Trastuzumab in the Treatment of Metastatic Breast Cancer
Anticancer Therapy Versus Cardiotoxicity

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Abstract—Trastuzumab, a monoclonal antibody against the HER2 receptor, was recently approved for the treatment of metastatic breast cancer. However, 28% of patients receiving both an anthracycline and trastuzumab developed heart failure. Although HER2 overexpression has been associated with the development of cancer, HER2 receptors seem to be cardioprotective because they mediate the activation of important cardiac survival pathways. Because the morbidity and mortality of heart failure surpasses that of many cancers, prudent medical practice mandates that physicians learn more about the mechanisms of trastuzumab-induced cardiotoxicity and develop algorithms for assessing risk/benefit ratios before extending the use of this agent to patients with less invasive forms of breast cancer. (Circulation. 2000;102:272-274.)

Key Words: heart failure □ breast neoplasms □ drug toxicity

Trastuzumab (Herceptin) is a monoclonal antibody that was recently approved by the Food and Drug Administration (FDA) for the treatment of metastatic breast cancer. Although it has been lauded as being beneficial in the treatment of breast cancer, its use was associated with a high incidence of cardiac toxicity. Therefore, the use of trastuzumab raises important questions about mechanisms of action, appropriate patient monitoring, and the risk/benefit ratio.

The HER2 proto-oncogene (also called c-neu or ErbB-2) is a transmembrane receptor tyrosine kinase that belongs to the epidermal growth factor family.¹ The overexpression or mutation of this receptor causes neoplastic transformation and the development of tumors in animal models. Trastuzumab is a monoclonal antibody that binds to HER2 and inhibits HER2-mediated malignant transformation.² Trastuzumab improved the chemotherapeutic response rate and the median duration of response when used in combination with other chemotherapeutic agents.³ In a single randomized study (the results of which were presented to the Oncologic Drugs Advisory Committee of the FDA), the combination of trastuzumab and a chemotherapeutic agent improved 1-year survival in women with metastatic breast cancer by 16%.⁴ The survival benefit was 13% when the chemotherapeutic agent was an anthracycline⁴; however, this benefit was not evident at 18 months.⁴

As cited in FDA product labeling, a substantial number of women treated with trastuzumab developed congestive heart failure. When receiving trastuzumab alone in an open-label study, 7% of women developed heart failure; 28% did when treated with a combination of trastuzumab, anthracycline, and cyclophosphamide in a randomized study. Furthermore, 19% of women had New York Heart Association class III to IV symptoms, whereas severe symptoms were seen in only a small percentage of patients receiving anthracycline alone. The investigators reported that the new onset of cardiac dysfunction was “manageable with medications in most cases.”³ These data are cited in the package labeling, but they have not been published in the medical literature.

Assessing the Risk/Benefit Ratio of Trastuzumab
Despite the enthusiasm of oncologists, the potential significance of the high incidence of trastuzumab-induced cardiotoxicity deserves attention. Long-term survival of women with congestive heart failure (6 years, 33%)³ approximates that of women with breast cancer and distant metastases (5 years, 22%).⁶ yet it is far worse than that of women with breast cancer and regional metastases (5 years, 77%)⁶ or women without identifiable metastases (5 years, 97%).⁶ Indeed, 33% of women with heart failure die within 2 years of the initial diagnosis³ (Figure). In addition, heart failure is associated with substantial morbidity. Although most women who developed heart failure after trastuzumab therapy had symptomatic improvement with appropriate therapy,³ heart failure, like many cancers, is a progressive disease, and mortality remains high despite improvement in symptoms. Thus, in view of the significance of the heart failure side effect, it is imperative that physicians perform long-term cardiac follow-up of women receiving trastuzumab and that more be learned about the drug’s cardiotoxicity to ensure that patients do not trade one lethal disease for another. Unfortunately, no prospective studies have assessed trastuzumab-induced cardiotoxicity. However, the rapid increase in trastuzumab use and the planned expansion of use to breast cancer patients without metastasis and to patients with other...
forms of cancer mandate that such information be obtained in a timely fashion.

The Pathobiology of Trastuzumab

The ability of clinicians to use drugs rationally and to monitor their effects carefully, especially those with toxic side effects, is usually facilitated by an understanding of the pathobiology of their toxic effects. In the case of trastuzumab, the cellular and biochemical mechanisms responsible for its cardiotoxicity are undefined; however, recent studies provide potential clues. The development of HER2 as a therapeutic target came from observations that (1) the receptor is overexpressed in 20% to 30% of primary breast cancers and other adenocarcinomas, (2) receptor overexpression portends a worse prognosis, and (3) receptor activation creates strong transforming activity and the development of tumors. However, both HER receptors and HER ligands are expressed in the heart, and their activation creates a hypertrophic response. In addition, heregulin-HER2 signaling promotes cell survival and growth and protects against apoptosis. In contrast, the deletion of HER proteins abrogates normal cardiac development. Importantly, the transition from compensated cardiac hypertrophy to heart failure is associated with a decrease in the expression of the HER2 and HER4 proteins.

Furthermore, the ability of the heart to withstand stress is due, at least in part, to a program of cell survival that is activated by HER ligands. Thus, the HER proteins and ligands play an important and heretofore unrecognized role in cardiac development and cardioprotection.

Although downstream pathways responsible for the cardioprotective effects of HER2 have not been defined, HER2 activates important transcription factors, including activator protein-1 (AP-1) and nuclear factor-κB (NF-κB). AP-1 regulates the expression of a group of cardiac proteins important in the development of cardiac hypertrophy, and NF-κB regulates the genes involved in the cellular response to stress.

A potent activator of NF-κB is the proinflammatory cytokine tumor necrosis factor-α (TNFα). Activation of NF-κB counteracts the apoptosis induced by TNFα, whereas the blockade of NF-κB facilitates apoptosis. These anti-apoptotic effects of NF-κB in the presence of TNFα overexpression may have important implications for the heart, because the overexpression of TNFα plays a critical role in the pathophysiology of a variety of cardiovascular diseases and may contribute to anthracycline-induced cardiotoxicity. Furthermore, disabling heregulin-HER2 signaling increases the risk of cell death in response to a second insult.

Taken together, these observations strongly suggest that HER2 blockade and the subsequent inhibition of downstream myocardial signaling by a HER2 antagonist would have effects on the heart and that these effects would be markedly enhanced in the presence of a second stress and/or activators of proinflammatory pathways, including ischemia, increased cardiac load, or cardiotoxic agents. These observations help explain the high incidence of heart failure in patients receiving both anthracyclines and trastuzumab when compared with an anthracycline alone. Anthracyclines produce a well-described, although incompletely understood, cardiac toxicity. Because anthracycline cardiotoxicity can be found in asymptomatic patients or in patients who received low doses of anthracycline, anti-HER2 strategies might cause heart failure, even in patients with presumably normal hearts. Furthermore, because heart failure can occur many years after anthracycline treatment, the risk of trastuzumab cardiotoxicity may exist for months or years. Indeed, trastuzumab might be associated with an increased risk of heart failure in patients with any form of cardiac stress.

Evaluation of Patients Receiving Trastuzumab

A conundrum that overshadows attempts to evaluate trastuzumab cardiotoxicity is the complete lack of information regarding its short- and long-term effects on cardiac structure and function. This lack of information makes the development of both diagnostic and treatment algorithms problematic. In addition, although the warning in the package insert suggests that trastuzumab be discontinued in patients with a “clinically significant” decrease in ventricular function, the descriptor “clinically significant” remains undefined, and no information is provided to identify which clinical tests would be appropriate for assessing cardiac function in these patients. Thus, it is imperative that studies be performed to acquire fundamental information regarding trastuzumab-induced cardiotoxicity.

The diagnostic test with the greatest specificity and sensitivity for doxorubicin-induced cardiomyopathy is the endomyocardial biopsy. Although trastuzumab-induced cardio-
toxicity may differ substantially from doxorubicin-induced pathophysiology, the biopsy might provide important histological and ultrastructural information. Biopsies can be performed with relative safety by experienced operators, and biological measurements can be performed using well-described techniques. However, histological changes may be nonspecific or absent. Thus, the evaluation of trastuzumab-induced heart failure must also rely on an ability to noninvasively detect asymptomatic cardiovascular disease with a high degree of sensitivity and specificity. It is also critical to perform prospective studies to understand whether patients with asymptomatic coronary disease or left ventricular hypertrophy are at increased risk.

Although the pathophysiology of disease may be different, measures of resting cardiac function have proven of little value in evaluating and following cardiac function in patients receiving anthracyclines. Despite this fact, a resting assessment of left ventricular function is the only evaluation suggested for pretrastuzumab surveillance. The combination of echocardiographic or radionuclide imaging and exercise stress testing can provide a moderate level of sensitivity when following patients after anthracycline therapy, although it lacks the specificity of pathological assessment. Unfortunately, the usefulness of these tests in assessing trastuzumab-induced toxicity is undefined. Unique biological markers, such as TNF-α, atrial natriuretic peptide, and troponin T, may provide sensitive indicators of trastuzumab-induced cardiotoxicity.

Conclusions
The systolic dysfunction associated with cardiac dilatation after exposure to a cardiotoxic agent is usually irreversible, progressive, and lethal. Thus, the development of clinical heart failure in 28% of women receiving the combination of trastuzumab and an anthracycline is disturbing. Although metastatic breast cancer is itself associated with significant morbidity and mortality, published clinical studies to date suggest that trastuzumab provided only an improvement in the risk/benefit ratio in each patient who is a candidate for trastuzumab therapy.

Timely and aggressive evaluation of the mechanisms of trastuzumab-induced cardiotoxicity must be pursued to construct rational algorithms for screening potential candidates for trastuzumab therapy, following their clinical course, and better recognizing risks in defined populations. Furthermore, the extension of trastuzumab use to patients with less invasive forms of breast cancer seems imprudent in view of the untoward cardiac effects; this should be reconsidered until additional information is available. Taken together, experimental data and human studies suggest the hypothesis that anthracycline-induced disease or preexisting cardiac disease and attenuation of the cardioprotective actions of cardiac survival pathways synergize to create marked cardiotoxicity in patients receiving trastuzumab. Thus, aggressive use of this agent could test the time-worn dictum that physicians should do no harm.

References
8. Deleted in proof.
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