Cardiotoxicity in Patients Receiving Trastuzumab (Herceptin): Primary Toxicity, Synergistic or Sequential Stress, or Surveillance Artifact?

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Human epidermal growth factor receptor-2 (HER2) is a member of the epidermal growth factor receptor family, which produces factors that are considered to be important mediators of cell growth. Overexpression of HER2, which occurs in approximately 25% to 30% of human breast cancers, has fostered considerable interest in innovative therapeutic modalities designed to target tumor cells demonstrating such overexpression. Trastuzumab (Herceptin; Genentech, San Francisco, CA), a humanized monoclonal antibody developed to target the HER2 receptor, is the most widely studied example of such a modality. In early clinical studies with trastuzumab, cardiomyopathy was observed with a clinical expression similar to that seen with the anthracyclines (ie, a potentially progressive decrease in cardiac systolic function). A number of possible explanations for this cardiotoxicity are explored in this report. The first is that trastuzumab has inherent toxicity. This consideration has some theoretical interest, since fetal myocardial cells exhibit HER2 receptors and the adult myocardium expresses HER3 receptors. A second possibility is that sequential stresses following doxorubicin administration contribute to cardiac dysfunction. A third explanation is that observational artifacts lead to an overestimation of trastuzumab cardiotoxicity. Approaches for additional study of the extent and severity of trastuzumab cardiotoxicity are briefly addressed.

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HUMAN EPIDERMAL growth factor receptor-2 (HER2), also known as c-*erb*B-2 or HER2/*neu*, is a member of the epidermal growth factor receptor family of receptor tyrosine kinases, which are considered to be important mediators of cell growth, differentiation, and survival.[1] Overexpression or amplification of HER2 is present in a variety of human malignancies. HER2 overexpression is detectable in approximately 25% to 30% of human breast cancers and is most often caused by gene amplification.[2] However, overexpression of HER2 is not unique to breast cancer. It is also observed in other malignancies, including those arising from the uterine endometrium, pancreas, colon, ovaries, lungs, stomach, salivary glands, and head and neck tumors.

Results from a number of studies have suggested that breast cancers that overexpress HER2 have an increased growth rate of malignant cells. Patients with such tumors have a less favorable prognosis when treated with conventional chemotherapy compared with patients whose tumors do not overexpress HER2.[3] While the initial response to therapy may be similar, a significant decrease in the disease-free survival is often observed in patients with HER2 overexpression. This difference may be due in part to the relatively higher growth rates of tumors with HER2 overexpression.[4-6] Overexpression also appears to be associated with resistance to tamoxifen.[5] As therapeutic options may be more limited in patients with HER2 overexpression than in those without overexpression, innovative therapies capable of manipulating HER2 overexpression are of special interest to physicians caring for these patients.

Selective targeting and inhibition of HER2 using monoclonal antibody therapy is now under investigation. One such agent is trastuzumab (Herceptin; Genentech, San Francisco, CA), a humanized monoclonal antibody. Trastuzumab exhibits modest antineoplastic activity when used as a single agent in patients whose breast tumors overexpress HER2, but appears to have far greater potential, at least in some patients, when used in conjunction with established chemotherapy regimens. Anthracyclines are a mainstay of treatment for breast cancer. They are likely to be used in conjunction with trastuzumab and have been combined in a phase III multinational trial (see Shak et al, pp 71-77). The issue of cardiac damage

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associated with such regimens is a matter of increasing interest and is the focus of this report.

CARDIOTOXICITY OF TRASTUZUMAB

Preliminary information suggests that a decrease in cardiac systolic function is a clinical characteristic of trastuzumab cardiotoxicity. While little is known about the mechanism of this cardiotoxicity, a number of anecdotal observations may shed some light on this phenomenon. When trastuzumab alone was administered in three trials to groups of patients who had previously received standard chemotherapy, an increased incidence of suppressed cardiac systolic function was seen; the crude risk estimate at 12 months was estimated to be 0.03. When trastuzumab was given together with an anthracycline in one of these trials, this risk increased significantly to 0.26. The crude risk for patients in the randomly assigned anthracycline-only arm was intermediate at 0.06 (S. Shak, personal communication, November 1998). The suspected cardiotoxic reaction took the form of a decrease in systolic function, the same clinical manifestation seen with anthracyclines. The details of these various studies and the cardiac assessment used to generate these data are addressed in other reports in this supplement.

A superficial overview of these data suggests that trastuzumab is associated with low-grade cardiotoxicity, with significant positive additive or synergistic effects when administered concomitantly or sequentially with anthracyclines. The true nature of the cardiotoxic effects of trastuzumab, as well as the nature of the cardiotoxicity observed with the trastuzumab-doxorubicin combination, is clearly a much more complex issue that will require considerable additional study to be placed in clinical perspective.

Lessons From the Anthracyclines

The decrease in cardiac function reported in the preliminary trastuzumab studies has been evaluated predominantly by estimations of systolic function using nuclear multigated (MUGA) cardiac blood pool scans. Because congestive heart failure and a decrease in cardiac systolic function are the primary clinical characteristics of anthracycline toxicity, it is appropriate to review anthracycline cardiotoxicity and its clinical manifestations to gain insight into what may be a similar clinical scenario with trastuzumab. In the case of anthracyclines and anthraquinolones, the eventual destruction of myocytes is the final pathway leading to cardiac dysfunction. With regard to cardiac changes associated with trastuzumab, the mechanism is unknown and unexplored.

Doxorubicin cardiotoxicity. It has been well described that clinical cardiotoxicity of doxorubicin is rare at low cumulative doses but becomes increasingly more likely as the cumulative dose increases. The original correlation of cardiotoxicity and cumulative doxorubicin dose of $\geq$550 mg/m^2 was reported in 1973.[7] The cumulative-incidence curve, reported in 1979, is well known,[8] and suggested that approximately 5% of patients who received a cumulative dose of 550 mg/m^2 would be expected to develop symptoms of congestive heart failure.

Over the past 20 years, our group has performed a large number of clinical evaluations and noninvasive cardiac studies in patients who have received anthracyclines. These evaluations have been carried out for a variety of clinical indications, but the majority have been performed in an attempt to identify patients who had demonstrated premature cardiac changes at relatively low cumulative anthracycline doses. It was hoped that identifying such patients would allow us to administer higher cumulative doses to patients without premature cardiac dysfunction. This strategy has been largely unsuccessful. A comparison of the original cumulative dose-cardiotoxicity curve, defined before frequent noninvasive follow-up of patients, with a similar curve based on more recent cases has not allowed a higher cumulative dose as a consequence of heightened surveillance. What has been shown is that doxorubicin is considerably more toxic than had been previously thought and that the cumulative dose associated with a 5% risk of congestive heart failure is approximately 400 mg/m^2.[8] The only clear benefit of careful scrutiny of a very large group of doxorubicin-treated patients was the discovery of cardiotoxicity when it would otherwise have gone unrecognized. Although the information gained from this surveillance did not allow us to use higher doses of the drug, it has clearly demonstrated that it is prudent to use less.[9-11]

Noninvasive tests for evaluating cardiac dysfunction. In screening for cardiotoxicity with tests measuring cardiac systolic function, two additional factors became evident: the tests were imperfect

and the cancer patient population being observed for anthracycline-related cardiotoxicity is uniquely unsuited for such evaluation.

Most determinations of systolic function use either nuclear imaging blood pool scans or echocardiography. Both of these techniques have their proponents, but neither is clearly recognized to be superior. When performed with great care, both techniques have considerable predictive value, but they are not infallible; some false-positive and false-negative results cannot be avoided. If the criteria for positivity of results are selected narrowly, some patients with cardiac dysfunction will not have positive results; if the criteria are selected too broadly, some patients who do not have cardiac dysfunction will be reported as having a positive result. Most nuclear medicine centers would be pleased if their technique was sufficiently precise and their reporting criteria appropriately selective so that a predictive value of 90% could be achieved in any given clinical setting. In centers that perform most of their nuclear cardiology procedures in patients with coronary artery disease, for whom the nuclear test offered is often a screening test, false-negative results may be considered a greater risk for patients than false-positive results because patients with positive test results will be further assessed with additional, usually invasive procedures. Such a bias may result in overreporting of false-positive versus false-negative results in anthracycline-treated patients.

Fortunately, anthracycline-associated clinical cardiotoxicity is rare at low cumulative doses. At cumulative doses of less than 300 mg/m^2, the probability of a doxorubicin-treated patient having cardiotoxicity is approximately 1%; at a 90% predictive value, a positive test report implies that for each true-positive result there will be nine false-positive results. With the likelihood of cardiotoxicity associated with a cumulative doxorubicin dose less than 300 mg/m^2 and the uncertainty of the test procedure, the test is totally useless as either a screening or diagnostic test for the desired clinical application. If the test could be improved to the 95% predictive value level, there would still be many more false-positive than true-positive results, suggesting cardiotoxicity. Even at a cumulative dose of 450 mg/m^2, the test must be evaluated with great caution.

Another factor contributing to the clinical problems of functional tests in the evaluation of doxorubicin cardiotoxicity is more complex and cannot be explained by simple statistical analysis. The normal physiologic variation seen in any given patient over time is augmented in the cancer patient by the disease process itself and its inherent pathologic turmoil that alters metabolism, as well as by the effects of the antineoplastic treatments administered. These effects are often further augmented or diminished by the impact of supportive care therapies. Changes in the hemoglobin level, the presence of effusions, nutritional status, alterations in activity level, decreases in muscle mass, and hormonal effects all tend to increase or decrease the ejection fraction independent of heart rate. We have not yet learned how to neutralize these effects to obtain a pure therapy-dependent change in ejection fraction that can be evaluated independently. Unfortunately, these effects tend to cluster as the patient's disease worsens. Thus, the greater the need for an accurate determination of ejection fraction in a cancer patient, the more difficult it may be to make useful and accurate observations from the deceivingly precise numbers often generated through the use of noninvasive studies. Nowhere has this been as clearly demonstrated as in the evaluation of anthracycline cardiotoxicity.

Cardiac biopsies. The heart has considerable compensatory reserves, and the results of cardiac function tests often remain unchanged despite cardiac damage and structural alteration of cardiac muscle. Morphologic evaluation overcomes some of the problems of quantifying anthracycline cardiotoxicity, especially at relatively low cumulative doses, where spurious false-positive results are likely to appear and compensatory mechanisms may mask subtle changes in cardiac function. Morphologic changes in myocardial cells caused by anthracyclines have been well described.[12] At low cumulative anthracycline doses, vacuole formation may be noted; at higher cumulative doses, myofibril dropout and frank necroses are seen. The actual grading follows a scale ranging from 0 to 3, and may include half-steps in grade. The alterations detected by electron microscopy are clearly seen and quite specific.

Cardiac changes can be detected far earlier by biopsy than with noninvasive screening tests. Biopsy results, especially in patients who have received relatively low doses of cardiotoxic drugs, have a far greater predictive value than those of

functional tests. Unlike functional tests, however, a biopsy does not detect the effects of other factors that may influence cardiac performance. While the biopsy may only detect a minimal change caused by an anthracycline, a MUGA scan may also determine the effects of coexisting ischemic and nonanthracycline-producing myopathic consequences, which may result in a substantial clinical effect. When a biopsy is used to make clinical decisions, the information from the biopsy is often used together with the results of functional tests and clinical observations.[9]

The primary role of a cardiac biopsy is to compare the relative toxicity of various anthracyclines and cardioprotective strategies. The biopsy allows such comparisons to be made at lower cumulative doses than would otherwise be possible and with a considerably smaller sample size. Cardiac biopsy is also useful in selected clinical situations in which the etiology of cardiac dysfunction is in question, and the decision to stop or continue cardiotoxic chemotherapy is crucial.

Cardiac biopsies are clearly invasive as well as expensive. In experienced hands, however, they are safe: no deaths from cardiac biopsy were reported in a series of 1,350 consecutive studies performed in patients with cancer.[13] Cardiac biopsy offers a unique opportunity to explore cardiac damage in an objective, focused way at a much earlier phase of treatment than is possible with other techniques.

Trastuzumab Cardiotoxicity

Detailed and conclusive studies of trastuzumab cardiac effects have not been carried out. Preliminary trials have identified a number of patients who have experienced cardiotoxicity associated with administration of the drug. In a phase III comparative trial of patients with metastatic breast cancer who were treated with either chemotherapy alone or chemotherapy plus trastuzumab, cardiac dysfunction was noted in 6% of patients in the doxorubicin-alone arm and in 27% of patients in the doxorubicin plus trastuzumab arm. For the purposes of this study, cardiotoxicity was defined as (1) cardiomyopathy, characterized by a decrease in cardiac ejection fraction associated with abnormal myocardial wall motion that was either global or more severe in the septum; (2) symptoms of congestive heart failure; (3) associated signs of congestive heart failure including but not limited to a diastolic gallop and/or tachycardia; or (4) a decline in cardiac ejection fraction from baseline of at least 5 percentage points to below 55% with signs and symptoms or a decrease in cardiac ejection fraction of at least 10 percentage points to below 55% without signs and symptoms (S. Shak, personal communication, November 1998).

A number of hypotheses regarding the observed toxicity can be considered. The first is that trastuzumab has inherent toxicity. Thus, like the anthracyclines, it is independently cardiotoxic. The second hypothesis is that the drug amplifies the cardiotoxic effect or has an additive or expressive toxic effect when given together or sequentially with anthracyclines or other agents that have inherent toxicity. A third hypothesis is that the described toxicity of trastuzumab represents some form of observational artifact. A combination of these possibilities (ie, additive effects plus inherent toxicity) may also occur. The three possible explanations will be considered in their pure form.

Inherent trastuzumab cardiac toxicity. Larger doses of the drug, longer periods of observation, or more sensitive cardiac testing will be needed to demonstrate, confirm, and quantify any inherent trastuzumab toxicity. The mechanism underlying the reported cardiac changes, if they in fact exist, is unknown. There have been no reported evaluations of cardiac biopsy in patients who have received trastuzumab without other agents; only infrequent decreases in the ejection fractions of these patients have been reported. Based on the limited data at hand, it seems unlikely that inherent cardiac toxicity will be a significant limiting factor in the clinical use of trastuzumab.

Toxic sequelae related to additive or sequential effects of trastuzumab with anthracyclines or other agents exhibiting inherent toxicity. The natural history of anthracycline cardiotoxicity is complex. A simple explanation of the variation among patients in susceptibility to toxic reactions is not available, and much is yet to be learned as to why some patients experience cardiotoxicity sooner than others following exposure to the anthracycline. One explanation is that sequential stresses play a role in the clinical spectrum of toxicity.[14] Our group has hypothesized that subclinical damage occurs on or shortly after exposure to the toxic agent. However, while apparent at an ultrastructural level, this damage is not easily detectable with conventional methods of studying cardiac

changes in the clinical setting. Cardiac reserves and compensatory mechanisms may mask the damage until the ability to compensate becomes compromised. It is possible that the cardiac changes noted with trastuzumab may represent some form of sequential stress on a previously altered myocardium or an inhibition of an ongoing repair mechanism. In the studies noted above, the great majority of patients who experienced changes in cardiac parameters following trastuzumab administration had been previously exposed to doxorubicin. The sequential stresses or inhibited repair may not necessarily be caused by the administration of trastuzumab, but may be related to one or a combination of several secondary metabolic effects seen following such administration (eg, electrolyte shifts or fluctuations in circulating biologic mediators).

Observational artifacts as an explanation for trastuzumab cardiotoxicity. The pitfalls regarding the recognition of a possible cardiotoxic effect in patients who have received prior cardiotoxic medication with a widely variable expression were alluded to above. Moreover, the underlying disease often mimics the very signs and symptoms used to define the nature of cardiotoxicity when studied by methods of suboptimal predictive value, discussed above. Clearly, focused surveillance will increase the likelihood of finding signs and symptoms of cardiotoxicity in any study population. This form of study artifact must be considered in any objective overview of the relationship between trastuzumab and the clinical recognition of cardiotoxicity.

SUMMARY AND CONCLUSIONS

This report has discussed the possible nature of cardiotoxicity associated with trastuzumab. The task of placing this new, potentially important agent into perspective would have been facilitated and the end-product would have been more useful had the drug been uniformly studied and cardiac changes been analyzed by methods with better predictive value. This luxury, however, is not available. Nevertheless, we can apply some of what we know about the observed cardiac changes in patients who received trastuzumab and can offer some suggestions for future paths to explore.

If trastuzumab demonstrates inherent toxicity, it will probably be best detected in clinical studies using cardiac biopsies evaluated by a pathologist who is highly trained in recognizing and grading cardiac changes. It is possible that the morphologic changes caused by trastuzumab may be different from those caused by anthracyclines; this possibility should be actively investigated. As with anthracyclines, a combination of functional and morphologic parameters may be more useful than either modality alone for detecting cardiotoxicity.

Sequential stresses caused by trastuzumab and observational artifacts of the clinical data will be much more difficult to evaluate than inherent toxicity. Sequential stresses involve two or more variables with very different biological and clinical expression that occur simultaneously; detection of observational artifacts will require large, blinded studies. Again, a combination of biopsy and functional determinations may offer the best chance of gaining insight into these problems.

A better understanding of trastuzumab cardiotoxicity is essential, as a large number of patients who received prior treatment with anthracyclines are likely to benefit from this interesting new agent. The true risk of toxicity must be defined if our patients are to enjoy maximal benefit from these new treatment strategies without undue iatrogenic complications.

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