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Trastuzumab-induced cardiotoxicity: testing a clinical risk score in a real-world cardio-oncology population

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ABSTRACT

Background Trastuzumab has improved survival for women with HER2-positive breast cancer, but its use is associated with an increased risk of cardiotoxicity. With increased survivorship, the long-term effects of cancer treatment are an important consideration for clinicians and patients. We reviewed the current literature on predicting trastuzumab-related cardiotoxicity and tested a clinical risk score (CRS) in a real-world breast cancer population to assess its utility in predicting permanent cardiotoxicity.

Methods In this retrospective exploratory cohort study of breast cancer patients referred to a cardio-oncology clinic at a tertiary care centre between October 2008 and August 2014, a CRS was calculated for each patient, and a sensitivity analysis was performed.

Results Of the 143 patients included in the study, 62 (43%) experienced a cardiac event, and of those 62 patients, 43 (69%) experienced full recovery of cardiac function. In applying the CRS, 119 patients (83%) would be considered at low risk, 14 (10%) at moderate risk, and 10 (7%) at high risk to develop heart failure or cardiomyopathy. When applied to the study population, the high-risk cut-off score had a sensitivity of 0.13 [95% confidence interval (CI): 0.08 to 0.20] and a specificity of 0.94 (95% CI: 0.87 to 0.97). The positive predictive value was 0.07 (95% CI: 0.03 to 0.13), and the negative predictive value was 0.93 (95% CI: 0.87 to 0.96).

Conclusions The CRS demonstrated good specificity and negative predictive value for the development of permanent cardiotoxicity in a real-world population of breast cancer patients, suggesting that intensive cardiac monitoring might not be warranted in low-risk patients, but that high-risk patients might benefit from early referral to cardio-oncology for optimization. Further study using the CRS in a larger breast cancer population is warranted to identify patients at low risk of long-term trastuzumab-related cardiotoxicity.

Key Words Breast cancer, trastuzumab, cardiotoxicity, heart failure

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INTRODUCTION

Breast cancer (BCA) is the most common cancer diagnosed in North America, with an estimated 252,710 new cases in the United States in 2017[1] and 26,000 new cases in Canada[2] in 2016. Early detection and advances in screening have led to a 5-year survival rate approaching 90%, and in the United States, almost 3 million people are living with a prior diagnosis of BCA[1]. With increased survivorship, the long-term effects of cancer treatment become an important consideration for clinicians and patients.

Cardiovascular disease is the leading cause of death in women in North America[3], and it is now a common cause of death among women who survive BCA beyond 9 years[4]. Cancer and cardiac disease share common risk factors such as obesity and physical inactivity, and those risk factors can worsen over the course of cancer therapy[5–8]. Given the long-term cardiac risks faced by BCA survivors, the effect of cancer therapy on cardiovascular health is a major concern.

Cardiotoxicity associated with BCA treatment can be multifactorial. Radiation therapy is effective in reducing local recurrence, but it is associated with an increased

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risk of ischemic heart disease and coronary artery disease 20 years or longer after treatment[9]. Use of anthracycline-based chemotherapy regimens in adjuvant BCA treatment has been shown to improve overall survival[10], but those regimens carry a dose-related risk of cardiomyopathy (CM) because of the cytotoxic effects of anthracyclines on the heart[11], which can be irreversible. Targeted agents such as trastuzumab have improved clinical outcomes for the 20% of women with BCA who overexpress HER2 (the human epidermal growth factor receptor)[12]; however, concurrent administration of anthracycline–trastuzumab in women with metastatic BCA is associated with a high rate (28%) of heart failure (HF)[13].

In contrast to anthracycline-induced cardiotoxicity, trastuzumab-related cardiotoxicity is not associated with the dose received and is often reversible. In adjuvant BCA trials using sequential anthracycline-based chemotherapy and trastuzumab, the relative risk of HF was 5.11 [90% confidence interval (CI): 3 to 8.72], and the absolute rate of HF was only 2.5% (range: 0%–4%)[14]. Currently, it is difficult to predict which patients are at highest risk of developing cardiotoxicity from trastuzumab-based therapy.

Predicting Cardiotoxicity: The Current State of Clinical Practice

Two clinical prediction tools have been published in the setting of early-stage HER2-positive BCA treated with trastuzumab. In 2012, Romond *et al.*[15] used 7-year follow-up data from the National Surgical Adjuvant Breast and Bowel Project B-31 adjuvant trastuzumab study to derive a prediction tool for cardiotoxicity (defined as probable or definite cardiac death; or HF manifested by a decrease in LVEF greater than 10% below the threshold of 55%, or 5% below the lower limit of normal, or asymptomatic patients who stopped trastuzumab because of a decline in LVEF). The overall rate of cardiac events at the 7-year follow-up was 4.0%. All but 2 of 944 events occurred within 2 years after initiation of trastuzumab therapy. Regression analysis revealed 2 predictors of cardiotoxicity: age and baseline LVEF. A second prediction tool was derived by Ezaz *et al.*[16], who used data from the U.S. Surveillance, Epidemiology, and End Results database. In their study of 1664 women with previous exposure to trastuzumab (median age: 76.4 years), they identified cardiac events using the *International Classification of Diseases* (version 9) codes for HF and CM. Regression analysis attributed risk to age, adjuvant chemotherapy, history of cardiac disease, and cardiac risk factors. To date, cardiac biomarkers (for example, troponin) and advanced imaging (for instance, echocardiography with strain) to predict cardiotoxicity have not been incorporated into clinical risk scores and prediction models.

Here, we report the results of an exploratory analysis evaluating the utility of the clinical risk score (CRS) developed by Ezaz *et al.*[16] in BCA patients referred to our cardio-oncology clinic (COC)[17] in predicting permanent trastuzumab-related cardiotoxicity.

METHODS

The study included all early-stage (I–III) BCA patients referred to the COC at The Ottawa Hospital between October 2008 and August 2014 who received adjuvant trastuzumab. Referral criteria for the clinic included a diagnosis of HF or arrhythmia, or pre-treatment assessment for patients with a cardiac history or drop in LVEF by 10% or more below a threshold of 50%. Patients with metastatic disease at diagnosis or a history of HF were excluded from the analysis. Patients were followed prospectively from time of referral until resolution of cardiotoxicity or referral back to the primary care provider. Data on demographics, cancer characteristics, cancer therapies received, cardiac risk factors, cardiac investigations, and cardiac therapies were collected, as were data on measured outcomes (cancer therapy delays or early termination, hospitalizations, and deaths).

For each patient, a CRS was calculated as described by Ezaz *et al.*[16]. Their method assigns patients 1 point for a past medical history of hypertension, diabetes, or age 75–79 years, and it assigns 2 points if patients have a history of coronary artery disease, renal failure, or atrial fibrillation or flutter, or if they have received any chemotherapy or are more than 80 years of age. A score less than 4 is considered low risk; 4–5, moderate risk; and more than 6, high risk. Based on the points scale, a low-risk patient has a less than 20% risk of developing HF or CM, and a high-risk patient had a greater than 40% risk.

Sensitivity analysis of the Ezaz[16] CRS was performed using the VassarStats online statistical analytics software [http://vassarstats.net (Lowry R, Avon, CT, U.S.A.)]. The analysis used permanent HF or CM as the primary endpoint. A cardiac event was defined as a drop of at least 10% below baseline LVEF to an LVEF below 50%. Events were considered transient if a patient's LVEF returned to normal during the study period (it either rose to within 10 percentage points of baseline value or returned to above 50%, depending on the criteria that defined the particular cardiac event); events were considered permanent if the LVEF was sustained either below 50% or more than 10% below the baseline LVEF, or if CM was diagnosed by a cardiologist.

Two sensitivity analyses were performed. In the first analysis, a true positive was defined as a patient in the moderate- or high-risk score group who experienced permanent HF or CM at 3 years (that is, all patients with a CRS of 4 or higher), and a true negative was defined as a low-risk patient (CRS of 0–3) who experienced complete recovery of cardiac function at 3 years. For the second sensitivity analysis, a true positive was defined as a high-risk patient (CRS of 6 or greater) who experienced permanent HF or CM at 3 years, and a true negative was defined as a patient at low or moderate risk (CRS of 0–5) who experienced either no cardiotoxicity or full cardiac function recovery. Using those cut-points, sensitivity and specificity, and positive and negative prediction values were calculated.

This study was approved by The Ottawa Hospital research ethics board.

RESULTS

Between 2008 and 2014, 143 patients with early-stage HER2-positive BCA were referred to the COC. Table I outlines their demographics and baseline characteristics. Mean age in the cohort was 56 years (range: 25–86 years; standard deviation: 12 years). Almost half the patients had stage II

disease at the time of diagnosis (*n* = 68, 48%); 94 (66%) were estrogen receptor–positive; and 99% (*n* = 142) had received adjuvant chemotherapy. Median baseline LVEF in the cohort was 60% (standard deviation: 8%), and almost three quarters of the patients (*n* = 103, 72%) had been referred for decreased LVEF or left ventricular dysfunction, with the others having been referred for other reasons, including arrhythmia, history of cardiac disease, and request for cardiac optimization before treatment.

Applying the prediction tool, 119 of the patients (83%) would be considered at low risk to develop HF or CM; 14 (10%), at moderate risk; and 10 (7%), at high risk. Table II details the cardiac events that occurred in the patients (stratified by CRS) and the recoveries that occurred within 3 years of treatment start. A cardiac event was experienced by 62 patients (43%), with 43 patients (69%) experiencing full recovery of cardiac function. The low-risk group had a 42% cardiac event rate (50 of 119), with 70% of affected patients (*n* = 35) experiencing full recovery of cardiac function. The moderate-risk group had a 64% cardiac event rate (9 of 14), with 22% (*n* = 2) experiencing full recovery. In the high-risk group, 30% of patients experienced a cardiac event (3 of 10), with 33% (*n* = 1) experiencing complete recovery of cardiac function. Moderate-risk patients were the least likely to complete trastuzumab therapy without the drug being delayed or stopped because of cardiotoxicity; high-risk patients were the most likely to have their trastuzumab therapy permanently discontinued (Table III).

Table IV presents the results of the sensitivity analyses. In the first analysis (patients with a low CRS vs. those with a moderate or high CRS), sensitivity was 0.21 (95% CI: 0.07 to 0.46), and specificity was 0.83 (95% CI: 0.76 to 0.90), with a positive predictive value of 0.17 (95% CI: 0.11 to 0.24) and a negative predictive value of 0.83 (95% CI: CI: 0.76 to 0.89). For the second sensitivity analysis (patients with a low or moderate CRS vs. those with a high CRS), sensitivity was 0.13 (95% CI: 0.08 to 0.20), and specificity was 0.94 (95% CI: 0.87 to 0.97), with a positive predictive value of 0.07 (95% CI: 0.03 to 0.13) and a negative predictive value of 0.93 (95% CI: 0.87 to 0.96).

TABLE I Baseline patient characteristics

Characteristic	Value
Patients	138
Mean age (years)	56±11.7
Mean body mass index	26±5
Mean baseline LVEF	60%±8%
Sex [*n* (%) women]	134 (97)
Stage [*n* (%)]	
I	40 (28)
II	68 (48)
III	35 (24)
Receptor positivity [*n* (%)]	
Estrogen receptor	94 (66)
Progesterone receptor	76 (53)
Chemotherapy [*n* (%)]	
Any	142 (99)
Anthracycline-based	114 (79)

LVEF = left ventricular ejection fraction.

TABLE II Cardiotoxicity events by clinical risk score

Variable	Clinical risk score		
	Low (0–3)	Moderate (4–5)	High (≥6)
Patients (*n*)	119	14	10
Cardiac events [*n* (%)]	50 (42)	9 (64)	3 (30)
Recovered within 3 years [*n* (%)]	35 (29)	7 (50)	1 (10)
Permanent heart failure or cardiomyopathy [*n* (%)]	15 (13)	2 (14)	2 (20)

DISCUSSION

Randomized clinical trial data and real-world experience with trastuzumab therapy in the setting of HER2-positive BCA has highlighted the importance of short- and long-term cardiotoxicity. During the first year of trastuzumab therapy, cardiotoxicity is an important potential cause of treatment delay and early discontinuation of treatment, which results in suboptimal cancer therapy for up to one third of patients[18].

In addition to monitoring and providing treatment to patients who experience transient cardiac dysfunction

TABLE III Impact of cardiotoxicity on timing and completion of trastuzumab therapy

Variable	Clinical risk score		
	Low (0–3)	Moderate (4–5)	High (≥6)
Patients (*n*)	119	14	10
Trastuzumab treatment [*n* (%)]			
Not affected by cardiotoxicity	71 (60)	4 (29)	5 (50)
Delayed because of cardiac event	37 (31)	7 (50)	2 (20)
Discontinued because of cardiac event	11 (9)	3 (21)	3 (30)

TABLE IV Sensitivity analyses

Variable	Clinical risk score group			
	Moderate + high (≥4)		High (≥6)	
	Value	95% CI	Value	95% CI
Sensitivity	0.21	0.07 to 0.46	0.13	0.08 to 0.20
Specificity	0.83	0.76 to 0.90	0.94	0.87 to 0.97
Positive predictive value	0.17	0.11 to 0.24	0.07	0.03 to 0.13
Negative predictive value	0.83	0.76 to 0.89	0.93	0.87 to 0.96

CI = confidence interval.

during trastuzumab therapy, there is a need to identify patients at risk for long-term or permanent cardiotoxicity. Given the growing number of long-term BCA survivors, such identification has important public health implications[4]. The development of effective, practical, and inexpensive tools to risk-stratify patients for cardiotoxicity during trastuzumab administration would facilitate the management of cardiac risk during treatment.

Using a referral population of patients evaluated and followed in our COC, we applied a simple clinical risk tool to predict cardiotoxicity during, and immediately after, trastuzumab therapy[16]. The tool relies on easily obtained clinical information to stratify risk and does not require cardiac imaging.

The application of the CRS was helpful in identifying those at low risk of permanent cardiac dysfunction, but did not perform as well in identifying high-risk patients. A low CRS had a negative predictive value of 94% for permanent cardiotoxicity. Low-risk patients had the highest rate of full recovery of cardiac function. The positive predictive value of the CRS was low, which was expected, given that most patients will not develop permanent cardiotoxicity from trastuzumab. However, with a positive predictive value of 0.17, the CRS performs poorly when trying to identify the patients most at risk of cardiotoxicity. Some patients with a low CRS will develop short-term and long-term cardiotoxicity, suggesting that, in isolation, the CRS would be inadequate to risk-stratify patients for trastuzumab-related cardiotoxicity. On the other hand, the CRS shows promise for use in clinical practice to help identify patients at low risk of permanent cardiotoxicity caused by trastuzumab.

It is important to note that we evaluated the performance of the CRS in a biased sample of patients who were referred to a COC during trastuzumab therapy, with most being referred for reductions in LVEF. If the tool were to be applied to a broader BCA population, we would expect the CRS to have an even higher negative predictive value for avoiding cardiotoxicity. The fact that the CRS was able to effectively risk-stratify patients in spite of a referral population bias toward high cardiotoxicity risk indicates that it is promising as a simple, inexpensive, clinical risk-stratification tool to help identify the patients least at risk among those receiving trastuzumab.

In addition to clinical risk factors to predict cardiotoxicity, strain imaging using echocardiography and cardiac biomarkers has been evaluated in predicting cardiotoxicity. Global longitudinal strain (GLS) is a reproducible echocardiographic method to measure changes in left ventricular contractility before ejection fraction declines[19]. A prospective trial of serial strain monitoring in patients receiving trastuzumab after a course of anthracycline showed that a GLS of –19% or more identified patients at increased risk of cardiotoxicity with the use of trastuzumab[20].

Cardiac biomarkers have also been used to identify patients at increased risk of cardiotoxicity. Elevations in troponin I have been demonstrated to provide useful prognostic value in the early detection of chemotherapy-associated cardiotoxicity[21–23].

Any strategy that uses cardiac imaging faces concerns about cost, which is increasingly scrutinized in the setting of long-term monitoring in cancer survivors[24,25]. We envision an approach to cardiotoxicity risk stratification that incorporates a clinical risk tool, such as the one studied here, in combination with post-chemotherapy cardiac biomarkers and strain imaging. A prediction algorithm combining CRS, advanced imaging, and cardiac biomarkers might maximize sensitivity for detecting patients at high risk of treatment-related cardiac dysfunction that could warrant early evaluation in a COC for more intense monitoring, while also identifying patients at sufficiently low risk to safely forego intensive cardiac imaging and clinical assessment. In addition, long-term cardiac surveillance could be focused on high-risk patients, sparing low-risk patients from costly long-term cardiac testing. Validation of such a combined-risk stratification strategy should be a high priority for clinical research in cardio-oncology.

Our study is not without limitations. All BCA patients were cared for in a single tertiary centre, which could potentially have reduced the event rate, given that patients receiving appropriate cardiac intervention might be more likely to recover their cardiac function. That factor reduces the generalizability of our findings. Our sample size was small, and our findings should therefore be considered exploratory. We also acknowledge that the derived CRS was applied in a manner slightly different from its initial intent (by focusing on permanent cardiac dysfunction rather than all cardiac events). We would argue that looking at permanent loss of heart function is more clinically meaningful and has greater implications for long-term cardiac monitoring and the burden of cardiac disease in BCA survivors. Future work in cardiotoxicity has to focus on separating patients with a transient drop in ejection fraction from those who develop permanent cardiac dysfunction.

CONCLUSIONS

Despite long-term follow-up from adjuvant trastuzumab trials and more than a decade of research on the prediction of cardiotoxicity, no widely accepted standard model is currently available to guide risk-stratification for trastuzumab-related cardiotoxicity in routine clinical practice. It is clear that such cardiotoxicity is different from the cardiotoxicity associated with anthracyclines. The CRS developed by Ezaz *et al.* performed reasonably well to identify patients at low risk of developing permanent cardiotoxicity, but did not have sufficient accuracy to be used in isolation. We believe that, by incorporating the CRS with cardiac biomarkers such as troponin I and with strain imaging, patients can be accurately risk-stratified as low or high risk for cardiotoxicity during cancer therapy. Low-risk patients might not require intensive cardiac monitoring, and high-risk patients can be referred to a COC for risk-factor optimization and more intensive cardiac imaging surveillance. Such an approach warrants further study to confirm that tailoring cardiac surveillance and intervention based on a combined risk-assessment strategy is feasible and safe. In addition, effective risk stratification could be important in future trials evaluating the use of medical therapy to prevent cardiotoxicity, given that those at highest risk for cardiotoxicity will derive the greatest absolute benefit from effective prevention strategies.

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CONFLICT OF INTEREST DISCLOSURES
We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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