnatal heart (see diagram). The induction of cardiac stress pathways by either hemodynamic overload or the cardiotoxicity of anthracyclines promotes the onset of left ventricular dysfunction in mice that are deficient in ErbB2 protein. These studies support a two-hit model of trastuzumab cardiotoxicity, in which there is a loss of ErbB2-mediated pathways that normally blunt the effects of stress-signaling pathways that anthracyclines activate in the heart. These results, and findings in other relevant mouse models, have suggested an explanation of the cardiotoxicity of trastuzumab. Its basis is the fundamental role of ErbB2–ErbB4 heterodimeric receptors in triggering the myocyte-survival pathways that are required during the activation of acute stress signals. The loss of these survival cues after trastuzumab treatment can lead to the irreversible loss of cardiac myocytes during exposure to chemotherapeutic agents, such as the anthracyclines, that mediate overt heart dysfunction. This reasoning is consistent with the clinical finding that trastuzumab also increases the risk of cardiac side effects in patients with existing forms of heart disease in which the cardiac stress signals are presumably already activated. However, direct proof of this concept has been elusive — it would require the dissociation of exposure to trastuzumab from cardiotoxic effects in humans.

In this issue of the *Journal*, Joensuu et al. (pages 809–820) report their experience with trastuzumab as adjuvant therapy for ErbB2-positive breast cancer. The antibody was administered alone as the first agent and was not given concomitantly with or after agents known to be cardiotoxic, such as anthracyclines. With this regimen, there were no recorded episodes of heart failure, and there was a negligible effect on baseline cardiac function. Moreover, recurrence-free survival at three years approached 90 percent among women who were treated in this way. Thus, the therapeutic effect of trastuzumab in ErbB2-positive breast cancer was completely dissociated from its modifying effect on anthracycline-induced cardiotoxic effects.

The mechanism of this advance in the treatment of breast cancer might have been influenced by the doses and durations of trastuzumab therapy and anthracycline therapy, but the most



Working Model of Trastuzumab as a Molecular Modifier of Anthracycline Cardiotoxicity.

Studies in a genetically engineered mutant mouse model document that the loss of ErbB2 in the heart can lead to heart failure and increased susceptibility to anthracycline cardiotoxicity (Panel A). Clinical studies support the concept that trastuzumab acts as a molecular modifier of anthracycline-induced cardiotoxic effects and associated heart failure (Panel B). Panel C shows the proposed pathway by which trastuzumab modifies anthracycline cardiotoxicity. In response to a variety of pathological stimuli causing biomechanical stress, including exposure to anthracyclines, pathways leading to the death of cardiomyocytes are activated. The irreversible loss of viable cardiac muscle is normally prevented by the concomitant activation of cardiomyocyte-survival pathways, including gp130 cytokines and neuregulin. Trastuzumab, by inhibiting the ErbB2 receptor, leads to a loss of the neuregulin-dependent pathways that result in the survival of cardiac myocytes. In most patients, the activation of other survival pathways is sufficient to prevent the loss of viable muscle cells and the onset of heart failure. However, in a subgroup of patients, the loss of the ErbB2-dependent survival pathways promotes the cardiotoxic effects of anthracyclines. Adapted from Chien[1] and Crone et al.[2] LIFR denotes leukemia inhibitory factor receptor.

likely explanation for the elimination of cardiotoxicity is the avoidance of either the concomitant administration of trastuzumab and anthracycline or the use of trastuzumab after anthracycline. It seems, therefore, that the risk of heart failure associated with trastuzumab was negated because cardiac stress signals had not been activated by anthracyclines. The study by Joensuu et al. demonstrates that trastuzumab can be given in therapeutically active doses with negligible cardiac side effects, but whether a similar result might hold in larger numbers of patients or in women with preexisting heart disease is now a pressing question.

The translational research exemplified by trastuzumab has implications that reach well beyond the boundaries of breast-cancer therapy. Recently, a number of molecular defects have been found to be capable of causing heart failure, including defects in cytoskeletal proteins, sarcomeric proteins, and calcium-cycling regulatory proteins. However, relatively few molecular modifiers of human heart failure have been identified. Experiments in mouse models have pointed to several candidate pathways, but as in studies of cancer, these modifying pathways in mice do not always have correlates with similar effects in humans. Given the similarity between signaling pathways in cancer and those in the heart, there is a strong possibility that clinical observations made in large-scale clinical oncology trials will uncover unsuspected modifiers of cardiovascular disease. In turn, these clinical studies are likely to spur a new round of basic research to identify the downstream targets that mediate adverse effects in the heart. One of the most exciting aspects of this new era of biologically targeted therapy is the increasing number of new fundamental scientific insights that are being generated by clinical trials in oncology. Perhaps we should prepare ourselves for a new mantra: reverse translation.

Dr. Chien is the director of the Cardiovascular Research Center, Massachusetts General Hospital, and a professor at Harvard Medical School — both in Boston.

1. Chien KR. Stress pathways and heart failure. Cell 1999;98:555-8.
2. Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 2002;8:459-65.