Original Article

Trastuzumab-Related Cardiac Dysfunction

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Key Words

Trastuzumab, HER2, cardiotoxicity, congestive heart failure, troponin I

Abstract

The use of trastuzumab in the adjuvant and metastatic treatment of breast cancer is associated with both symptomatic and asymptomatic cardiotoxicity. The long-term significance of these events, isolating known cardiotoxic effects of anthracyclines from those of trastuzumab, and the appropriateness of referring to trastuzumab-related cardiotoxicity as reversible rather than responsive to trastuzumab withdrawal and heart failure medical therapy, are issues that continue to be debated. This article provides an overview of the available cardiac safety data from the major trastuzumab clinical trials in breast cancer, highlighting areas of ongoing controversy. Important recent data documenting the occurrence and prognostic use of cardiac troponin I elevations among patients treated with trastuzumab are placed into context with the mechanistic insight these data provide and the implications for clinical practice today. (*JNCCN* 2011;9:243–249)

Trastuzumab, a humanized monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER2), has dramatically impacted the natural history of HER2-positive breast cancer in both the metastatic and early-stage disease settings. After its initial FDA approval in 1998 for first-line treatment of HER2-positive metastatic breast cancer in combination with paclitaxel, a series of pivotal adjuvant studies documented statistically significant improvements in both disease-free and overall survival when trastuzumab was added to standard chemotherapy.[1–3]

The pivotal phase III trial in metastatic breast cancer involving trastuzumab in combination with doxorubicin and cyclophosphamide or paclitaxel chemotherapy provided the first indication of potential cardiotoxicity risk associated with this agent.[4] An independent Cardiac Review and Evaluation Committee was subsequently convened to retrospectively review the cardiotoxicity data for patients treated with trastuzumab on 7 phase II and III clinical trials.[5]

This analysis documented that the combination of doxorubicin and cyclophosphamide (AC) alone was associated with an 8% rate of cardiac dysfunction and a 4% rate of New York Heart Association (NYHA) class III/IV heart failure. When trastuzumab was combined with concurrent AC chemotherapy, the overall cardiac dysfunction rate climbed to 27% and the rate of symptomatic NYHA class III/IV heart failure was 16%. The addition of trastuzumab to paclitaxel resulted in a cardiac dysfunction rate of 13% and an NYHA class III/IV heart failure rate of 2%.

This concern for cardiotoxicity greatly influenced the development of subsequent adjuvant trials in that concurrent anthracyclines and trastuzumab use was avoided and strict cardiac exclusion criteria were incorporated. Rigorous prospective cardiac monitoring was performed and interim cardiac safety analyses were included that would have triggered termination of accrual if an absolute difference of more than 4 percentage points in the incidence of severe congestive heart failure or cardiac death was observed between the trastuzumab and nontrastuzumab arms. With these safeguards in place, the adjuvant trials uniformly showed a difference in the rate of cardiac death and severe congestive heart failure between the trastuzumab- and non–trastuzumab-treated

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patients of less than 4%. Although the low rates of severe cardiotoxicity were reassuring, a large number of patients on these trials experienced some form of cardiotoxicity, generally an asymptomatic decline in left ventricular ejection fraction (LVEF), which ultimately required discontinuation of trastuzumab.

This topic has continued to be of great interest, and several questions continue to be debated, particularly the long-term significance of these events, isolating known cardiotoxic effects of anthracyclines from those of trastuzumab, and the appropriateness of referring to trastuzumab-related cardiotoxicity as reversible rather than responsive to trastuzumab withdrawal and heart failure medical therapy.[6] This article provides an overview of the available cardiac safety data from the adjuvant trastuzumab clinical trials in breast cancer, highlighting areas of ongoing controversy. Important recent data documenting the occurrence and prognostic utility of cardiac troponin I elevations among patients treated with trastuzumab will be placed into context with the mechanistic insight this data provides and the implications it carries for clinical practice today.

Cardiotoxicity Data From the Adjuvant Trials

Four large randomized trials of adjuvant trastuzumab have been reported, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, Herceptin Adjuvant (HERA), and Breast Cancer International Research Group (BCIRG) 006 trial.[1–3] Two additional studies, the Finland Herceptin (FinHer) and Programme Adjuvant Cancer Sein (PACS) 04 trials, randomized a subset of patients with HER2-positive early-stage breast cancer to receive trastuzumab or not.[7,8] NSABP B-31 (n = 2006) randomized patients to receive AC followed by paclitaxel with or without trastuzumab initiated concurrently with the paclitaxel and continued for 1 year. NCCTG N9831 (n = 3505) included the same 2 arms, but also included a third arm in which the trastuzumab was initiated sequentially after completion of all chemotherapy and continued for 1 year. The HERA study (n = 5102) evaluated 1 or 2 years of adjuvant trastuzumab monotherapy initiated after the completion of (neo)adjuvant chemotherapy and adjuvant radiotherapy versus observation. BCIRG 006 (n = 3222) contained 3 arms, including AC followed by docetaxel, with or without 1 year of trastuzumab initiated concurrently with the docetaxel, and a third nonanthracycline arm that examined concurrent docetaxel, carboplatin, and trastuzumab for 6 cycles with trastuzumab continued to complete 1 year of therapy. The FinHer study evaluated a 9-week course of trastuzumab administered concurrently with docetaxel or vinorelbine followed by fluorouracil, epirubicin, and cyclophosphamide (FEC) compared with the same chemotherapy alone in a subset of HER2-positive patients (n = 232). PACS 04 randomized a subset of HER2-positive patients (n = 528) to 1 year of trastuzumab or observation after completion of FEC or epirubicin plus docetaxel chemotherapy.

Serial prospective cardiac monitoring with multiple gated acquisition (MUGA) scan or echocardiography was performed in all studies, although defined criteria for cardiac events have important differences.[6] Great emphasis was placed on capturing the occurrence of severe symptomatic congestive heart failure or cardiac death, which resulted in an underappreciation of the more common but less severe forms of cardiotoxicity. Furthermore, prospective capture of cardiac safety data over time was hindered by the limited posttreatment evaluations of cardiac function in NSABP B-31 and NCCTG N9831, in which the last per-protocol cardiac evaluation occurred 18 months from randomization.

Table 1 details the adjuvant trastuzumab cardiotoxicity data from the NSABP B-31, NCCTG N9831, HERA, BCIRG 006, FinHer, and PACS 04 trials. In the NSABP B-31, NCCTG N9831, HERA, and BCIRG 006 trials, the difference in the rate of cardiac death and severe congestive heart failure was less than a 4% between the trastuzumab- and non–trastuzumab-treated patients. Despite this, trastuzumab was permanently discontinued for cardiac reasons in a far greater number of patients in these studies. For example, 14% patients in the NSABP B-31 trial had trastuzumab discontinued because of confirmed asymptomatic decreases in LVEF; approximately 31% had trastuzumab either temporarily or permanently held for cardiac reasons.[9] This trend was similarly seen in the other trials, although rates of symptomatic and asymptomatic cardiotoxicity were lower when trastuzumab was given sequentially after chemotherapy (Arm C of N9831, HERA, and PACS

Table 1 Summary of Cardiotoxicity Data From the Adjuvant Trastuzumab Trials

End Point	NSABP B-31[1,9,24]	NCCTG N9831[1,12]	HERA[3,13]	BCIRG 006[2,11]	FinHer[7,10]	PACS 04[8]
Cardiac death and severe CHF	Cardiac event rate: NYHA III/IV HF or death from cardiac causes *At 3 years:* Co: 0.8% H: 4.1% *At 5 years:* Co: 0.9% H: 3.8%	Cardiac event rate: NYHA III/IV HF or death from cardiac causes *At 3 years:* Co: 0.3% AC → TH: 3.3% AC → T → H: 2.8%	Cardiac death Co: 0.06% H: 0% Severe HF (NYHA III/IV symptoms and LVEF < 50% with a decrease of ≥ 10% from baseline) *At 3.6 years:* Co: 0% H: 0.8%	Cardiac death AC → D: 0% AC → DH: 0% DCpH: 0% Grade 3/4 HF AC → D: 0.7% AC → DH: 2.0% DCpH: 0.4%	Cardiac death Co: 0% H: 0%	Cardiac death Co: 0% H: 0%
Symptomatic CHF	Patients with symptoms of cardiac dysfunction not meeting criteria for a cardiac event at 3 years Co: 1% H: 5.1%	NA	Symptomatic HF, including severe HF (any degree of symptoms and LVEF < 50% with decrease of ≥ 10% from baseline at any time) *At 3.6 years:* Co: 0.1% H: 1.9%	NA	Symptomatic HF Co: 1.7% H: 0.9%	Symptomatic HF Co: 0.4% H: 1.5%
Decrease in LVEF	Confirmed asymptomatic decrease in LVEF requiring discontinuation of trastuzumab H: 14%	Confirmed asymptomatic decrease in LVEF requiring discontinuation of trastuzumab AC → TH: 6.6% AC → T → H: 5%	Confirmed decrease in LVEF (LVEF < 50% with absolute decrease of ≥ 10% from baseline) *At 3.6 years:* Co: 0.6% H: 3.6%	Patients with > 10% relative LVEF decline from baseline AC → D: 11% AC → DH: 19% DCpH: 9%	Patients with ≥ 1 measurement of LVEF > 15 % below baseline Co: 6.0% H: 3.5% Patients with drop in LVEF > 10% resulting in LVEF < 50 Co: 2.6% H: 0%	Asymptomatic LVEF decrease to < 45% Co: 1.5% H: 3.8%

Abbreviations: AC, doxorubicin, cyclophosphamide; BCIRG, Breast Cancer International Research Group; Co, control; CHF, congestive heart failure; Cp, carboplatin; D, docetaxel; FinHer, Finland Herceptin; H, trastuzumab; HERA, Herceptin Adjuvant trial; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not available; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; NYHA, New York Heart Association; PACS, Programme Adjuvant Cancer Sein; T, paclitaxel.

04) as opposed to concurrent with chemotherapy. In the FinHer trial, cardiac end points assessed among patients receiving the short 9-week course of trastuzumab compared favorably with those of the control group.[7,10] Similarly, the nonanthracycline arm of docetaxel, carboplatin, and trastuzumab in BCIRG 006 documented that this therapy could be delivered with rates of cardiotoxicity that approximated those among the nontrastuzumab-, anthracycline-treated control subjects.[2,11] In the NSABP B-31 and NCCTG N9831 trials, clinical risk factors for heart failure included age of 50 years or older, requirement for hypertension medications, and post-AC LVEF values of 50% to 54%.[9,12]

Detailed cardiac follow-up data among patients experiencing adverse cardiac events have been reported for NSABP B-31 and HERA.[9,13,14] These data are especially valuable because they offer insight into the natural history of trastuzumab-related cardiotoxicity. Among 31 patients who received trastuzumab and developed a cardiac event in NSABP B-31, 27 were followed up for 6 or more months after their diagnosis of heart failure. Although 26 were reported to be asymptomatic for at least 6 months, 18 of these

(67%) continued to receive cardiac medications. Among these patients with an LVEF measurement 6 months or more from their diagnosis of heart failure, 17 of 24 (71%) had a sustained decrease in LVEF relative to their baseline (range, 25%–69%). Among 102 patients who had trastuzumab discontinued because of a confirmed asymptomatic decrease in LVEF, 13 of 52 (25%) had a LVEF less than 50% when reassessed 6 months or more after discontinuation.

Some of the most informative follow-up data comes from the HERA study, in which prospective cardiac evaluations were performed at baseline and at 3, 6, 12, 18, 24, 30, 36, and 60 months from randomization.[13] Among 73 patients experiencing a cardiac end point (13 with severe heart failure and 60 with a confirmed significant LVEF decrease), 59 (80.8%) experienced acute recovery defined as 2 or more sequential LVEF assessments of 50% or greater after the date of first reaching the cardiac end point. Among patients with severe heart failure and confirmed significant LVEF declines, 31% and 17%, respectively, did not reach acute recovery. More concerning was the longer follow-up data (range, 2.5–51.6 months), documenting that 17 of 59 (28.8%) of patients classified as experiencing acute recovery had subsequent LVEF declines to less than 50% after acute recovery.

Is Trastuzumab-Related Cardiotoxicity Reversible?

Although many refer to trastuzumab-induced cardiotoxicity as a reversible form of cardiotoxicity distinct from the dose-related cardiotoxicity of the anthracyclines, available data suggest that this view may be overstated.[15,16] Historical data suggest that anthracycline-induced cardiotoxicity is associated with an extremely poor prognosis and is often treatment-refractory.[17]

A recent study evaluated the response of patients with symptomatic and asymptomatic (LVEF ≤ 45%) anthracycline-induced cardiotoxicity to prompt initiation of modern heart failure therapy consisting of an angiotensin-converting enzyme (ACE) inhibitor and β-blocker.[18] Responders to therapy were those who experienced an increase in LVEF to 50% or greater; partial responders had an increase in LVEF of at least 10 percentage points with an LVEF still less than 50%; and nonresponders had an LVEF increase fewer than 10 percentage points and did not reach the recovery threshold of 50%. In this study, a short time to initiation of heart failure therapy was an independent predictor of LVEF recovery. Overall, 42% of patients were responders, 13% were partial responders, and 45% were nonresponders.

These data are not markedly different from those of a recent study of trastuzumab-induced cardiotoxicity showing recovery to an LVEF greater than 50% in 60% of patients (25 of 62), and lack of recovery in 40% (17 of 42) after withdrawal of trastuzumab and initiation of heart failure therapy with an ACE inhibitor and β-blocker.[19]

With trastuzumab-induced cardiotoxicity, isolating the cardiac effects of trastuzumab is often confounded by the fact that most women with early-stage HER2-positive breast cancer also receive anthracyclines as part of their adjuvant treatment. Experts have suggested that myocyte necrosis caused by the anthracycline injury is the primary mediator of cardiotoxicity when anthracyclines and trastuzumab are given together, trastuzumab inhibiting normal cellular repair and thus modulating the normal repair response to the anthracycline injury.[15]

However, recent data from one of the most important studies on trastuzumab-induced cardiotoxicity to date are not consistent with that hypothesis. Cardinale et al.[19] repeatedly assessed the serum marker troponin I pre- and post-dose in a series of 251 patients receiving trastuzumab in the adjuvant and metastatic treatment of breast cancer. Although 78% of patients enrolled had received prior anthracyclines, 19 +/– 27 months had elapsed since the receipt of the anthracycline, and patients were treated with trastuzumab monotherapy or trastuzumab in combination with a taxane, vinorelbine, capecitabine or cyclophosphamide, and methotrexate, thus enabling an analysis focused on troponin I elevation during trastuzumab therapy. In this study, 42 of 251 (17%) patients experienced trastuzumab-induced cardiotoxicity defined as an LVEF decrease of greater than 10 percentage points and below 50%. Only 7 of 251 experienced overt heart failure. Troponin I was elevated in 36 of 251 (14%) of patients overall at some time point, with 7 of 36 (14%) having a baseline elevation before trastuzumab initiation. Troponin I was elevated in 26 of 42 (62%) of patients experiencing trastuzumab-induced cardiotoxicity compared with 10 of 209 (5%) who did not ($P < .001$). Troponin I elevations occurred soon after

initiation of trastuzumab in most cases, with subsequent trastuzumab-induced cardiotoxicity occurring 1 to 8 months from the date of the first detectable troponin I.

Consistent with other studies primarily evaluating effects of anthracyclines, the troponin I elevations were mainly transient and low-level 0.31 +/– 0.45 ng/mL. In multivariate analyses, troponin I was the strongest independent predictor of cardiotoxicity (hazard ratio, 17.5 [8.85–35.0]; $P < .001$) and prior anthracycline treatment did not meet statistical significance as an independent predictor in this study (hazard ratio, 3.25 [0.93–11.4]; $P = .066$). The observation that troponin I elevations were seen shortly after initiation of trastuzumab and at a significant period of time after initial anthracycline exposure, documents most unequivocally that the intrinsic cardiotoxicity of trastuzumab is real and results in myocyte necrosis. Troponin I is released from a cardiomyocyte when it is irreversibly injured.[20] Hence, as is the case with anthracyclines, real damage is occurring any time troponin I is detectable. Although the ejection fraction often recovers to normal levels after a cardiotoxic insult (often with initiation of medical therapy), this does not mean that the heart is fully recovered.[21] With all other forms of cardiac insults (e.g., myocardial infarction, myocarditis), the heart remains more susceptible to further insults even if the overall ejection fraction has recovered to normal. Therefore, the authors of this review suggest that the term *reversible* be avoided when discussing trastuzumab-induced cardiotoxicity because it is not accurate based on available data and is open to significant misinterpretation. Although the findings of Cardinale et al.[19] are important and provocative, further confirmatory studies on the use of troponin I as a predictor of trastuzumab-induced cardiotoxicity are necessary.

Optimizing Cardiotoxicity Detection and Treatment

For patients initiating therapy with trastuzumab, obtaining a baseline assessment of cardiac function with either MUGA or echocardiography is standard care. With the use of the adjuvant regimen of AC followed by paclitaxel and trastuzumab, a repeat assessment of cardiac function after doxorubicin and before the initiation of trastuzumab is important, because the NSABP B-31 trial showed that approximately 6.6% of patients had significant declines in ejection fraction after doxorubicin (LVEF less than the lower limit of normal or a ≥ 16% decline from baseline).[9] The authors' practice is to assess cardiac function every 3 months during treatment. Trastuzumab should be discontinued if symptomatic cardiac dysfunction develops. Experts generally agree that trastuzumab should be held in cases of significant asymptomatic LVEF declines (≥ 16% decrease from baseline or 10%–15% decrease from baseline to a value below the lower limit of normal).[22] The authors' practice is to reassess the LVEF at 4 weeks and permanently discontinue trastuzumab if the cardiac function fails to improve to a level above the hold criteria.

Patients with symptomatic left ventricular systolic dysfunction and those with persistent asymptomatic declines in cardiac function should have trastuzumab permanently discontinued. These patients should be promptly referred to a cardiologist and standard medical heart failure therapy with an ACE inhibitor, and β-blocker should be initiated. The 2005 American College of Cardiology/American Heart Association Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult supports continuation of medical heart failure therapy indefinitely for the indication of both symptomatic and asymptomatic left ventricular dysfunction.[21] Despite limited reports of successful reintroduction of trastuzumab in patients with metastatic breast cancer who developed cardiotoxicity,[16,23] the risk in the adjuvant setting is too great, and rechallenging with trastuzumab is not recommended after symptomatic cardiac events or after documentation of persistent LVEF drops.[22]

Recent data suggest that serial serum troponin I assessment is an extremely powerful strategy to monitor patients on trastuzumab, with a positive predictive value of 65% and a negative predictive value of 100%.[19] Not only was it prognostic in this study, it was predictive of subsequent trastuzumab-induced cardiotoxicity that occurred 1 to 8 months after the troponin I elevation. An important point to consider regarding this study is that troponin I was measured before and shortly after each dose of trastuzumab. Whether these results would have been observed if the troponin I was measured only once per cycle predose is unknown and this has important implications

for more widespread clinical application because it can be logistically challenging to have blood redrawn on another day after undergoing chemotherapy treatment in the outpatient setting. It is also important to note that the threshold level of troponin I positivity (> 0.08 ng/mL in the Cardinale et al.[19] study) for the detection of chemotherapy-related cardiotoxicity is far below threshold used for detection of a myocardial infarction and therefore an ultrasensitive troponin I assay must be used if this monitoring strategy is to be accurately followed. Assuming these technicalities can be followed and the logistical hurdles overcome, the authors believe that troponin I monitoring for detection of subsequent cardiac dysfunction in patients undergoing trastuzumab therapy is appropriate and supported by data. Although the Cardinale data provided proof-of-principle that serum troponin I monitoring can be useful as a prognostic and predictive tool for detecting trastuzumab-induced cardiotoxicity, confirmatory studies are needed and further assessment of the most appropriate serum sampling times will be important in the optimization of this strategy for outpatients treated with trastuzumab in the adjuvant and advanced disease settings. An ongoing area of debate relates to the role of cardiac monitoring beyond the period of active treatment, an issue particularly pertinent to patients with early-stage breast cancer. Further follow-up data from the HERA trial will contribute to answering this important question, particularly because the potential for LVEF recovery is closely tied to early initiation of medical therapy for heart failure.

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