

Trastuzumab and cardiac toxicity: monitoring in the adjuvant setting

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Although trastuzumab has been approved for use in patients with metastatic breast cancer, recent trials have shown a significant impact of adding trastuzumab to adjuvant therapy for patients with early breast cancer. A major limiting toxicity for trastuzumab is the potential to precipitate heart failure, particularly after anthracycline-based treatment. We have analyzed the phase III adjuvant trials to generate universal guidelines for trastuzumab treatment in patients with early breast cancer.

Trastuzumab (Herceptin) was first approved for treatment of metastatic breast cancer by the US Food and Drug Administration (FDA) in September 1998. Approximately 20%–30% of breast cancers overexpress the 185-kD tyrosine kinase growth factor receptor HER2/*neu* (ErbB2).¹ Such binding results in inhibition of growth of cancer cells that overexpress HER2/*neu*.² Binding of trastuzumab to the extracellular domain of HER2/*neu* can also downregulate these receptors.³

Overexpression of HER2/*neu* by breast cancer cells is associated with a poor prognosis as well as resistance to tamoxifen but possibly an improved response to anthracyclines. Tamoxifen resistance is mediated through estrogen receptor-HER2/*neu* cross-talk.⁴ In addition, treatment with trastuzumab has been shown to increase the susceptibility of cancer cells to cisplatin, doxorubicin, and paclitaxel when grown as heterografts in nude mice.⁵

In most studies, only those breast cancers with strong expression of HER2/*neu* driven by amplification of the gene responded to the antibody alone or to a combination of the antibody with chemotherapy. Immunohistochemistry can provide an initial screen for HER2/*neu* overexpression, but 2+ reactions should be confirmed with the more reliable fluorescence in situ hybridization (FISH) assay.⁶

Trastuzumab can achieve an objective regression of metastatic breast carcinoma in 12%–15% of heavily pretreated women.^{7,8} It can also enhance the response rate when added to different chemotherapeutic agents, such as cisplatin,⁹ docetaxel (Taxotere), paclitaxel, vinorelbine,¹⁰ and gemcitabine (Gemzar)¹¹ in metastatic breast cancer.

Trastuzumab-associated cardiotoxicity

In the initial studies of patients with metastatic breast cancer treated with trastuzumab, cardiac dysfunction (reduced left ventricular ejection fraction [LVEF]) occurred in about 27% of patients treated with trastuzumab plus concurrent anthracycline and in 13% of patients treated with trastuzumab plus concurrent paclitaxel (after using anthracycline in the past; Table 1).¹² In this trial, New York Heart Association (NYHA) cardiac dysfunction (classes III and IV) occurred in 16% of the group given trastuzumab with anthracycline and cyclophosphamide, compared with 3% of the group given anthracycline and cyclophosphamide alone (Table 1). Data about the use of trastuzumab in anthracycline-naïve breast cancer patients are limited. However, available data suggest that there are no significant cardiac side effects when trastuzumab is

KEY POINTS

Trastuzumab is an essential component of adjuvant therapy for node-positive HER2/*neu*-positive early breast cancer.

Trastuzumab use has been associated with cardiac toxicity, particularly after anthracycline-based treatment.

Appropriate clinical guidelines can be implemented to limit the cardiac toxicity of trastuzumab use in the adjuvant setting.

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TABLE 1
Incidence of cardiac dysfunction

Regimen	Incidence of cardiac dysfunction (%)	Incidence of NYHA class III or IV cardiac dysfunction (%)
AC + trastuzumab	27	16
AC alone	8	3
Paclitaxel + trastuzumab	13	2
Paclitaxel alone	1	1

AC = anthracycline + cyclophosphamide; NYHA = New York Heart Association

Adapted from Slamon et al¹²

used without anthracycline in patients with no cardiac disease.

The unexpected cardiac toxicity in the initial trials prompted strict monitoring of LVEF in the recently published adjuvant trials to minimize the cardiac toxicity of trastuzumab, particularly when used with chemotherapeutic agents. In a recent trial, trastuzumab was used in combination with docetaxel as neoadjuvant therapy for patients with early T1–2, N0–2 HER2/*neu*-positive breast cancer. Treatment was generally well tolerated. All patients underwent assessment of LVEF before enrollment in the study and then repeated evaluation at 6 months after finishing neoadjuvant therapy. No symptomatic cardiac dysfunction was reported. There was one case of an asymptomatic decrease in LVEF to 46% (after cycle 3), which

TABLE 2
Assessment of LVEF and cardiac toxicity criteria in adjuvant trials of trastuzumab

Trial	Method of LVEF assessment	Toxicity criteria
NSABP B-31 ^{21,25}	MUGA scanning	NYHA
NCCTG N9831 ²¹	MUGA scanning or echocardiography	NYHA
HERA ²²	MUGA scanning or echocardiography	NCI-CTC v2.0
FinHer ²³	MUGA scanning or echocardiography	NCI-CTC v2.0
BCIRG 006 ²⁴	Not reported	Not reported

LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NCI-CTC = National Cancer Institute–Common Toxicity Criteria; NYHA = New York Heart Association

normalized 1 month after discontinuation of treatment.¹³

Mechanism of toxicity

Denis Slamon's initial trial¹² clearly shows that the incidence of the cardiotoxic effects of trastuzumab increases with exposure to anthracyclines, which have a known direct dose-dependent cardiac toxicity.¹⁴

Efforts have been made to elucidate the biologic mechanism of cardiac toxicity of trastuzumab. Low levels of HER2/*neu* are found on cardiac myocytes, where they apparently are critical to fetal development and survival of cardiac tissue.¹⁵ Studies of mutant mouse models have shown that the HER2/*neu* gene plays an indispensable role in the embryonic and postnatal development of the heart.¹⁶ Moreover, the induction of cardiac stress pathways by either hemodynamic overload or the cardiotoxicity of anthracyclines promoted the onset of left ventricular dysfunction in mice that were deficient in the HER2/*neu* protein.¹⁶ These results imply that the HER2/*neu* gene mediates survival signals not only for HER2/*neu*-positive breast cancer cells, but also for normal human cardiac muscles.

Furthermore, heterodimerization of HER2/HER4 receptors is essential for myocytes to survive acute stress signals.¹⁷ The loss of these survival signals after trastuzumab treatment can lead to injury of myocytes upon exposure to stress, such as the anthracyclines, or hemodynamic overload.

Impairment of mitochondrial function and disruption of cellular energetics have also been postulated as a mechanism for trastuzumab-associated cardiac toxicity.¹⁸

Classifying dysfunction

Cardiac function is assessed by different methods in clinical trials, and the lower limit of normal LVEF depends on the method of assessment. Moreover, it may also vary among different radiolog-

ic facilities, even when the same assessment method is used. Some trials used only multigated acquisition (MUGA) scanning, whereas others used either MUGA scanning or echocardiography.

The most commonly used criterion for assessment of cardiac toxicity in clinical trials as well as in clinical practice is the NYHA functional classification of heart failure.¹⁹ However, cardiac toxicity is reported in other trials using the National Cancer Institute–Common Toxicity Criteria (NCI-CTC version 2.0). Unfortunately, both NYHA and CTC cardiac assessment tools do not properly match but can be correlated. The assessment methods and toxicity classification of cardiac function in the adjuvant trials of trastuzumab are shown in Table 2.

In the past few years, guidelines have been established for cardiac monitoring during trastuzumab treatment in metastatic breast cancer (Table 3).²⁰ However, analysis of the trials that used trastuzumab in the adjuvant setting provides a different perspective for cardiac monitoring.

Trials of trastuzumab

Early analyses of five phase III randomized controlled trials provide solid evidence that adding trastuzumab to adjuvant chemotherapy increases progression-free survival, time to first distant recurrence, and overall survival in women with early invasive breast cancer.^{21–25} Five major randomized trials have proven the benefit of adjuvant trastuzumab in early breast cancer patients. A major concern in designing all the adjuvant trials is the cardiac toxicity associated with trastuzumab. For that reason, the trials required strict cardiac assessment prior to enrollment and monitoring at regular intervals during therapy.

NSABP and NCCTG trials

Both the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and the North Central Cancer Treatment Group (NCCTG) N9831 were stopped early after a combined interim analysis showed that the time to first

distant recurrence was significantly improved (11.5% of women in the control arm vs 5.7% in the trastuzumab arm), a highly statistically significant reduction in the risk of recurrence.²¹

LVEF was evaluated serially at the following points:

- Before starting AC (anthracycline and cyclophosphamide) treatment (baseline);
- After completion of the AC regimen (3 months from starting treatment);
- 6 months, 9 months, or 18 months from starting AC treatment.

Cardiac monitoring: In the NSABP B-31 trial (Table 4), trastuzumab treatment was monitored according to symptoms. Patients who developed clinically significant cardiac symptoms while they were receiving AC treatment were excluded from subsequent trastuzumab therapy. For asymptomatic patients, the initiation/continuation of trastuzumab treatment required an LVEF that met or exceeded the lower limit of normal. Only a decrease of less than 16% from baseline was allowed, provided the LVEF was still at or above the lower limit of normal. For example, asymptomatic reduction of LVEF from 68% to 53% (a reduction of 15%) was acceptable (provided that 53% meets the normal limit of the LVEF of the radiologic facility), whereas asymptomatic reduction from 68% to 52% (a reduction of 16%) was not acceptable to proceed with trastuzumab treatment (even if 52% was still within the normal limit for LVEF for the radiologic facility).

If LVEF was declined 16% or more from baseline or below the lower limit of normal, trastuzumab was withheld for 4 weeks, at which time the LVEF was reassessed. If the LVEF was improved, trastuzumab therapy was allowed. If the LVEF remained below these levels or the patient had symptomatic cardiac dysfunction while receiving trastuzumab, administration of the antibody was permanently discontinued.

Cardiac toxicity: The combined data analysis of both NSABP B-31 and NCCTG N9831 showed that 6.7% of

TABLE 3

Guidelines for use of trastuzumab in metastatic breast cancer

Physical status	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic	↓ but normal	Continue	Repeat in 4 wk	None
	↓ > 10 points but normal	Continue	Repeat in 4 wk	Consider beta-blockers
	↓ 10–20 points and LVEF > 40%	Continue	Repeat in 2–4 wk; if improved, then monitor; if not improved, then stop trastuzumab	Treat for left ventricular dysfunction
	↓ > 20 points to < 40% or LVEF < 30%	Hold	Repeat in 2 wk; if improved to > 45%, then restart; if not improved, then stop trastuzumab	Treat for left ventricular dysfunction
Symptomatic*	↓ < 10 points	Continue	Repeat in 2–4 wk; if stable or improved, then monitor; if worsened, then stop trastuzumab	Search for noncardiac pathology (eg, anemia)
	↓ > 10 points and LVEF > 50%	Continue	Same as above	Treat for heart failure
	↓ > 30 points	Stop	Same as above	Treat for heart failure

LVEF = left ventricular ejection fraction

* Spontaneous (unsolicited) cardiac symptoms (eg, dyspnea on exertion, edema)

Adapted from Keefe²⁰

patients enrolled in these trials could not start trastuzumab treatment because of a decline in LVEF to a subnormal level or a decline by $\geq 16\%$ from baseline after completion of AC treatment. Also, 19% of patients discontinued trastuzumab treatment due to failure to meet the LVEF guidelines during the study.

The incidence of NYHA class III or IV congestive heart failure (CHF) or death from cardiac causes at 3 years was 4.1% in the trastuzumab group (31 patients had CHF), compared with 0.8% in the control group (4 patients had CHF, and 1 died of cardiac causes). Of the 31 women in the trastuzumab group who had CHF, 27 have been followed for at least 6 months after the onset of heart failure, and only 1 patient reported persistent symptoms of heart failure at the most recent follow-up visit. In this trial, patients who were \geq age 50 with a post-AC treatment LVEF < 55% had a higher incidence (20%) of CHF within 7 months of initiating trastuzumab.

In NCCTG N9831, the 3-year cumulative incidence of NYHA class III or IV CHF or death from cardiac causes was 2.9% in the trastuzumab group (20 patients had CHF, 1 of whom died of cardiomyopathy), compared with 0% in the control group.

Based on the data of the NSABP B-31 trial, the following significant risk factors for cardiac dysfunction during trastuzumab treatment have been identified²⁵: age > 50 years, baseline (prior to chemotherapy) LVEF < 55%, post-chemotherapy LVEF < 55%, and anthracycline treatment.

The following factors were not shown to impose a significant risk of cardiac toxicity during trastuzumab treatment: prior radiotherapy to a left-sided breast cancer, race, hypertension, diabetes mellitus, hyperlipidemia, or history of smoking.

Patients with cardiac arrhythmia and coronary artery disease were excluded from these trials.

TABLE 4

Guidelines for monitoring trastuzumab therapy in the NSABP B-31 trial

Relationship of LVEF to LLN	Absolute decrease in LVEF of < 10%	Absolute decrease in LVEF of 10%–15%	Absolute decrease in LVEF of ≥ 16%
Within normal limits	Continue	Continue	Hold*
1%–5% below LLN	Continue	Hold*	Hold*
≥ 6% below LLN	Continue	Hold*	Hold*

LVEF = left ventricular ejection fraction; LLN = lower limit of normal

* Repeat LVEF assessment after 4 weeks. If the criteria for continuation are met, resume trastuzumab treatment; if two consecutive holds or a total of three holds occurs, discontinue trastuzumab treatment.

HERA trial

The Herceptin Adjuvant (HERA) trial,²² an international, multicenter, randomized trial, compared 1 or 2 years of adjuvant trastuzumab treatment given every 3 weeks with observation in patients with HER2/*neu*-positive and either node-negative or node-positive breast cancer who had completed locoregional therapy (surgery with or without radiotherapy) and a minimum of 4 cycles of chemotherapy (administered as adjuvant treatment postoperatively [89%] or preoperatively [5%] or as both adjuvant and neoadjuvant chemotherapies [6%]). The trial showed a statistically significant improvement in 2-year disease-free survival in the trastuzumab group. However, the 2-year overall survival was not significantly different in both the trastuzumab and control groups.

Cardiac monitoring: The HERA trial used the NCI-CTC version 2.0 for assessment of toxicity. Patients received trastuzumab only if they had a normal LVEF (≥ 55% as measured on echocardiography or MUGA scanning). Patients with a history of cardiac disease were excluded.

LVEF was assessed by echocardiography or MUGA scanning at baseline before starting treatment and at 3-, 6-, 12-, 18-, 24-, 30-, 36-, and 6-month intervals. Trastuzumab was stopped if symptomatic CHF occurred or an asymptomatic reduction in LVEF to < 50% was noted. If trastuzumab was held for asymptomatic reduced LVEF, repeated assessment of LVEF was performed after 3 weeks. If left ventricular function did not return to a level above

the criteria for withholding treatment, trastuzumab therapy was terminated.

Cardiac toxicity: A higher incidence of NCI-CTC grade 3 or 4 adverse events was noted in the trastuzumab group than in the observation group. The cumulative grades 3 and 4 cardiac toxicity (CHF) occurred in 1.7% of patients in the trastuzumab group and in 0.1% of patients in the observation group. The only cardiac death in the trial occurred in the observation group. Asymptomatic reduction in the LVEF occurred in 7% of the trastuzumab group and in 2% of the observation group.

FinHer Trial

FinHer (Finland Herceptin) trial²³ randomly assigned women with early breast cancer to receive 3 adjuvant cycles of docetaxel or vinorelbine, followed by 3 cycles of 5-fluorouracil (5-FU), epirubicin (Ellence), and cyclophosphamide in both groups. Those with HER2/*neu*-positive breast cancer were further assigned to receive or not to receive nine weekly trastuzumab infusions.

The study showed that the 3-year recurrence-free survival was better with docetaxel than with vinorelbine. Within the subgroup of patients who had HER2/*neu*-positive cancer, those who received trastuzumab had better 3-year recurrence-free survival than those who did not receive the antibody.

Cardiac monitoring: In this trial, LVEF was checked before starting chemotherapy, at the end of treatment, and 12 months after treatment.

Cardiac toxicity: Trastuzumab was not associated with a decrease in LVEF or cardiac failure.

BCIRG 006

The BCIRG (Breast Cancer International Research Group) 006 study²⁴ is a phase III randomized trial that compared doxorubicin and cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin, and trastuzumab (TCH) in HER2/*neu*-positive early breast cancer patients. The study showed statistically significant superior disease-free survival in the two trastuzumab-containing arms.

Cardiac monitoring: Since the study has not been published yet, data on cardiac monitoring are not known.

Cardiac toxicity: Symptomatic cardiac events were reported in 1.2% of the AC→T, 2.3% of the AC→TH, and 1.2% of the TCH arms. Absolute LVEF decline > 15% and below the lower limit of normal occurred in 0.6% of patients in the AC→T, 2.4% of those in the AC→TH, and 0.4% of patients in the TCH arms, respectively. This study has shown that both combinations of TCH and AC→T result in the same risk of cardiac toxicity ($P = 0.54$).

Managing CHF

In contrast to anthracycline-related cardiotoxicity, trastuzumab-associated toxicity does not appear to be dose-related and usually responds to standard medical treatment or the discontinuation of trastuzumab. In one trial,²⁶ continued trastuzumab therapy in women who developed cardiac dysfunction was shown to be relatively safe. However, if the patient developed significant reduction in LVEF, it is invaluable to hold trastuzumab treatment. When the LVEF is normalized, restarting treatment is allowed and does not necessarily result in clinical deterioration.²⁷

The Heart Failure Society of America updated its guidelines for treatment of heart failure in 2006.²⁸ Angiotensin-converting enzyme (ACE) inhibitors should be considered for both symptomatic and asymptomatic patients

whose LVEF is $\leq 40\%$. For patients who are intolerant of ACE inhibitors, angiotensin receptor blockers (ARBs) should be considered. Treatment with the combination of hydralazine and isosorbide dinitrate is an option if renal insufficiency or hyperkalemia develops with ACE inhibitors. Other medications that can be used to control CHF include diuretics, β -blockers, and aldosterone antagonists.

Cautious use

The most appropriate strategy is to decrease the potential for anthracycline-induced toxicity. This step may be accomplished through close monitoring, maintaining the cumulative dose within the "safe" range (ie, $< 450 \text{ mg/m}^2$), or through the use of less cardiotoxic anthracyclines such as epirubicin. For decades, anthracycline has been a keystone in treating high-risk breast cancer patients.

Overexpression of topoisomerase II alpha gene (topo II alpha) has been identified as a genetic marker that correlates with poor disease-free survival in patients with invasive breast cancer.²⁹ A Scandinavian study showed topo II alpha to be coamplified in about 35% of HER2/*neu*-positive patients,³⁰ where it can confer a therapeutic advantage to anthracycline/trastuzumab-based combination regimens. In this study, HER2/*neu*-positive patients who do not experience coamplification of topo II alpha (about 65%) do not appear to have this same benefit and may be ideal candidates for efficacious, non-anthracycline-based regimens, thus avoiding potential cardiac toxicity.³⁰

Cardiac isotopic study

Cardiac isotopic study has been attempted to identify patients who are predisposed to the cardiotoxic effects of trastuzumab. An initial study by Behr et al in 2001 suggested that radiolabeled trastuzumab (indium-DTPA-trastuzumab) can identify patients who may be susceptible to trastuzumab-associated cardiotoxicity.³¹ However, a more

TABLE 5

Guidelines for use of adjuvant trastuzumab therapy

Physical status	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic	Normal	Continue	As scheduled	None
	$\downarrow < 16\%$ but normal	Continue	As scheduled	If LVEF $< 40\%$, treat with an ACE inhibitor
	$\downarrow \geq 16\%$ or subnormal (regardless of the amount of reduction)	Hold temporarily	Repeat after 4 wk; if improved, then restart treatment; if not improved, stop trastuzumab	If LVEF $< 40\%$, treat with an ACE inhibitor
Symptomatic	$< \text{Normal}$	Hold permanently	Per cardiologist's discretion	Treat for heart failure

LVEF = left ventricular ejection fraction; ACE = angiotensin-converting enzyme

recent (2006) study was performed using indium-111-labeled trastuzumab scintigraphy in 17 patients with HER2/*neu*-positive metastatic breast cancer.³² It showed that radiolabeled trastuzumab scintigraphy was not valuable in predicting trastuzumab-related cardiotoxicity.

Final recommendations

- Strict follow-up of guidelines for cardiac assessment during adjuvant trastuzumab therapy may preclude long-term serious cardiac dysfunction.
- LVEF should be evaluated before starting AC treatment (baseline); after completion of AC regimen (ie, at 3 months); and then at 6, 9, and 18 months from starting AC treatment provided the patient is asymptomatic.
- Cardiac monitoring for patients receiving trastuzumab should be individualized based upon their risk for developing CHF. A reasonable approach is to follow the available data from published clinical trials in the adjuvant setting (Table 5).
- Serial assessment of LVEF should be performed by a consistent method (MUGA scanning or echocardiography), preferably in the same radiologic facility.

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