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Christine C. Davis, *Beaufort Memorial Hospital*
Amelia Zelnak, *Northside Hospital Cancer Institute*
[John Eley](#), *Emory University*
Daniel Goldstein, *Emory University*
[Jeffrey Switchenko](#), *Emory University*
[Trevor McKibbin](#), *Emory University*

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Clinical Utility of Routine Cardiac Monitoring in Breast Cancer Patients Receiving Trastuzumab

Christine C. Davis, PharmD, BCOP¹, Amelia Zelnak, MD, MSc², J. William Eley, MD, MPH³, Daniel A. Goldstein, MD^{3,4}, Jeffrey M. Switchenko, PhD⁵, and Trevor McKibbin, PharmD, MS, BCOP⁶

¹Beaufort Memorial Hospital, Beaufort, SC, USA

²Northside Hospital Cancer Institute, Cumming, GA, USA

³Emory University School of Medicine, Atlanta, GA, USA

⁴Rabin Medical Center, Petach Tikvah, Israel

⁵Winship Cancer Institute, Atlanta, GA, USA

⁶AstraZeneca, Atlanta, GA, USA

Abstract

Background—Trastuzumab targets the human epidermal growth factor receptor-2 (HER2). Cardiotoxicity is a potential adverse effect, manifesting as either an asymptomatic decline in left-ventricular ejection fraction or infrequently as largely reversible symptomatic heart failure (HF). Monitoring recommendations differ between product labeling and 2012 guidelines, and the clinical utility of serial cardiac monitoring in patients with metastatic breast cancer remains controversial.

Objective—The objectives of this study were to describe the frequency of monitoring, incidence of symptomatic or asymptomatic HF, overall effect on treatment, and cost of monitoring for cardiotoxicity.

Methods—We performed an institutional review board–approved retrospective chart review of breast cancer patients receiving trastuzumab from January 1, 2009, through January 1, 2014, at an academic medical center.

Results—Out of 154 treatments, 72% were adjuvant, and 28% were metastatic. In the adjuvant setting, a mean of 4.5 (interquartile range [IQR] = 4–5) echocardiograms (echos) over a mean of 11.5 (IQR = 11–12) months were performed. In the metastatic setting, a mean of 3.1 (IQR = 1–5) echos over a mean of 20.2 (IQR = 9–31) months were performed. Symptomatic HF events

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Corresponding Author: Christine C. Davis, Beaufort Memorial Hospital, 989 Ribaut Road, Suite 122, Beaufort, SC 29902, USA. christinecdavis12@gmail.com.

Authors' Note

This research project complies with the current laws of the United States.

Declaration of Conflicting Interests

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occurred in 4 adjuvant (3.6%) and 2 metastatic patients (6.5%); 10 patients (6.5%) had a treatment interruption, with 9 (90%) tolerating restart of trastuzumab. Two patients (1.3%) changed treatment as a result of cardiotoxicity. Using population incidence of HER2-positive breast cancer, \$13 million could be saved if monitoring were reduced by 1 echo per patient.

Conclusions—Given the low incidence of clinically significant HF and cost of monitoring, less frequent monitoring may be justified.

Keywords

breast cancer; cardiotoxicity; trastuzumab; cardiac monitoring

Introduction

Breast cancer is one of the most common malignancies in women and accounts for 29% of cancer diagnoses.¹ Approximately 25% of breast cancers overexpress the cell surface receptor human epidermal growth factor receptor-2 (HER2).² HER2 is a transmembrane tyrosine kinase receptor in the epidermal growth factor receptor family, which regulates cellular responses, including growth, survival, adhesion, migration, and differentiation. Breast cancers that overexpress HER2 are generally more aggressive tumors and have decreased response rates with cytotoxic chemotherapy and radiation compared with breast cancers that are HER2 negative; however, several Food and Drug Administration (FDA)–approved targeted therapies have been shown to improve survival in this population.^{3,4} A humanized monoclonal antibody, trastuzumab, targets the extracellular domain of HER2 and is approved for the treatment of early-stage and metastatic HER2-positive breast cancer. Trastuzumab is given intravenously weekly or every 3 weeks, either as a single agent or in combination with chemotherapy or hormone therapy. The standard duration of adjuvant trastuzumab treatment for breast cancer is 1 year, whereas in metastatic disease, trastuzumab is continued until disease progression or unacceptable toxicity.⁵

Potential adverse effects for trastuzumab generally include rash, infusion reactions, nausea, diarrhea, and cardiotoxicity. The mechanism of cardiotoxicity is not completely understood. Differing from the cardiotoxicity of anthracyclines, trastuzumab does not cause cellular death, is not related to cumulative doses, and appears to be at least partially reversible.⁶ One proposed mechanism involves inhibition of HER2 signaling in cell survival pathways in cardiomyocytes. Pathways that include mitogen-activated protein kinase, phosphoinositide 3 kinase/protein kinase B (PI3K/AKT), and focal adhesion kinase, which inhibit apoptosis and maintain cardiac function, are unable to be activated without HER2. Inhibition of HER2 leads to the accumulation of excess reactive oxygen species, particularly when used closely following other well known cardiotoxic agents such as anthracyclines.⁷ The incidence of symptomatic heart failure (HF) and cardiac death observed in the large adjuvant trastuzumab trials ranged from 0.4% to 4%, whereas asymptomatic decreases in left-ventricular ejection fraction (LVEF) ranged from 3% to 34%.^{8–11} Both symptomatic and asymptomatic events are largely reversible and manageable.¹²

The product labeling of trastuzumab approved by the United States (US) FDA recommends monitoring LVEF at baseline as well as every 3 months during treatment for all patients and

every 6 months for 2 years on completion in the adjuvant setting. In addition, if treatment with trastuzumab is withheld because of a decline in LVEF, patients should have repeat monitoring 4 weeks after discontinuation to monitor for improvement.¹³ However, the 2012 European Society of Medical Oncology (ESMO) guidelines on cardiotoxicity specify that in the metastatic setting, LVEF should be monitored at baseline and then infrequently in the absence of symptoms.¹⁴ The 2016 National Comprehensive Cancer Network Breast Cancer guidelines specify that the optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known.¹⁵ Among persons who previously received trastuzumab, the American Society of Clinical Oncology states that the optimal interval and duration as well the cost-effectiveness of cardiac monitoring remains undefined.¹⁶

With conflicting recommendations on monitoring frequency and previous reports describing symptomatic HF as infrequent and largely reversible with treatment, we questioned the clinical utility of serial, routine LVEF monitoring in patients with breast cancer. The objectives of this study included evaluating current monitoring practices, describing the incidence of symptomatic and asymptomatic HF, assessing the effect of monitoring on treatment decisions, and analyzing the cost of routine cardiac monitoring with trastuzumab.

Patients and Methods

This study was approved by the Emory University Institutional Review Board and Winship Cancer Institute Clinical and Translational Review Committee. This was a retrospective cohort study that included patients with a histological diagnosis of HER2-positive breast cancer and treatment with trastuzumab in either the adjuvant or metastatic setting at Emory University Hospital/Winship Cancer Institute between January 1, 2009, and August 1, 2014. Eligible patients were selected consecutively until 150 patients were included. Patients with incomplete records, defined as less than 1 follow-up visit after treatment with trastuzumab, were excluded.

Data collected included patient demographics, stage of breast cancer, comorbidities, concomitant medications, previous treatments, dose and duration of trastuzumab, frequency of monitoring, symptomatic or asymptomatic cardiac dysfunction, and changes in treatment. We used the Cardiac Review and Evaluation Committee definition of cardiac dysfunction, which includes at least 1 of the following: (1) cardiomyopathy, characterized by a decrease in cardiac LVEF that was either global or more severe in the septum; (2) symptoms of HF; (3) associated signs of HF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 5% to less than 55% with accompanying signs or symptoms of HF (symptomatic HF), or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms (asymptomatic HF).¹⁷ An a priori power analysis assuming an observed rate of symptomatic HF of 5% determined that inclusion of 150 patients would provide 95% confidence intervals (CIs) of 2% to 10% incidence of HF determined to be acceptable by the authors.¹⁸ Descriptive statistics were performed for patient characteristics, cardiac monitoring frequency, and changes in treatment. Univariate analysis of risk factors for symptomatic HF and asymptomatic HF was performed using χ^2 tests or Fisher's exact tests, where appropriate for categorical risk factors, and either ANOVA or Kruskal-Wallis tests, where appropriate for continuous risk factors. Echo costs

were calculated according to the Medicare physician fee schedule for 2015 using previously described methods.^{19,20} CPT code 93306 was used for the purpose of an echo, which included spectral or color flow Doppler.

Results

A total of 342 patients received trastuzumab between January 1, 2009, and August 1, 2014, at Emory University Hospital/Winship Cancer Institute. Of these, 150 patients' charts were reviewed, with 4 patients included in both the adjuvant and metastatic treatment settings, resulting in 154 treatment courses. The results in Table 1 reflect the patients' baseline characteristics. The majority (72%) of patients were treated in the adjuvant setting for HER2-positive breast cancer; 99% of patients were female, with a mean age of 54 years in the adjuvant group and 46 years in the metastatic group.

In the adjuvant setting, patients were treated for a mean of 11.5 months, with an interquartile range (IQR) of 11 to 12 months (Table 2). Patients had an average of 4.5 echo-cardiograms (echos) during the year of treatment with trastuzumab or monitoring every 2.6 months (IQR = 2.2–3 months). In the metastatic setting, patients were treated with trastuzumab for a mean of 20.2 months (IQR = 9–31 months), with a mean of 3.1 echos per patient, resulting in an average time of 8 months between monitoring (IQR = 3.5–10 months). Of note, 15 patients (35%) treated in the metastatic setting underwent evaluation by echo only before trastuzumab treatment began.

Overall, symptomatic HF occurred in the adjuvant group 3.6% (n = 4) and in the metastatic group 6.5% (n = 2). The overall symptomatic HF rate was 3.9%, with an exact binomial CI of 1.5% to 8.3%. Evidence for asymptomatic HF occurred in 16.2% (n = 18) of the patients in the adjuvant group and 12.9% (n = 4) in the metastatic group. Among 15 patients with metastatic disease, 12 patients had cardiac status evaluated by echo only at baseline, and 3 patients who underwent evaluation by cardiac echo after subsequent therapy could be assessed. Of the patients treated with trastuzumab, 6% (n = 7) in the adjuvant and 7% (n = 3) in the metastatic setting had a treatment interruption for a cardiac reason, including but not limited to cough, dyspnea, or edema. The 10 patients with a treatment interruption received a mean of 9 months (range = 5–15 months) of trastuzumab prior to the interruption. The mean time to restarting trastuzumab after the treatment interruption was 49 days. See Figure 1 for reversibility of LVEF decline. A trastuzumab treatment was withheld in 50% (n = 5) of patients because of symptomatic HF and in 50% of patients (n = 5) because of an asymptomatic decrease in LVEF. The 2012 ESMO guidelines provide criteria for treatment interruption of a dose of trastuzumab for asymptomatic HF, which includes LVEF <40% or at least a 10% decrease from baseline LVEF to 40% to 50%.¹⁵ In our cohort, 5 patients met criteria; of these, 3 patients had a dose of trastuzumab held, and 2 patients demonstrated recovery of LVEF despite continuing trastuzumab.

A treatment change for a cardiac reason occurred in 2 patients (1.3%). Both these patients were associated with symptomatic HF. The first patient was a 57-year-old woman with stage IIa breast cancer treated with 4 cycles of neoadjuvant pertuzumab, trastuzumab, and docetaxel followed by bilateral mastectomies. After surgery, LVEF was 45%, and the patient

experienced dyspnea on exertion. The patient was scheduled to receive adjuvant chemotherapy with an anthracycline-containing regimen; however, it was cancelled given the decline in LVEF. The patient was started on carvedilol and lisinopril, and when the LVEF recovered to >50%, trastuzumab alone was restarted and was tolerated to complete a year of treatment. The second patient was 68 years old and had stage IIIa breast cancer at diagnosis, with a past medical history including hypertension, diabetes mellitus, hyperlipidemia, HF (previous LVEF of 45%), coronary artery disease (CAD), and arrhythmia. At treatment initiation, the LVEF was 65%; however, 11 months after starting trastuzumab, LVEF dropped to 42.5% and did not recover; therefore, trastuzumab treatment was never restarted.

A univariate analysis of baseline characteristics, including risk factors for HF, and previous treatments, including anthracyclines predicting either symptomatic HF or asymptomatic HF, was performed. Most patient characteristics and treatments were not found to predict HF, likely because of the limited number of patients and low incidence of HF. Radiation to the internal mammary lymph node was associated with an increase in asymptomatic HF in the metastatic setting ($P=0.014$). In addition, aspirin use was associated with an increase in symptomatic HF in the adjuvant setting ($P=0.048$). In all patients, aspirin use and hyperlipidemia were both associated with increased symptomatic HF ($P=0.010$ and $P=0.022$). A post hoc analysis was performed to determine whether relationship of aspirin use and hyperlipidemia were associated with CAD. Hyperlipidemia had an association with CAD ($P=0.01$), whereas aspirin use did not ($P=0.25$); however, the population of patients with documented CAD was small ($n=3$).

Based on Medicare data for the physician fee schedule for 2015, the total cost of an echo, including physician and technical components in the outpatient setting, is \$228.83.^{19,20} In 2015, there will be approximately 234,190 new cases of breast cancer.¹ Assuming that 25% of these cases are HER2 positive, approximately 58,547 new HER2-positive breast cancer cases are expected in the US in 2015. If applied nationally, a decrease of 1 echo in each patient would result in approximately \$13 million in savings annually.

Discussion

Monitoring for cardiac dysfunction in the adjuvant setting occurred approximately every 3 months as recommended; however, in the metastatic setting, practice varied, including 35% of patients with baseline LVEF only. Rates of symptomatic HF and asymptomatic HF were low (3.8% and 15.5%, respectively). Overall, only 2 patients (1.3%) had a change in treatment plan, and both these cases were associated with symptomatic HF and would have been discovered without preemptive echo monitoring. Treatment was withheld in 6.5% of patients ($n=10$), with 90% of those restarting treatment after LVEF recovery. Among the 10 doses held, 2 patients had an asymptomatic decrease in LVEFs to 50%, which according to ESMO criteria, would not require a treatment interruption. The limitations of this retrospective review are that it is a single-institution study; the small sample size was small; and there was potential for selection bias. In calculating the cost savings, an assumption was made that all HER2-positive patients are treated with trastuzumab. This may be an overestimate because not all patients with tumors <5 mm (T1a) are treated with

trastuzumab.¹⁵ In addition, the time span of 2009 through 2014 included the publishing of 2012 ESMO guidelines suggesting decreased monitoring in the metastatic setting, which may have affected physicians' monitoring practices; however, this potential change in practice was not analyzed in this study. This was also a descriptive study and did not analyze patient outcomes related to frequency of cardiac assessment.

The reversibility of trastuzumab cardiotoxicity has been reported.²¹ Of 15 metastatic breast cancer patients in a published case series who developed symptomatic HF after long-term trastuzumab therapy, 79% recovered with appropriate medical therapy. Of the 34 patients with asymptomatic LVEF decline, 50% discontinued trastuzumab, and the other 50% continued. Of these, 30 patients had follow-up LVEF measurements demonstrating complete recovery with or without therapy, and the 2 patients continuing as well as the 2 discontinuing trastuzumab without LVEF measurements did not experience cardiac symptoms.²¹ An Australian retrospective review recently determined patterns of cardiac function assessment among a large cohort of metastatic breast cancer patients receiving trastuzumab over the past decade. A third of patients were monitored in the first 3 months, and half were monitored during therapy. Patients with a history of cardiovascular disease, exposure to anthracyclines, and older age were more likely to be monitored during therapy.²² In addition, an observational study in France had 623 metastatic breast cancer patients, where only 57% had baseline LVEF assessment, and 75% had at least 1 LVEF assessment after a year of follow-up.²³ A retrospective study using Medco insurance claims in the adjuvant setting analyzed patterns of cardiac testing and found that 80% of 643 patients were monitored for cardiac function during trastuzumab treatment, but only 16% received monitoring according to baseline, interval and final assessment recommendations.²⁴ A retrospective analysis of cardiac monitoring used Surveillance, Epidemiology, and End Results (SEER) Medicare data in patients ≥ 66 years old treated with adjuvant trastuzumab from 2005 to 2009.²⁵ Adequate monitoring was defined as at least every 4 months and occurred only in 36% ($n = 793$) of patients, with factors predicting adequate monitoring including a more recent year of diagnosis defined as 2009, anthracycline use, female prescribing physician, and physician graduating after 1990.

The ESMO guidelines identify risk factors for trastuzumab-associated cardiotoxicity; these include prior treatment with anthracycline chemotherapy, a borderline lower limit of normal LVEF, prior treatment with antihypertensive medication, older age, and—a poorly understood result found in 1 trial—a body mass index >25 kg/m².¹⁴ Recommendations on timing and dosing of anthracyclines and definition of older age are not specified in the ESMO guidelines. The present study did not identify these same risk factors based on univariate analysis, likely because of low overall rates of cardiotoxicity and limited number of patients included. The guidelines also state that optimal surveillance for patients on trastuzumab is not well established and suggested that in the absence of anthracyclines and symptoms, trastuzumab should be continued if LVEF $\geq 40\%$.¹⁴ Overall, monitoring recommendations are not based on patient outcomes but on expert opinion and the stringent monitoring used in large clinical trials to evaluate cardiac functioning closely. Monitoring recommendations vary between countries, with the United Kingdom National Cancer Research Institute recommending baseline and every 4-month cardiac monitoring with either echo or multigated acquisition (MUGA) scan during adjuvant treatment.²⁶ Of note, other

methods of monitoring, including troponin measurement, are discussed in the literature as potentially more robust methods of screening because echos are insensitive for detecting cardiac dysfunction at an early stage and may have interobserver variability ranging from 7% to 14%.^{27,28} This was not routinely evaluated in this cohort of patients and is beyond the scope of this analysis. Of note, based on Medicare data, another common method for assessing LVEF include MUGA scans, which cost \$238.48 and would result in a similar cost analysis.

The value of monitoring for cardiotoxicity in a metastatic cancer patient is likely low because the benefit of the treatment outweighs the cardiac risk, particularly in patients without risk factors. The clinical significance of asymptomatic HF is uncertain, particularly when cardiac effects are reversible and, therefore, assessment other than history, physical exam, and baseline echo may not be necessary unless the patient is experiencing signs or symptoms of HF. The half-life of trastuzumab ranges from 1 to 32 days; therefore, trastuzumab still may be present during cardiac recovery, even while doses are held, and recovery has been documented even when therapy has continued.¹³ With the current changes in health care, any opportunity to cut down on costs while maintaining quality patient care, especially within cancer treatment, may be beneficial to society as a whole.

Our data suggest that limited monitoring of LVEF in the metastatic setting, as suggested by the 2012 ESMO guidelines, may be appropriate.¹⁴ Cardiac assessment in this setting should be based on symptoms of HF. In addition, it may be worthwhile to discuss changing recommendations for cardiac assessment in the adjuvant setting. For the year of treatment with trastuzumab, if asymptomatic LVEF monitoring occurred every 4 months instead of every 3 months, this would decrease treatment cost by more than \$250 for each patient. If implemented on a large scale, there is significant cost-saving potential with unlikely implications on overall patient safety. Ideally, prospective, randomized controlled trials or reviews from other institutions should be used to assess for the potential of delayed detection of compromised cardiac function, resulting in increased long-term costs and complications.

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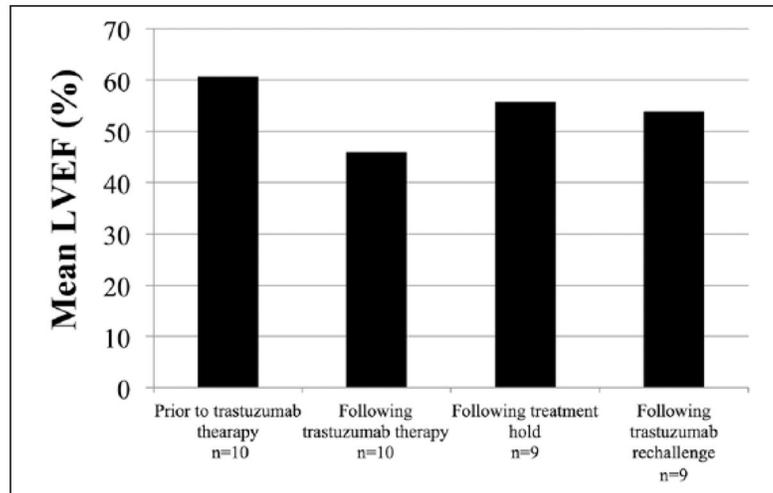


Figure 1. Reversibility of trastuzumab cardiotoxicity: mean LVEF of patients treated with trastuzumab with a dose held for cardiac reasons.
Abbreviations: LVEF, left-ventricular ejection fraction.

Table 1

Patient Demographics.

Characteristic	Adjuvant	Metastatic
Total number of patients (%)	111 (72)	43 (28)
Age at diagnosis in years (mean, range)	54 (24–96)	46 (23–64)
Female gender	110 (99)	43 (100)
Race		
White	54 (49)	15 (35)
Black	49 (44)	23 (54)
Asian	1 (0.9)	3 (7)
Other	4 (3)	2 (5)
BSA		
Mean, m ²	1.86	1.81
Range, m ²	1.33–2.51	1.42–2.34
Stage of disease		NA
0–1	30 (27)	
2	53 (48)	
3	28 (25)	
Smoking status		
Never smoker	79 (72)	27 (64)
Past smoker	22 (20)	9 (21)
Current smoker	9 (8)	6 (14)
Comorbidities		
Hypertension	40 (36)	16 (37)
Hyperlipidemia	24 (21)	10 (23)
Diabetes mellitus	15 (13)	5 (12)
Heart failure	5 (5)	2 (5)
Coronary artery disease	3 (3)	0 (0)
Arrhythmia	2 (2)	1 (2)
Cardiovascular medications, n (%)		
Statin	24 (22)	2 (5)
β-Blocker	15 (14)	4 (9)
ACE inhibitor	14 (13)	6 (14)
ARB	13 (12)	3 (7)
Aspirin	11 (10)	3 (7)
Other BP treatment	28 (25)	6 (14)
Previous treatment		
Taxane	107 (96)	38 (91)
Hormone therapy	57 (51)	26 (61)
Cyclophosphamide	21 (19)	17 (42)
Anthracycline	20 (18)	16 (39)
Left chest radiation	45 (41)	14 (33)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BSA, body surface area; NA, not applicable.

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Table 2

Results.

	Adjuvant, n = 111	Metastatic, n = 43
Cardiac monitoring frequency, mean (IQR)		
Months of trastuzumab treatment	11.5 (11–12)	20.2 (9–31)
Number of echos on trastuzumab	4.5 (2–10)	3.1 (0–9)
Months of trastuzumab/Number of echos	2.6 (2.2–3)	8 (3.5–10)
Cardiac dysfunction, n (%)		
Decline in LVEF 5% to <55% with signs or symptoms of HF	4 (3.6)	2 (6.5) ^a
Decline in LVEF 10% to <55% without signs or symptoms of HF	18 (16.2)	4 (12.9) ^a
Clinical relevance, n (%)		
Dose held for cardiac reasons	7 (6)	3 (7)
Restarted	6 (86)	3 (100)
Treatment change for cardiac reasons	2 (1.8)	0 (0)

Abbreviations: echo, echocardiogram; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction.

^aOnly 31 patients had 1 LVEF measurements to assess for decline.