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Cardiac Safety of Non-Anthracycline Trastuzumab-Based Therapy for HER2-Positive Breast Cancer

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Abstract

Purpose—Trastuzumab improves overall survival for women with HER2-positive breast cancer but is associated with cardiotoxicity, especially when administered after anthracyclines. Use of non-anthracycline trastuzumab-based regimens is rising, particularly for patients with low risk disease or with multiple cardiovascular risk factors. We performed a single center retrospective cohort study to assess the cardiac safety of trastuzumab without anthracyclines outside of a clinical trial setting.

Methods—A retrospective chart review was conducted of patients with HER2-positive early-stage breast cancer receiving non-anthracycline trastuzumab-based therapy between January 2010 and June 2014. Cardiovascular risk factors, left ventricular ejection fraction (LVEF), and treatment interruption data were collected. The primary outcome was a cardiac event (CE), defined by New York Heart Association class III or IV heart failure or cardiac death. The secondary outcome was a significant asymptomatic decline of LVEF (≥ 10% to < 55% or ≥ 16% from baseline).

Results—A total of 165 patients were identified with a median age of 59 years (range, 32 to 85 years). Seventy (42%) had hypertension, 52 (32%) had hyperlipidemia, 29 (18%) had diabetes, and 5 (3%) had coronary artery disease. All patients had a LVEF ≥ 50% (median, 67%; range, 50% to 80%) at baseline. Two (1.2%) patients with multiple cardiovascular risk factors developed a CE. After discontinuation of trastuzumab, both patients had recovery of LVEF to > 50% and

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resolution of heart failure symptoms. Ten (6.1%) patients developed significant asymptomatic LVEF decline during trastuzumab therapy.

Conclusions—The overall incidence of symptomatic heart failure and asymptomatic LVEF decline among patients receiving trastuzumab without anthracyclines remains low. These findings suggest that less intensive cardiac monitoring may be appropriate during trastuzumab therapy without anthracyclines.

Keywords

cardiotoxicity; heart failure; trastuzumab; cardio-oncology

INTRODUCTION

Trastuzumab administered with standard chemotherapy improves the outcomes for women with human epidermal growth factor 2 (HER2) positive breast cancer, with a 40%–50% risk reduction in breast cancer recurrence and 33% risk reduction in all-cause death.[1, 2] Cardiotoxicity, manifest by symptomatic heart failure (HF) or significant asymptomatic decline of left ventricular ejection fraction (LVEF), is a well known toxicity of trastuzumab, particularly when administered as part of an anthracycline-based regimen. Based on findings from phase III clinical trials of sequential anthracycline chemotherapy and trastuzumab in women with early-stage breast cancer, the incidence of symptomatic HF ranged from 2% to 4%.[1, 2] Clinical risk models for trastuzumab cardiotoxicity based on both retrospective and prospective data have consistently identified anthracyclines as a primary risk factor for trastuzumab cardiotoxicity.[3–6]

The role of anthracyclines for the treatment of breast cancer has remained a source of controversy, in part due to the increased risk of cardiotoxicity.[7–10] In a single-arm multicenter trial of 406 patients treated with paclitaxel plus trastuzumab (without an anthracycline) for stage I HER2-positive breast cancer, the 3-year disease-free survival rate was 98.7% with a low incidence of severe heart failure of 0.5%.[11, 12] In a similar phase II study of 493 patients with early stage HER2-positive breast cancer treated with docetaxel plus cyclophosphamide plus trastuzumab, the 3-year disease-free survival rate was 96.9% with only 2 (0.4%) patients developing severe heart failure.[13] Because many clinical trials exclude patients with known cardiovascular disease, this raises the concern that cardiotoxicity estimates may not be generalizable to the real-world population. For example, patients with a prior myocardial infarction, congestive heart failure, or use of any treatment specifically for heart failure were excluded from the study by Tolaney, et al.[11]

We performed a single institutional retrospective cohort study to assess the risk of cardiotoxicity with non-anthracycline trastuzumab-based regimens among HER2-positive breast cancer patients with cardiovascular risk factors representative of routine clinical practice.

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METHODS

Women diagnosed with HER2-positive early breast cancer and received trastuzumab-based therapy without an anthracycline between January 1, 2010 and June 30, 2014 were studied. Patients with any prior anthracycline exposure and patients participating in a clinical trial were excluded. A retrospective chart review was performed with the following data extracted: patient demographics, tumor characteristics, cancer treatment details, and baseline cardiovascular risk factors. Data from all LVEF assessments by two-dimensional echocardiography, multi-gated acquisition scan (MUGA), or cardiac MRI performed at baseline and at 3, 6, 9, and 12 months (+/− 45 days) after initiation of trastuzumab were obtained. The primary outcome was a cardiac event, defined as New York Heart Association (NYHA) class III/IV heart failure or cardiac death, as previously described.[1] The secondary cardiac outcome was an asymptomatic LVEF decline, defined by an absolute decline of ≥ 10% from baseline to below the lower limit of normal (55% at our institution during the study period)[14] or ≥ 16% (and above the lower limit of normal) without symptoms of heart failure (NYHA class III/IV). Interruption of trastuzumab was defined by interruption of 1 or more doses, or ≥ 6 weeks between doses. All patients were followed until completion of one year of trastuzumab-based therapy or interruption of trastuzumab-based therapy. This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center.

Descriptive statistics were used for patient characteristics. Continuous measures were summarized as median and range or mean and standard deviation, whereas categorical measures were summarized as frequency and percent. Comparisons in LVEF from baseline to 3, 6, 9, and 12 months (+/− 6 weeks) of anti-HER2 therapy were made using paired Student's *t*-test.

RESULTS

A total of 165 patients were treated with trastuzumab in the adjuvant or neoadjuvant setting without an anthracycline during the study period. Baseline characteristics are summarized in Table 1. The median age at breast cancer diagnosis was 59 years (range, 32 to 85 years). Overall, 125 (76%) received paclitaxel and trastuzumab, 16 (9%) received cyclophosphamide, methotrexate, 5-fluorouracil (CMF), and trastuzumab, 13 (8%) received docetaxel, carboplatin, and trastuzumab, 3 (2%) received docetaxel, cyclophosphamide, and trastuzumab, and 8 (5%) received trastuzumab monotherapy.

Baseline risk factors and cardiac function

Cardiovascular risk factors were prevalent at baseline, including hypertension, diabetes, hyperlipidemia, and smoking history in 70 (42%), 29 (18%), 52 (32%), and 42 (25%) of patients, respectively. The majority of patients [96/165 (58%)] were overweight, with a median BMI of 26.1 kg/m^2 (range 18.2 to 46.2 kg/m^2). Overall, the cohort had an increased cardiovascular risk with 99 (60%) participants having at least two risk factors (i.e. hypertension, diabetes, hyperlipidemia, coronary artery disease, tobacco history, obesity, or age ≥ 50 years). Although 5 participants had a prior history of non-ischemic cardiomyopathy, all had a LVEF of at least 50% at baseline prior to beginning trastuzumab

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with a median LVEF of 67% (range 50% to 80%). The baseline LVEF assessment was performed a median of 11 days (range 0 to 102 days) prior to beginning trastuzumab in 162 (98%) patients, and within 1 week of beginning trastuzumab in the remaining 3 patients. Only 4 patients had a borderline LVEF between 50% and 54% prior to beginning trastuzumab.

Change in cardiac function during breast cancer treatment

In total, 165 participants contributed 519 LVEF assessments during the trastuzumab treatment period to this study, with a median of 3 LVEF assessments (IQR 3, 4) (Table 2). Overall, a LVEF assessment was performed at baseline, 3, 6, 9, and 12 months in 165 (100%), 117 (72%), 85 (55%), 95 (63%), and 35 (25%) of patients. There was a modest decline in median LVEF compared to baseline (67%, range 50% to 80%) at 3 months (65%, range 33% to 81%, $p > 0.05$), 6 months (64%, range 20% to 80%, $p=0.003$), 9 months (65%, range 48% to 78%, $p=0.01$), and 12 months (63%, range 53% to 78%, $p>0.05$) (Table 2).

Asymptomatic LVEF decline

Ten (6.1%) patients developed an asymptomatic LVEF decline (95% CI, 2.9%–10.9%) (Table 3). Five patients completed a full course of trastuzumab therapy without interruption despite an asymptomatic LVEF decline (nadir LVEF range 46% to 55%). Four patients permanently discontinued trastuzumab due to a persistent asymptomatic LVEF decline (nadir LVEF range 33% to 52%) and all had a recovery of LVEF to > 55%. One patient had a temporary interruption of trastuzumab for asymptomatic LVEF decline, subsequently was rechallenged with trastuzumab after LVEF recovery, and successfully completed therapy. New cardiac medications (i.e. beta blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or diuretic) were initiated or the dose of a preexisting cardiac medication was up-titrated in 5 of the 10 patients with asymptomatic LVEF decline. Additional clinical details can be found in the Supplementary Table.

Symptomatic Heart Failure

Of 165 evaluable patients, 2 (1.2%) patients with multiple cardiovascular risk factors at baseline developed symptomatic heart failure (95% CI, 0.2%–4.3%). The first patient was a 55 year old woman with stage II invasive ductal carcinoma of the right breast who underwent a partial mastectomy followed by adjuvant paclitaxel and trastuzumab. She had a history of possible diagnosis of arrhythmogenic right ventricular cardiomyopathy, obesity ($BMI=39kg/m^2$) and frequent premature ventricular contractions treated with a beta-blocker. Her baseline LVEF was 66%. After approximately 6 months of trastuzumab, she developed lower extremity edema, orthopnea, and exertional dyspnea, leading to an emergency room visit where a repeat echocardiogram showed a LVEF of 50% and moderate diastolic dysfunction. Laboratory and imaging testing were notable for an elevated B-type natriuretic peptide of 282mg/dL, and CT of the chest showed diffuse bilateral ground glass opacities suggestive of pulmonary edema. A repeat echocardiogram 1 week later confirmed a mild reduction in LV systolic function with a LVEF of 47%. She improved symptomatically with diuresis, and an ACE inhibitor was initiated. Three months after permanent discontinuation of trastuzumab, her LVEF improved to 56%.

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The second patient was a 76 year old woman with stage II invasive ductal carcinoma of the left breast who underwent a total mastectomy followed by adjuvant paclitaxel and trastuzumab. She had a history of hypertension managed with a calcium channel blocker, hyperlipidemia, obesity (BMI=31kg/m^2), and a left bundle branch block. Her baseline LVEF was borderline reduced at 52%. Five months after initiation of trastuzumab she was hospitalized for severe symptomatic heart failure with a LVEF of 20% and respiratory failure requiring a short period of mechanical ventilation. Trastuzumab was permanently discontinued and she was treated with a beta-blocker, ACE-inhibitor, and diuretic. Her heart failure symptoms resolved and LV systolic function normalized with LVEF of 58% at 15 months after discontinuation of trastuzumab.

DISCUSSION

In this single-institutional retrospective cohort study, we demonstrate that trastuzumab administered in the absence of anthracycline chemotherapy is well-tolerated from a cardiac standpoint. Overall, trastuzumab results in a modest decline in LVEF during active therapy (median LVEF of 67% at baseline and 63% at 12 months) and with a low incidence of significant asymptomatic LVEF decline of 6.1% and symptomatic heart failure of 1.2%. The majority of patients in this cohort study received paclitaxel plus trastuzumab, with fewer patients receiving trastuzumab in combination with docetaxel and carboplatin, docetaxel and cyclophosphamide, or CMF. Prior studies have reported the clinical efficacy of non-anthracycline trastuzumab-based regimens also with low cardiac events.[2, 11, 13] This cohort study is encouraging on the low cardiac event rate outside of a clinical trial setting.

The clinical relevance and optimal management of significant asymptomatic LVEF declines that develop during trastuzumab remain an area of controversy. Half of patients who developed asymptomatic LVEF decline in this study were able to complete the full course of trastuzumab without interruption, without further worsening of LVEF or progression to symptomatic heart failure. This is consistent with a previous study showing the tolerability of uninterrupted trastuzumab among patients who developed significant LVEF decline but remained greater than or equal to 50%.[15] Moving forward, it is important to determine the safety of continuing anti-HER2 therapy in patients with significant asymptomatic LVEF decline with LVEF of < 50%. Notably, SAFE-HEaRt is one such study which is a prospective clinical trial that is evaluating the cardiac safety of continuous trastuzumab, ado trastuzumab, or pertuzumab for patients with LVEF decline between 40% and 49% (NCT01904903).

Symptomatic heart failure events reported in our cohort were infrequent and occurred in two (1.2%) participants, both with an elevated cardiovascular risk profile prior to being treated with trastuzumab. The incidence of symptomatic heart failure in patients treated with non-anthracycline trastuzumab-based regimens has previously been reported between 0.4%–0.5%.[2, 12, 13] The modest increase in heart failure observed in our cohort may be attributable to the higher cardiovascular risk profile seen in our real-world patient cohort outside of the clinical trial setting. For example, in the non-anthracycline (docetaxel, carboplatin, trastuzumab) arm of the BCIRG 006 study, 18% had hypertension and 3% had diabetes. In contrast, among the participants in our study cohort, 42% had hypertension and

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18% had diabetes. Furthermore, the median age in our group was higher than those in clinical trials.[2, 11, 13]

Current trends in breast cancer treatment indicate a rise in the use of non-anthracycline based regimens, especially among older patients who are likely to have concomitant cardiovascular risk factors.[8] Despite the lower risk of cardiotoxicity observed with non-anthracycline trastuzumab-based regimens, routine serial LVEF assessments continue to be recommended for all patients treated with trastuzumab.[16] This raises the question of whether current cardiac monitoring guidelines, originally implemented to detect cardiotoxicity associated with anthracycline-based regimens (i.e. ACTH), should be updated to take into account the variability and improved cardiac safety profile of trastuzumab regimens in use today. For example, intensive serial cardiac monitoring at baseline and every 3 months could be reserved for patients with at least two cardiovascular risk factors, including prior anthracycline exposure, and less frequent cardiac monitoring employed for patients with less than two cardiovascular risk factors, especially for those treated with a non-anthracycline regimen. Although less frequent cardiac monitoring could result in missed cases of asymptomatic LVEF decline, preliminary data suggest that continued trastuzumab may be well tolerated in this setting.[15] Additionally, it is still unclear on the long-term clinical significance of asymptomatic LVEF decline in the oncology setting. Limited cardiac monitoring, however, would minimize interruption of life-saving trastuzumab-based therapy and decrease healthcare costs by reducing unnecessary medical testing. A carefully designed prospective study is needed to adequately address the safety of a modified cardiac monitoring strategy.

This study has several possible limitations. First, in this retrospective study the timing, frequency, and modality of LVEF assessment were at the discretion of the treating physician. Therefore, it is possible that the incidence of asymptomatic LVEF decline is underestimated. However, a thorough review of the electronic health record was performed to identify and adjudicate the clinical endpoint of symptomatic heart failure, a pragmatic endpoint of greater clinical significance than a change in LVEF. The inclusion of patients treated in the real-world, outside of a clinical trial setting, with concomitant cardiac history (i.e. prior myocardial infarction or cardiomyopathy) adds to the generalizability of our findings. In a recent update on BCIRG 006, with a median follow-up of 10 years, there was no increase in the incidence of symptomatic heart failure in all arms, including the non-anthracycline group.[17] Thus, it is encouraging to note that late cardiac events with trastuzumab-based therapy will be rare with a non-anthracycline based treatment, but notably also with anthracycline therapies.[17–20]

In conclusion, treatment with non-anthracycline trastuzumab-based regimens results in a modest decline in LVEF during the trastuzumab treatment period. In an unselected cohort of patients outside of a clinical trial setting, including those with multiple cardiovascular risk factors, the incidence of asymptomatic LVEF decline and symptomatic heart failure was low. With the growing use of non-anthracycline trastuzumab-based regimens, there is a need to critically examine the utility of intensive and routine cardiac monitoring during breast cancer treatment to ensure that the highest level of cardiac safety is achieved without jeopardizing cancer outcomes or incurring unnecessary medical expense.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of patients treated with trastuzumab without anthracyclines who developed or did not develop cardiotoxicity

Characteristic	Entire Cohort (N=165)
Age (y)	
Median (range)	59 (32–85)
Body mass index (BMI), kg/m^2	26.1 (18.2 – 46.2)
< 25	69 (42)
25–29.9	52 (31)
≥ 30	44 (27)
Histologic type:	
Ductal	161 (98)
Lobular	4 (2)
Estrogen Hormone receptor status	
Positive	122 (74)
Negative	43 (26)
Progesterone Hormone receptor status	
Positive	88 (53)
Negative	77 (47)
Cumulative trastuzumab dose, median (mg/kg), (range)	108 (14–146)
CV risk factors	
Hypertension	70 (42)
Diabetes mellitus	29 (18)
Hyperlipidemia	52 (32)
Coronary artery disease	5 (3)
Tobacco history	42 (25)
≥ 2 cardiac risk factors *	99 (60)
Chemotherapy regimen	
Cyclophosphamide, methotrexate, 5-fluorouracil (CMF), trastuzumab	16 (9)
Docetaxel, carboplatin, trastuzumab (TCH)	13 (8)
Docetaxel, cyclophosphamide, trastuzumab	3 (2)
Paclitaxel, trastuzumab (TH)	125 (76)
Trastuzumab (single agent)	8 (5)

Data given as no. (%) unless otherwise indicated

* Cardiac risk factors include hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, tobacco history, obesity (BMI ≥ 30), and age older than 50 years.

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Table 2

Summary of LVEF during trastuzumab treatment period (baseline to 12 months) and changes from baseline values (N=165).

Variable	0 months (before trastuzumab)	3 months	6 months	9 months	12 months	Cumulative
Patients receiving T (n)	165	163	155	150	141	
TTE performed	165/165 (100)	117/163 (72)	85/155 (55)	95/150 (63)	35/141 (25)	
LVEF						
Median	67%	65%	64%	65%	63%	
Range	50–80%	33–81%	20–80%	48–78%	53–78%	
Mean ± SD	66.5 ± 6.0%	65.4 ± 7.0%	63.2 ± 8.1%	64.3 ± 5.3%	64.0 ± 5.7%	
LVEF decline						
≥ 10% to < LLN		4 (2.4)	5 (3.0)	0 (0)	0 (0)	9 (5.5)
≥ 16% to ≥ LLN		1 (0.6)	1 (0.6)	0 (0)	1 (0.6)	3 (1.8)
Number of LVEF assessments performed, median (range)						3 (1 – 6)
1–2						41 (25)
3–4						105 (64)
≥ 5						19 (11)

Data given as no. (%).

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Table 3

Cardiac Events

Events	Entire Cohort (n=165)
Cardiac Event (total)	12 (7.2)
LVEF Decline *	10 (6.1)
≥ 10% and < LLN	7 (4.2)
≥ 16% and ≥ LLN	3 (1.8)
Symptomatic heart failure (NYHA class III/IV)	2 (1.2)
Cardiac Death	0 (0)
Trastuzumab Interruption	
Cardiac	7 (4.2)
Non-cardiac	11 (6.7)

Data given as no. (%). NYHA, New York Heart Association.

* LVEF decline without severe (NYHA class III/IV) heart failure