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Cardiotoxicity Associated with Trastuzumab Treatment of HER2+ Breast Cancer

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ABSTRACT

Introduction: Although having high clinical efficacy in the treatment of human epidermal growth factor receptor-2 (HER2+) metastatic breast cancer, trastuzumab has been associated with cardiotoxicity, and the etiology and pathogenesis of this condition is currently under investigation. ***Methods:*** This paper reviews the cardiotoxicity, associated with trastuzumab use and discusses the risk assessment and management of cardiac dysfunction. ***Results:*** The increased risk of cardiotoxicity is lower when trastuzumab is given as monotherapy (3%-7%) compared with anthracyclines + trastuzumab therapy (27%). Type II cardiac changes occur in trastuzumab-treated patients, which do not appear to be dose-related, are not associated with histological changes, and are generally reversible. Several risk factors for cardiac events have been identified and assessing levels of troponin I and N-terminal pro-brain B-type natriuretic peptide before and after treatment with trastuzumab may allow early detection of cardiotoxicity. A symptomatic and functional evaluation scheme for patients indicated for treatment with trastuzumab has also been proposed to work alongside therapeutic options for the treatment of heart failure. ***Conclusion:*** The risk of cardiac dysfunction associated with trastuzumab can be justified given the increase in overall survival. This risk is lower when trastuzumab is given as monotherapy. The paradigm for cardiologists remains the same: treat the cancer effectively whilst preventing cardiotoxicity.

Keywords: breast cancer; cardiotoxicity; HER2+; trastuzumab

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INTRODUCTION

Major breakthroughs have been achieved in the treatment of breast cancer, both in metastatic disease and in the adjuvant treatment of the early stages of the disease.[1] About 20%-25% of breast cancers present with either overexpression of human epidermal growth factor receptor-2 (HER2) and/or amplification of the HER2 gene,[2] also known as erbB2 or HER2/*neu*. Clinically, these HER2+ tumors behave aggressively and are associated with poor prognosis.[3]

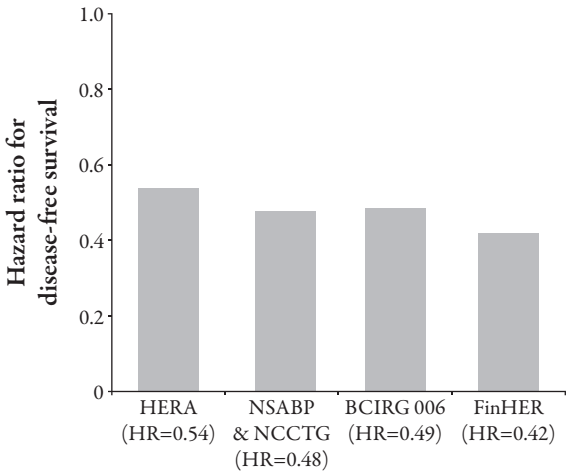
HER2 is a member of the family of epidermal growth factor receptors in which cellular signaling is mediated through the activation of tyrosine kinase and is associated with increased proliferation and cell survival.[4]

Trastuzumab is one of a group of smart drugs ("magic bullets"). It is a monoclonal antibody that binds selectively to HER2 and initially showed high clinical efficacy in the treatment of metastatic HER2+ breast cancer, either as monotherapy, in patients already treated with one or more regimens of chemotherapy, or in combination with taxanes (paclitaxel and docetaxel) in patients who have not undergone prior chemotherapy.[5-8] Trastuzumab is the most significant drug to be introduced as therapy for this type of more aggressive breast cancer, leading to a significant improvement in the overall objective response rate, disease-free survival in the adjuvant setting, and overall survival rates.[6-8]

Trastuzumab was approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of metastatic breast cancer. In 2006, the FDA expanded the approval to include adjuvant treatment of HER2+ breast cancer; since then it has become a fundamental part of HER2+ breast cancer therapy.[9] However, trastuzumab has a serious side effect that could limit its utility in some patients. Results of early studies of metastatic disease and, in particular, those with trastuzumab in combination with anthracyclines, indicated a surprisingly high incidence of congestive heart failure (27%), although trastuzumab was very well tolerated.[7] From a retrospective analysis of 218 metastatic breast cancer patients who received trastuzumab for at least 1 year, Guarneri et al.[10] found that 28% of patients had a cardiac event (compared with the 8% in those receiving anthracyclines alone). So the concurrent use of anthracyclines and trastuzumab has thus been abandoned. With this knowledge, subsequent trials, particularly those in the adjuvant setting, avoided the concurrent use of anthracyclines and trastuzumab therapy and included careful baseline and serial monitoring of cardiac function.

An analysis of five large, randomized studies that investigated the use of adjuvant therapy with trastuzumab in combination with chemotherapy in early HER2+ breast cancer was recently presented.[11] With an average follow-up of 12-28 months, the clinical studies Herceptin Adjuvant (HERA), National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31), North Central Cancer Treatment Group N9831 (NCCTG N9831), Breast Cancer International Research Group 006 (BCIRG 006), and Finland Herceptin trials (FinHER) showed that treatment with trastuzumab added to standard chemotherapy was associated with an approximately 50% reduction in breast cancer recurrence and a 33% reduction in the risk of death (Figure 1).[11-14]

Figure 1. Trastuzumab efficacy analysis in five clinical studies.[11] BCIRG 006=Breast Cancer International Research Group 006; FinHER=Finland Herceptin; HERA=Herceptin Adjuvant; HR=hazard ratio; NCCTG=North Central Cancer Treatment Group; NSABP=National Surgical Adjuvant Breast and Bowel Project. Reprinted with permission from Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol. 2007;25:3525-3533. © 2008 American Society of Clinical Oncology. All rights reserved.



A review of these randomized clinical trials in the adjuvant setting found that up to 4% of all patients will develop objective evidence of cardiac dysfunction and 1% will develop symptomatic heart failure.[1,3,14] The risk of severe heart failure ranged from 0.6% in the HERA trial to 4.1% in NSABP B-31, but important differences regarding cardiotoxicity definitions and inclusion/exclusion criteria make direct comparisons difficult.

Currently left ventricular ejection fraction (LVEF) is the reference standard for monitoring cardiac function with the use of trastuzumab, but this technique is relatively insensitive. New monitoring methods, for example, N-terminal pro-brain B-type natriuretic peptide (NT-proBNP) and troponin I measurements, can detect cardiac damage at an earlier stage so may prove more suitable.

CHEMOTHERAPY-ASSOCIATED CARDIOTOXICITY

Anthracyclines are classic chemotherapy drugs, used in the treatment of breast cancer; however, it is also well established that they present a high-dose cumulative cardiotoxicity risk.[15] Several risk factors increase this risk, such as previous or concomitant radiotherapy, age >60 years, and the existence of previous heart disease or hypertension.[16] Type I cardiac changes are observed in anthracycline-associated cardiotoxicity. These histological changes have been well documented in electron microscopy studies of heart biopsies and are characterized by disorganization of myofibrils and vacuoles and necrosis, and are generally irreversible.[2,17] More recently with the introduction of therapy with monoclonal antibodies, such as trastuzumab, type II cardiac changes have been described.[18] Unlike the type I changes associated with anthracycline therapy, these type II changes do not appear to be dose-related, are not associated with histological changes, and the cardiac dysfunction is usually transient and reversible.[9,14]

Risk factors for the development of cardiac dysfunction in patients treated with trastuzumab have been identified.[19] Previous or concurrent treatment with anthracyclines or paclitaxel and the previous existence of heart disease, with a low LVEF, may increase the risk of trastuzumab cardiotoxicity.[19] Other factors that may contribute are age >60 years and obesity (Table 1).[20] Cardiotoxicity has also been observed with the use of other drugs directed to the HER2 receptors.[21] One possible explanation appears to be that the blockade of HER2 could disrupt the process of cell survival and particularly those processes involved in the regulation of calcium in the cytoplasmic reticulum of cardiomyocytes, leading to a decrease in cell contractility and dilated cardiomyopathy.[17]

Although the benefit of trastuzumab is clear, the risk of some degree of cardiac dysfunction in these patients cannot be disregarded, either in the short- or long-term. It is important that the risks associated with trastuzumab therapy are weighed against the benefits so that one fatal disease is not substituted with another. However, some studies have shown evidence that most of the cardiac effects related to trastuzumab are mild to moderate, nonspecific, and medically treatable.[22] Once trastuzumab therapy

Table 1. Risk factors for cardiotoxicity.[20]

Documented	Treatment with trastuzumab + chemotherapy
	Age >60 years
Suspected	Anthracycline cumulative dose ≥400 mg/m^2
	Previous thoracic radiotherapy (left side)
	Previous heart failure

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is initiated, cardiac monitoring is essential and it seems reasonable that long-term follow-up could be imposed, as cardiac failure is a progressive disease that can first manifest some years after the introduction of therapy.[23]

RISK ASSESSMENT OF TRASTUZUMAB THERAPY

To assess the risk of cardiotoxicity associated with trastuzumab an independent Cardiac Review and Evaluation Committee (CREC) retrospectively reviewed data of patients treated with trastuzumab in seven phase II and III trials.[24] All clinical trials reviewed by the CREC were conducted on a background of anthracycline exposure. The CREC established criteria to confirm cardiac involvement and enable a uniform assessment of cardiotoxicity. Four criteria were proposed and the presence of any one is sufficient to confirm the diagnosis of cardiac dysfunction (Table 2). The CREC also classified the cardiac events according to the functional classification of the New York Heart Association (NYHA; Table 3),[24,25] as the functional classes described by the NYHA are more useful. These four classes are well defined and are a functional and clinical assessment of the levels of fatigue a patient experiences affecting their physical daily activities.

According to the analysis of CREC, a combination of trastuzumab added to anthracycline and cyclophosphamide (AC) chemotherapy increased the risk of cardiac events to 27%, 16% of which were classified as NYHA class III/IV events. In comparison, AC therapy alone was associated with an 8% increase in the risk of cardiac events; of these approximately 4% were NYHA class III/IV events. There was also an increased risk of cardiac events when trastuzumab was combined with paclitaxel. The risk of cardiac events increased to 13%, 2% of which were NYHA class III/IV events.

Table 2. Cardiac Review and Evaluation Committee criteria* for the diagnosis of cardiac dysfunction.[24]

(1) Cardiomyopathy characterized by a decrease in LVEF or changes of contraction most apparent in the interventricular septum
(2) Heart failure symptoms
(3) Signs of heart failure (eg, S3 gallop, tachycardia, edema)
(4) Decline in initial LVEF of at least 5% to <55% with signs and symptoms of heart failure, or asymptomatic decrease of initial LVEF of at least 10% to <55%

*Any of the four criteria is sufficient to confirm the diagnosis of cardiac dysfunction.
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LVEF =lef ventricular ejection fraction.

Table 3. T e stages of heart failure: New York Heart Association classification.

Class	Patient symptoms
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reprinted with permission from: T e Criteria Committee of the New York Heart Associaton (NYHA). Nomenclature and criteria for diagnosis of Diseases of the Heart and Great vessels.
9th edition. Boston, Mass: Little, Brown and Co; 1994.

This is compared with the use of paclitaxel alone, which was associated with only a 1% increased risk of NYHA class III/IV cardiac events. In patients receiving trastuzumab alone the increased risk of cardiac events was only 3%-7%, with 2%-4% of these classified as NYHA class III/IV events (Table 4). The majority of patients with cardiac events had symptoms (75%), but most improved with therapy (79%), which included diuretics, angiotensin-converting enzyme (ACE) inhibitors, cardiac glycosides, and other inotropic agents.[24] Based on this analysis, the CREC concluded that in HER2+ tumors the reduction of mortality by 25% assigned to treatment with trastuzumab justified the risk of cardiotoxicity.[24]

Strategies have been proposed to prevent or minimize the cardiotoxicity associated with trastuzumab, in particular avoiding adding trastuzumab to anthracyclines, and to identifying risk factors for cardiotoxicity (history, physical examination, and diagnostic procedures) prior to treatment.

The CREC observations raised several questions:[19] (1) Given the enormous benefit of trastuzumab, is the previous existence of cardiac dysfunction, especially if asymptomatic, reason enough to discontinue the drug? (2) Are the classic risk factors for heart disease (hypertension, diabetes, dyslipidemia, family history, etc.) predictive for the onset of heart failure induced by trastuzumab? (3) Is the heart failure induced by trastuzumab reversible if the drug is discontinued, and if so, is it safe to restart therapy in a patient who previously developed trastuzumab-induced heart failure? (4) Is there a possibility of preventing or minimizing the heart failure induced by trastuzumab? (5) Will the incidence of cardiotoxicity increase with longer follow-up?

At the 2007 annual meeting of the American Society of Clinical Oncology (ASCO) a proposal for a predictive model for the cumulative incidence of cardiac events in patients treated with trastuzumab and anthracyclines was presented as part of the updated results of NSABP B-31.[26] A risk factor score formula was proposed that considered age, LVEF, and hypertension during treatment. This model was considered important as it enables the physician to choose regimens containing trastuzumab based on an individual patients risk:benefit profile. This model should be validated in the "real world," in other data set with a regimen similar to that used in the present analysis.

Risk factor score = {[7.4 + (0.03 × age) – (0.1 × baseline LVEF) + (0.68 if high blood pressure on treatment)] ×100} / 4.82

To obtain the cardiac risk score (percentage of risk of a cardiac event within 3 years), take the constant of 7.4 plus 0.03 times the patient's age, minus 0.1 times the baseline LVEF, plus the addition of 0.68 if the patient is on blood pressure medications or 0 if the patient is not on blood pressure medicines, times 100, divided by 4.82.

Table 4. Retrospective analysis conducted by the Cardiac Review and Evalution Committee of seven studies to investigate the cardiotoxicity associated with trastuzumab.

	Incidence (%)				
Therapy	Trastuzumab monotherapy	Trastuzumab + AC	Trastuzumab + paclitaxel	AC	Paclitaxel monotherapy
CD	3-7	27	13	8	1
NYHA class III or IV	2-4	16	2	4	1

Adapted with permission from Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer. 2002;95:1592-1600.
AC=anthracycline plus cyclophosphamide; CD=cardiac disfunction; NYHA=New York Heart Association.

EARLY IDENTIFICATION OF PATIENTS AT HIGH RISK FOR CARDIOTOXICITY?

Troponin I, a protein found in the contractile apparatus of myocytes, is one of the most sensitive markers of myocardial injury.[27] It is routinely used in the diagnosis of acute coronary syndromes and has a very good correlation with short and long-term mortality.[28] The elevation of troponin I does not necessarily indicate a heart attack has occurred but that myocardial injury has occurred.[29] In a recent study troponin I levels were used in the early detection of cardiotoxicity after chemotherapy.[29] Troponin I levels were measured before, immediately after, and at 12, 24, 36, and 72 hours after the chemotherapy infusion (normal value <0.07 ng/mL).[30] Echocardiography was performed to evaluate cardiac function at baseline and 1, 3, 6, and 12 months after therapy. The researchers found a rise in plasma troponin in 33% of patients (80% of them treated with anthracyclines) and also found a direct link between elevated levels of troponin I and a lower LVEF.[30] These results corroborate earlier studies in which a correlation between increased plasma levels of troponin I and increased severity of cardiomyopathy were observed.[31,32]

The determination of NT-proBNP has also been proposed to be useful as a biomarker to determine whether a patient is at high risk for developing cardiotoxicity, although is not as reliable as troponin I. NT-proBNP is synthesized in the ventricles in response to an increase in cardiomyocyte tension and the increased serum levels of BNP correlate with the severity the heart failure.[33] According to these studies it has been proposed to include routine evaluations of troponin I and NT-proBNP levels at baseline and immediately and 1 month after administration of chemotherapy, in order to detect the signs of cardiotoxicity early in the treatment.[30]

Although evaluation of troponin I and NT-proBNP levels is not yet a recommended routine procedure, a protocol for this is being discussed. If implemented this could provide an opportunity for oncologists and cardiologists to be able to monitor heart function and modify oncologic treatment if required to prevent cardiotoxicity.

MANAGEMENT OF CARDIAC DYSFUNCTION

Often it is not necessary to image the heart to determine a decrease in cardiac function as there are clinical symptoms that should alert physicians to the possibility that a patient is entering into, or already in, heart failure.[34] These symptoms include tachycardia at rest or sudden weight gain, which may indicate that the patient has edema, and the appearance of dyspnea at exertion to the extent of NYHA class II or higher (Table 5).[2] In patients undergoing trastuzumab therapy an assessment of LVEF should be made when any of these symptoms occur.

For patients in whom analytical and/or functional noninvasive imaging methods (echocardiography or radionuclide angiography) detects cardiotoxicity, the currently

Table 5. Indication for assessment of lef ventricular ejection fraction.

Increase in heart rate from "at rest"
Heart rate <80 bpm at rest that increases to >90 bpm
Heart rate ≥80 ≥100 at rest that increases to >100 bpm
Heart rate >100 bpm at rest that increases to >120 bpm
Increase in weight ≥2 kg in 1 week
Emergence of dyspnea on exertion

Adapted with permission from Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer. 2002;95:1592-1600.
bpm=beats per minute.

Table 6. Proposal for the evaluation and treatment of heart failure in patients undergoing treatment with trastuzumab.

Physical status	LVEF	Trastuzumab	Monitor LVEF	Therapeutic guidelines
Asymptomatic	>50%	Continue	Repeat in 4 weeks	
	↓ >10 points but normal	Continue	Repeat in 4 weeks	Consider βB
	↓ 10-20 points and LVEF >40%	Continue	Repeat in 2-4 weeks	Treat CF
	↓>20 points or LVEF <30%	Suspend	If improved: surveillance	Treat CF
			If not improved/no change: stop	
			Repeat in 2 weeks	
			If improved (>45%): restart	
			If not improved/no change: stop	
Symptomatic	↓ <10 points	Continue		NC?
	↓ <10 points and LVEF >50%	Continue	Repeat in 2-4 weeks.	Anemia?
	↓ <30 points	Stop	If improved/no change:	Treat CF
			surveillance	Treat CF
			If not improved: stop	

Adapted with permission from Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer. 2002;95:1592-1600.
↓=decrease; βB=beta-blockers; CF=cardiac failure; LVEF=lef ventricular ejection fraction; NC=noncardiac pathology.

Table 7. Heart failure therapy in patients undergoing treatment with trastuzumab.

Diagnosis	Therapy	Details
Systolic dysfunction	ACE I/ARA-II	↓ LVEF
	Diuretics	↓ LVEF symptomatic
	Digoxin	↓ LVEF symptomatic
	Beta-blockers	↓ LVEF stable
	Aldosterone antagonists	↓ LVEF symptomatic and serious
Diastolic dysfunction	Diuretics	Symptomatic with normal LVEF
	Nitrates	
	Calcium antagonists	
	Beta-blockers	
	ACE I/ARA-II	

Adapted with permission from Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer. 2002;95:1592-1600.
↓=decrease; ACE I=angiotensin-converting enzyme inhibitors; ARA-II=angiotensin II receptor antagonists; LVEF=lef ventricular ejection fraction.

recommended therapy for heart failure should be initiated regardless of the presence or not of signs and symptoms of heart failure.[34] Patients with risk factors for heart disease should start (or continue) the specific therapy (eg, antihypertensives, statins). Therapy with ACE inhibitors or angiotensin antagonists to which beta-blockers, diuretics and digitalis may be added, has made a marked difference in the treatment of heart failure in these patients.[30] The question that arises now is whether to start an ACE inhibitor or an angiotensin antagonist prophylactically in high-risk patients (with known risk factors, increased troponin I and/or BNP levels) even with a normal LVEF, in order to prevent or minimize the occurrence of cardiac dysfunction.[35] This question remains unanswered, but perhaps this therapeutic regimen could possibly prevent the progression to heart failure.

A symptomatic and functional evaluation scheme for patients indicated for treatment with trastuzumab, alongside the therapeutic options for the treatment of heart failure has been proposed (Tables 6 and 7).[36] In the algorithm for

cardiac evaluation of these patients, the assessment of the LVEF should be included alongside the clinical history and objective examination. If the LVEF is greater than 50% (ie, the patient does not have systolic dysfunction), and is both asymptomatic and stable one should also assess the diastolic function every 3 months. If there is no systolic dysfunction, this should confirm that the patients are asymptomatic and monitoring the ejection fraction should be carried out to confirm the patient remains stable. If the patient is stable, therapy should not be altered.[36]

CONCLUSION

Trastuzumab-related cardiotoxicity may be reversible using pharmacological and non-pharmacological means. The risk of cardiac dysfunction associated with trastuzumab can be justified given the increase in overall survival. This risk is lower when trastuzumab is given as monotherapy. The paradigm for cardiologists remains the same: to treat the cancer effectively whilst preventing cardiotoxicity.

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