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Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer

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Abstract

Trastuzumab improves outcomes among patients with HER2-positive breast cancer but is associated with a risk of treatment-induced cardiotoxicity (TIC). It is unclear how frequently TIC leads to trastuzumab interruption outside of prospective trials, and how TIC is managed in clinical practice. Patients with HER2-positive breast cancer receiving adjuvant trastuzumab from 2005 to 2010 were identified ($n = 608$). We evaluated the incidence, risk factors, and management of trastuzumab interruption due to TIC. In total, 488 (80 %) patients were treated with anthracycline prior to trastuzumab. Trastuzumab was interrupted in 108 (18 %) patients. Cumulative trastuzumab dose was lower in the interrupted group (median 86 vs. 108 mg/kg, $p < 0.0001$). The most common

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reason for interruption was TIC (66 of 108 patients): 20 had symptomatic heart failure and 46 had asymptomatic left ventricular ejection fraction (LVEF) decline. Patients with trastuzumab interruption for TIC were older (54 vs. 50 years, $p = 0.014$) with lower LVEF before anthracycline (63 vs. 67 %, $p < 0.0001$) and trastuzumab (62 vs. 67 %, $p < 0.0001$) therapy. Mean LVEF at baseline, TIC diagnosis, and follow-up after trastuzumab interruption was 63, 45, and 55 %, respectively. Thirty-three of 66 patients with TIC were re-challenged with trastuzumab, and five patients had recurrent LVEF decline. In clinical practice, trastuzumab interruption is common and most often due to TIC, with most patients receiving anthracycline prior to trastuzumab. Cardiac dysfunction improves after trastuzumab interruption but may not fully recover to baseline. Strategies to minimize cardiotoxicity and treatment interruption should be investigated to prevent persistent left ventricular dysfunction in affected patients.

Keywords

Trastuzumab; Adjuvant therapy; Breast cancer; Cardiotoxicity; Heart failure

Introduction

Trastuzumab therapy has dramatically improved the clinical outcome of patients with breast cancer that overexpress human epidermal growth factor receptor-2 (HER-2, also known as ERBB2), estimated to occur in up to 25 % of breast cancers [1]. The addition of trastuzumab therapy to sequential anthracycline and taxane adjuvant treatment reduced the risk of breast cancer recurrence by nearly half and the risk of death by one-third [2, 3]. Despite this success, treatment-induced cardiotoxicity (TIC) has been identified as a potentially important clinical problem.

The concern over the cardiac safety of trastuzumab was first raised during early clinical trials among patients with metastatic disease, in which cardiac dysfunction was unexpectedly observed in 27 % of patients receiving anthracycline chemotherapy plus concurrent trastuzumab compared to 2–8 % of patients receiving trastuzumab or anthracyclines alone [4]. Subsequent trials of trastuzumab following anthracycline chemotherapy in the adjuvant setting have reported a lower rate of cardiac death or symptomatic congestive heart failure (CHF). In the joint analysis of the National Surgical Adjuvant Breast and Bowel (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, the cardiac event rate (defined as cardiac-related death or symptomatic CHF) was 4.1 % in the trastuzumab group [2, 5], and in the Herceptin Adjuvant (HERA) trial, the incidence of severe symptomatic CHF (defined as NYHA class III or IV) was 0.8 % in the trastuzumab group [6, 7].

Although the risk of symptomatic CHF due to trastuzumab is generally low, milder forms of cardiac dysfunction are more common and, even without clear evidence that they are harmful or risky, can result in premature interruption or discontinuation of therapy. Asymptomatic declines in left ventricular ejection fraction (LVEF) led to discontinuation of trastuzumab in 14 % of patients in NSABP B-31 [8]. In the HERA trial, 9.8 % of patients treated with trastuzumab compared to 2.9 % in the control group had at least one significant

decline in LVEF [6]. In clinical practice, up to 23 % of patients will develop asymptomatic left ventricular (LV) dysfunction [9–11].

In current practice, interruption or discontinuation of trastuzumab therapy is recommended for a significant decline of LVEF (symptomatic or asymptomatic), defined as a 16 % absolute decrease in LVEF from baseline or 10–15 % absolute decrease in LVEF from baseline to below the institution's lower limit of normal [12]. However, differing LVEF criteria for trastuzumab interruption have been utilized in clinical trials, and there are limited data on the frequency of trastuzumab interruption in clinical practice. Evidence is also lacking on the natural history of TIC and the efficacy of interventions [e.g., beta blocker or angiotensin converting enzyme (ACE) inhibition] to modify that natural history. To address these gaps in knowledge, we performed a retrospective study to determine the incidence of trastuzumab interruption due to TIC and examine the efficacy of therapy for managing symptomatic and asymptomatic LV dysfunction during the course of breast cancer therapy.

Methods

All women diagnosed with early stage HER2-positive breast cancer from January 1, 2005 to October 30, 2010 and treated with adjuvant trastuzumab were identified in the Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY) institutional medical records database. All patients underwent evaluation of LVEF by either multi-gated acquisition scan (MUGA) or two-dimensional (2D) transthoracic echocardiogram. Patients were ineligible for study if they received neoadjuvant trastuzumab or were enrolled in a clinical trial.

A retrospective chart review was performed with the following data extracted for each patient: age, body mass index (BMI), tumor characteristics [tumor size, estrogen receptor (ER) and progesterone receptor (PR) status, number of positive lymph nodes, histologic tumor grade], cancer treatment details (including radiation and surgical therapy), chemotherapy schedule and cumulative dose, and cardiac risk factors. Cardiac risk factors included hypertension, diabetes, hyperlipidemia, coronary artery disease, smoking status, and baseline LVEF. Treatment with beta blockers, ACE inhibitors, or angiotensin receptor blockers (ARB) prior to initiation of trastuzumab was also determined. When available, LVEF measurements as determined by MUGA scans or 2D-echocardiograms were collected at multiple time points including pre-anthracycline, pre-trastuzumab, and sequentially throughout trastuzumab therapy. If a given determination of LVEF was reported as a range, the mean of the range was used as the LVEF.

Trastuzumab dosing and administration guidelines recommend a loading dose of trastuzumab, followed by a maintenance dose at a standard schedule. A complete course of trastuzumab should result in approximately 1 year of therapy with a total dose of 104–110 mg/kg [12]. In this analysis, trastuzumab interruption was defined as an interruption of one or more doses. TIC was defined as an absolute decline of 16 % points from baseline LVEF, or an absolute decline of 10–15 % points from baseline LVEF to below the lower limit of normal (LLN = 55 %). The reason for treatment interruption, as well as the duration of interruption among patients whose treatment was re-initiated, was determined. When trastuzumab interruption occurred due to TIC, patients were classified as symptomatic or

asymptomatic. Symptomatic patients were further categorized into mild [New York Heart Association (NYHA) class I–II] or moderate–severe (NYHA class III–IV) CHF.

Statistical analysis

Descriptive statistics including mean (standard deviation), median (interquartile range), and frequencies for continuous and categorical variables were calculated for the entire cohort, stratified by continuous versus interrupted trastuzumab therapy. Comparisons between the continuous and interrupted groups were made using unpaired Student's *t* test for continuous variables and Chi-square test or Fisher's exact test as appropriate for categorical variables. All statistical analysis was performed using Stata 12 (StataCorp, College Station, TX). A *p* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Between January 1, 2005 and October 30, 2010, a total of 1,228 patients with HER2-positive early breast cancer were treated at our institution. The following patients were ineligible for study: 179 patients were enrolled in a clinical trial, 155 patients received neoadjuvant trastuzumab, and 286 patients received partial treatment outside of our institution. In total, 608 patients were included in this study. Baseline characteristics are listed in Table 1. Mean age at diagnosis was 51 years (range 26–81 years). Overall, 488 (80.3 %) patients were treated with anthracycline chemotherapy prior to trastuzumab (median doxorubicin isotoxic equivalent dose = 240 mg/m²). All patients underwent surgical resection prior to initiation of trastuzumab therapy.

Trastuzumab interruption

Trastuzumab therapy was interrupted in 108 (17.8 %) of 608 patients. Patients with trastuzumab interruption were older (55 vs. 50 years, $p < 0.0001$), had a higher BMI (28.2 vs. 26.9 kg/m², $p = 0.036$), and had a higher prevalence of ER negative (47.2 vs. 31.6 %, $p = 0.002$) and PR negative (57.4 vs. 46.2 %, $p = 0.034$) disease. TIC was the reason for interruption in 66 of these 108 (61 %) patients: 16 interrupted during the first quarter of therapy, 28 during the second quarter of therapy, 13 during the third quarter of therapy, and 9 during the final quarter of therapy. Other reasons for interruption included non-cardiac adverse events ($n = 16$), patient request ($n = 9$), disease progression during therapy ($n = 7$), patient non-compliance ($n = 4$), and other ($n = 6$) (Table 2). Patients with trastuzumab interruption received a significantly lower cumulative trastuzumab dose (median 86 vs. 108 mg/kg, $p < 0.0001$). Overall, 47 (43.5 %) of 108 patients with trastuzumab interruption were re-challenged with trastuzumab.

Treatment-induced cardiotoxicity

Of 66 patients who had trastuzumab interrupted due to TIC, 46 had an asymptomatic decline in LVEF, 9 had mild CHF, and 11 had moderate to severe CHF. Compared to patients receiving uninterrupted therapy, patients with treatment interruption for cardiotoxicity were older (54 vs. 50 years, $p = 0.014$) with lower LVEF prior to anthracycline chemotherapy (63.2 vs. 67.2 %, $p < 0.0001$) as well as prior to trastuzumab therapy (61.8 vs. 66.6 %, $p < 0.0001$).

$p < 0.0001$). Preexisting treatment with a beta blocker, ACE-I, or ARB prior to chemotherapy was more common in the interruption group, although this did not reach statistical significance (30 vs. 20 %, $p = 0.054$). Twenty-three (35 %) of the 66 interrupted patients did not have any cardiac risk factors at baseline (Table 3). The changes in LVEF from baseline to the time of trastuzumab interruption were as follows: 57 patients had a decrease in LVEF by 10–15 % to below the LLN, 5 with a decrease in LVEF by <10 % to below the LLN, 3 with a decrease of 10 % but above the LLN, and 1 with a decrease in LVEF by 16 %. The mean LVEF at the time of trastuzumab interruption was 44.8 ± 9 %.

Thirty-six of 66 patients were prescribed a new cardiac medication after developing treatment-induced cardiotoxicity. The pattern of LVEF decline and recovery is shown in Fig. 1. A follow-up LVEF assessment at least 3 months after diagnosis of cardiotoxicity was performed in 51 patients, and improvement in cardiac function was observed in patients with and without initiation of a new cardiac medication. Although LVEF increased after trastuzumab interruption (mean LVEF at recovery, 55.4 ± 7.5 %), it failed to fully recover to baseline levels. Nearly all patients (55 of 66) were referred to a cardiologist after diagnosis of TIC. Thirty-three of 66 (50 %) patients with treatment interruption due to TIC were re-challenged with trastuzumab after LVEF had recovered (median 55 %, range 50–67 %). The median interruption period was 64 days (range 42–144). Twenty-eight patients had a stable LVEF after reintroduction of trastuzumab with median additional treatment duration of 6.4 months (range 0–10.5 months). A recurrent decline in LVEF was observed in five patients leading to a second interruption in trastuzumab treatment; however, LVEF improved to >55 % in all five patients after trastuzumab was discontinued.

Discussion

Trastuzumab is a highly effective treatment that significantly improves cancer outcomes in patients with HER2-positive early breast cancer. The principal findings of this observational study indicate that trastuzumab therapy interruption most often occurs due to TIC. Since most patients are usually asymptomatic from a cardiac standpoint, LV dysfunction is detected during routine serial LVEF assessments. The majority of patients received anthracycline-based chemotherapy before trastuzumab therapy so the term “treatment (rather than trastuzumab) induced cardiotoxicity” is used, since any myocardial injury that may have occurred is likely secondary to the effects from both anthracycline and trastuzumab.

We found that patients in the trastuzumab interruption group received a lower cumulative dose of trastuzumab. Based on the results of several landmark clinical trials, 1 year of trastuzumab has been the standard course of therapy for patients with HER2-positive early breast cancer [2, 3], but several follow-up studies have been performed to investigate the optimal duration of treatment. The HERA trial compared breast cancer outcome between patients treated for 1 versus 2 years of trastuzumab and showed that 2 years of therapy was not more effective than 1 year of therapy but was associated with increased adverse events [13]. And the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial evaluated a shorter duration of adjuvant trastuzumab and failed to show that 6 months of trastuzumab therapy was non-inferior to 12 months of trastuzumab [14]. We await the results from other phase III randomized clinical trials looking at the efficacy of shorter versus

longer durations of trastuzumab, including Short-Her (3 months vs. 12 months of trastuzumab, NCT00629278), Synergism Or Long Duration (SOLD) (9 weeks vs. 12 months of trastuzumab, NCT00593697), and PERSEPHONE (6 vs. 12 months of trastuzumab, NCT00712140). Until additional prospective data are available, the goal of trastuzumab therapy should be a full year for a complete course, and interventions that minimize trastuzumab interruptions and prevent cardiotoxicity should be sought.

In a subgroup analysis, patients with trastuzumab interruption secondary to TIC were older with a lower LVEF prior to anthracycline and trastuzumab therapy compared to the continuous group. These patients were also more likely to have been treated with ACE inhibitors, ARBs, or beta blockers prior to the initiation of breast cancer therapy, although this association failed to reach statistical significance. Medicare claims-based data from Wang et al. recently showed that among older women, those with early discontinuation were more likely to have a cardiovascular event (e.g., heart failure, cardiomyopathy, or atrial fibrillation) within 45 days of the last trastuzumab treatment [15]. These data are consistent with our findings. And consistent with results from NSABP B-31, our results also suggest that age, baseline LVEF, and LVEF after chemotherapy may be important risk factors for the subsequent development of cardiotoxicity [8]. Given this information, several attempts have been made to devise a risk model for predicting cardiac events associated with cardiotoxic chemotherapy. For example, Ezaz et al. recently proposed a seven-factor clinical risk score to predict heart failure and cardiomyopathy among women treated with adjuvant trastuzumab [16]. The development of an individualized risk assessment tool would help clinicians to tailor appropriate chemotherapy treatment regimens and identify patients who would most benefit from intensive cardiac monitoring or prophylactic cardioprotective medications to prevent cardiotoxicity.

Several randomized clinical trials are currently underway to investigate the benefit of prophylactic cardiac medications for the prevention of TIC. The Multidisciplinary Approach to Novel Therapies In Cardiology Oncology Research trial (MANTICORE 101) is testing the effect of conventional heart failure therapy including perindopril or bisoprolol to prevent LV remodeling among women with early HER2-positive breast cancer [17]. The Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy (PRADA) study is a randomized trial testing an ARB (candesartan) and beta blocker (metoprolol) in a 2×2 factorial design among patients on adjuvant treatment for early breast cancer [18]. And a National Cancer Institute sponsored study is looking to determine whether administration of lisinopril or carvedilol phosphate, compared to placebo, will reduce the incidence of trastuzumab-associated cardiotoxicity (NCT01009918). These trials will provide invaluable insight into the potential of heart failure therapy to protect against cardiovascular damage caused by adjuvant therapy. The additional application of imaging and/or blood-based biomarkers could also be helpful for targeting patients at increased risk for cardiac injury and thus more likely to benefit from a cardioprotective strategy [19–22].

Although LVEF improved in most patients with TIC, with or without initiation of cardioprotective medications, it failed to recover to baseline levels despite treatment interruption. This calls into question whether TIC is indeed truly reversible, granted that the majority of these patients received an anthracycline along with trastuzumab [23]. Long-term

follow-up data from clinical trials of adjuvant therapy have shown that while the cardiac event rate remains low, subclinical cardiac dysfunction can persist for several years after completion of breast cancer treatment [5, 24]. The clinical implications that this may have on a patient's quality of life (e.g., fatigue or exercise capacity) or future risk of cardiac events remains unknown. Further studies are needed to determine the incremental benefit that cardioprotective medications provide in addition to trastuzumab interruption among patients diagnosed with TIC.

This study has several limitations. The frequency and modality of cardiac monitoring was variable, and follow-up LVEF assessments were performed at the discretion of the attending physicians. Changes in LVEF that led to trastuzumab interruption were heterogeneous, and this reflects the lack of a consensus definition for TIC as well as the variability inherent between different modalities of LVEF assessment. We observed that LVEF failed to return to baseline after treatment interruption; however, it is possible that LVEF may have continued to improve with additional long-term cardiac surveillance.

In conclusion, trastuzumab therapy interruption is common in clinical practice, occurred most often due to TIC, and resulted in a lower cumulative dose of trastuzumab therapy among women with HER2-positive early breast cancer. The impact of trastuzumab interruption on breast cancer outcomes remains unknown and warrants further investigation. Our results suggest that age and lower baseline LVEF (before and after anthracycline chemotherapy) may be useful factors to identify patients who may derive the most benefit from a cardioprotective strategy. Studies to determine the efficacy of beta blockers and ACE inhibitors for the prevention of TIC and to minimize treatment interruption are necessary and currently underway.

Abbreviations

2D	Two-dimensional
ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
BMI	Body mass index
CHF	Congestive heart failure
HER-2	Human epidermal growth factor receptor-2
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
MUGA	Multi-gated acquisition scan

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Fig. 1.

Left ventricular ejection fraction in patients with treatment-induced cardiotoxicity. Shown are the values for the mean LVEF at baseline, at diagnosis of cardiotoxicity, and at recovery among patients with trastuzumab interruption due to treatment-induced cardiotoxicity ($n = 66$). Improvement in LVEF was observed in patients treated with new cardiac medications at time of cardiotoxicity diagnosis (*blue line*, $n = 36$) as well as patients without new cardiac medications at time of cardiotoxicity diagnosis (*red line*, $n = 30$). Asterisk indicates follow-up LVEF assessment available in 51 of 66 patients

Table 1

Patient characteristics

	Total (<i>n</i> = 608)
Age (year)	51.3 ± 11.1
BMI (kg/m ²)	27.1 ± 5.8
Histologic type	
Ductal	588 (96.7)
Lobular	16 (2.6)
Other	4 (0.7)
Tumor size (cm)	2.2 ± 1.6
Histologically positive nodes, median (range)	1 (0–34)
Estrogen receptor status	
Positive	399 (65.6)
Negative	209 (34.4)
Progesterone receptor status	
Positive	315 (51.8)
Negative	293 (48.2)
Histologic grade	
Poorly differentiated	507 (83.4)
Moderately differentiated	83 (13.7)
Well differentiated	3 (0.5)
Surgery type	
Mastectomy	374 (61.5)
Breast conserving	234 (38.5)
XRT	369 (60.7)
Left chest wall XRT	208 (34.2)
Anthracycline exposure (year)	487 (80.1)
Trastuzumab dose (mg/kg), median (IQR)	106 (102–110)

Numbers are mean ± SD for continuous variables (unless otherwise specified), and *N*(%) for categorical variables

XRT radiation therapy, *IQR* interquartile range

Table 2

Indications for trastuzumab interruption

	Total (<i>n</i> = 608)
Treatment-associated cardiotoxicity	66 (10.9 %)
Asymptomatic LVEF decline	46 (7.6 %)
Symptomatic LVEF decline	20 (3.3 %)
NYHA class I–II	9 (1.5 %)
NYHA class III–IV	11 (1.8 %)
Non-cardiac adverse event	16 (2.6 %)
Back/joint pain	1
Nausea/vomiting	1
Pneumonitis/shortness of breath	4
Rash/hypersensitivity	3
Fatigue	2
Other	5
Patient request/withdrawal	9 (1.5 %)
Disease progression	7 (1.2 %)
Non-compliance	4 (0.7 %)
Other	6 (1.0 %)

LVEF left ventricular ejection fraction, *NYHA* New York Heart Association

Table 3

Baseline cardiac risk factors

	Continuous trastuzumab (<i>n</i> = 500)	Trastuzumab interruption, cardiac (<i>n</i> = 66)	<i>p</i> value
Age	50.4 ± 10.9	53.9 ± 10.7	0.014
Hypertension	128 (25.6)	22 (33.3)	0.181
Diabetes	31 (6.2)	7 (10.4)	0.179
Smoking, current or former	190 (38.0)	23 (34.8)	0.619
Hyperlipidemia	101 (20.2)	19 (28.4)	0.109
Known coronary artery disease	7 (1.4)	3 (4.5)	0.099
Cardiac medications, prior to cancer treatment	100 (20.0)	20 (29.9)	0.054
ACE inhibitor/ARB	61	6	
Beta blocker	24	9	
ACE inhibitor/ARB+beta blocker	15	5	
Pre-anthracycline LVEF	67.2 ± 6.0	63.2 ± 7.0	<0.0001
Pre-trastuzumab LVEF	66.6 ± 6.1	61.8 ± 7.3	<0.0001

Numbers are mean ± SD for continuous variables and *N*(%) for categorical variables

ACE *inhibitor* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *LVEF* left ventricular ejection fraction