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Emerging Evidence

Safety of Continuing Trastuzumab for Mild Cardiotoxicity: A Cardiovascular Magnetic Resonance Imaging Study

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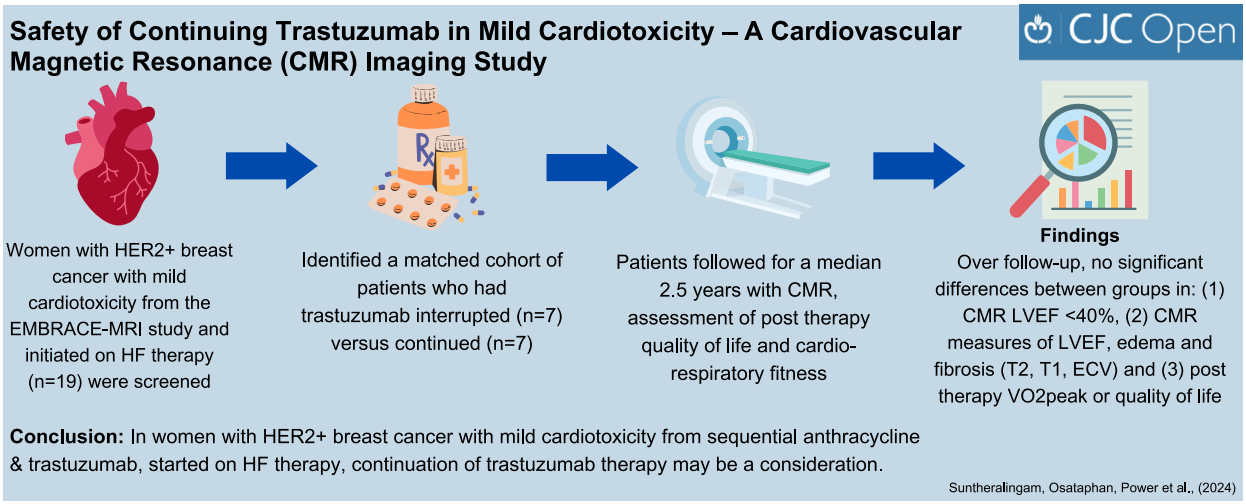

ABSTRACT

The safety of continuing human epidermal growth factor receptor 2 (HER2)–targeted therapy in women with mild cardiotoxicity remains unclear. We performed a retrospective matched cohort study of 14 patients with human epidermal growth factor receptor 2–positive breast cancer receiving sequential anthracycline and trastuzumab therapy, nested within the Evaluation of Myocardial Changes During Breast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI (EMBRACE-MRI) trial. Among patients who developed cardiotoxicity and were treated with heart failure therapy, we compared those who had trastuzumab therapy interrupted to a matched cohort who continued trastuzumab therapy. By a median of 2.5 years of follow-up,

RÉSUMÉ

La question de savoir s'il est sûr de poursuivre le traitement par un médicament ciblant le récepteur 2 du facteur de croissance épidermique humain (HER2) en présence d'une légère cardiotoxicité chez la femme demeure controversée. Nous avons réalisé une étude de cohortes appariées rétrospective auprès de 14 patientes atteintes d'un cancer du sein positif pour le HER2 qui recevaient un traitement séquentiel par l'anthracycline et le trastuzumab, dans le cadre du programme EMBRACE-MRI (*Evaluation of Myocardial Changes During Breast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI*). Parmi les patientes ayant développé une cardiotoxicité et ayant reçu un traitement pour l'insuffisance cardiaque, nous avons comparé

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no significant differences were present between the groups in the proportion with magnetic resonance imaging–measured left ventricular ejection fraction < 40%, magnetic resonance imaging–measured left ventricular volumes, left ventricular ejection fraction, edema, fibrotic markers, cardiopulmonary fitness, or quality of life.

celles dont le traitement par le trastuzumab a été interrompu à une cohorte appariée ayant poursuivi ce traitement. Après un suivi médian de 2,5 ans, aucune différence significative n'avait été observée entre les groupes en ce qui concerne le pourcentage de patientes dont la fraction d'éjection ventriculaire gauche était inférieure à 40 % à l'imagerie par résonance magnétique (IRM), le volume ventriculaire gauche à l'IRM, la fraction d'éjection ventriculaire gauche, l'œdème, les marqueurs fibrotiques, la bonne forme physique de l'appareil cardiopulmonaire ou la qualité de vie.

In patients with early-stage human epidermal growth factor receptor 2–positive (HER2+) breast cancer, use of trastuzumab improves outcomes,[1] but it is associated with a risk of cancer therapy–related cardiac dysfunction (CTRCD). In those receiving sequential anthracycline and trastuzumab therapy, the incidence of CTRCD has been reported to be as high as 27%,[2,3] with clinical heart failure (HF) in up to 10% of patients.[4] When CTRCD is identified (ie, by a fall in left ventricular ejection fraction [LVEF], by ≥ 10% compared to baseline, to a value below the upper limit of normal), the Canadian Trastuzumab Working Group recommends transient interruption of trastuzumab therapy.[5,6] However, trastuzumab therapy interruption is associated with a higher risk of cancer recurrence and death.[7,8]

Therefore, interest is growing in continuing trastuzumab therapy with the concurrent initiation of HF medications, especially in patients with mild CTRCD. Both the Cardiac **Safe**ty Study in Patients With **HER**2+ Breast Cancer (SAFE-HEaRT; n = 30 patients) and **S**afety of **C**ontinuing C**h**emotherapy in **O**vert **L**eft Ventricular Dysfunction Using **A**ntibodies to HE**R**-2 (SCHOLAR) trials (n = 20 patients) demonstrated that continuing trastuzumab therapy with initiation of HF medications for mild CTRCD (ie, LVEF > 40%) may be safe, as only ∼10% of patients developed further LVEF worsening or HF.[9,10] Although these studies are encouraging, they both used LVEF measured by echocardiography, did not have a control group, and did not report long-term outcomes or other prognostic measures.

To address these knowledge gaps, we performed an exploratory retrospective matched cohort study nested within a completed **E**valuation of **M**yocardial Changes During **Br**east **A**denocarcinoma Therapy to Detect **C**ardiotoxicity **E**arlier With **MRI** (EMBRACE-MRI) prospective cohort study at our institution. In women with HER2+ breast cancer treated with sequential anthracyclines and trastuzumab who developed mild CTRCD and were treated with HF therapy, we sought to compare the safety of continuing vs stopping trastuzumab therapy using measures of cardiac magnetic resonance (CMR) imaging left ventricular volumes and function, myocardial edema and fibrosis, cardiopulmonary fitness, quality of life (QOL), and long-term CMR and clinical follow-up.

Methods

We performed a retrospective matched cohort study of adult women with stage I-III HER2+ breast cancer receiving sequential therapy with anthracyclines and trastuzumab (with or without radiotherapy) nested within the EMBRACE-MRI trial (NCT02306538; 136 patients). Patients were followed with CMR pre–cancer therapy (baseline), every 3 months during (except at 9 months), immediately post–trastuzumab completion, and 2 years later (total of 6 CMR studies). All patients had cardiorespiratory fitness (CRF) assessment within 6 weeks post–trastuzumab completion, using a supine cycle ergometer. QOL was assessed post–trastuzumab completion using the **M**innesota **L**iving With **H**eart **F**ailure **Q**uestionnaire (MLHFQ) and **E**uro**Q**ol **5**-**D**imension **3**-**L**evel (EQ-5D-3L). Mild CTRCD was defined as a decline in LVEF of ≥ 10%, to a value < 55%, but to a nadir value > 40% by CMR. Among patients who developed mild CTRCD and were treated with HF therapy (beta-blockers and/or angiotensin-converting enzyme inhibitor [ACE] or angiotensin receptor blockers [ARBs]), we identified those who had trastuzumab therapy interruption (interrupted group) and matched them to patients who continued trastuzumab therapy (continued group), by age (± 10 years), baseline LVEF (± 5%), and LVEF at CTRCD (± 5%). Although the Canadian Trastuzumab Working Group recommends interruption of trastuzumab therapy when CTRCD is present, the final decision to continue or interrupt therapy was made by both the oncologist and the patient.

The primary outcome was the proportion of patients with CMR-measured LVEF < 40% post completion of trastuzumab therapy. Other outcomes included LVEF, left ventricular volumes, and CMR measures of edema (T2 maps) and fibrosis (T1 maps and/or extracellular volume fraction), post–trastuzumab therapy and at 2-year follow-up; and QOL measures and peak oxygen uptake ($VO_{2peak;}$ a measure of CRF) immediately post–trastuzumab completion.

Continuous data are presented as median and 25th-75th percentile (quartile Q1-Q3), and binary data are presented as absolute numbers and proportions. Comparisons between the groups were made using the Fisher exact test and the Mann-Whitney rank-sum test. To evaluate differences in time profiles of continuous measures, we applied general estimating equations to assess changes over the follow-up period and

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See page 834 for disclosure information.

Table 1. Summary of baseline characteristics of the whole cohort, stratified by whether trastzumab therapy was interrupted or continued

Characteristic	All patients, n = 14	Trastuzumab interrupted, n = 7	Trastuzumab continued, n = 7	*P*
Age, y	56 (51−60)	53 (50−56)	58 (53−62)	0.48
Breast cancer laterality				0.28
Left	8 (57)	3 (43)	5 (71)	
Right	6 (43)	4 (57)	2 (29)	
Breast cancer stage				0.67
1	1 (7)	1 (14)	0 (0)	
2	9 (64)	3 (43)	6 (86)	
3	4 (29)	3 (43)	1 (14)	
Cumulative doxorubicin equivalent, mg/m^2	205 (204−208)	204 (204−206)	206 (203−210)	0.44
Radiotherapy	12 (86)	6 (86)	6 (86)	0.99
Diabetes	1 (7)	0 (0)	1 (14)	0.30
Hypertension	1 (7)	0 (0)	1 (14)	0.30
Dyslipidemia	3 (21)	0 (0)	3 (43)	0.05
Smoker	4 (29)	3 (43)	1 (14)	0.24
At least 1 CVRF	5 (36)	3 (43)	2 (29)	0.91

Values are n (%), unless otherwise indicated. Continuous data are presented as median (quartile 1−quartile 3). Smoker category includes active and past smoking.

CVRF, cardiovascular risk factor.

evaluated between-group differences using χ^2 tests. A *P*-value < 0.05 denoted statistical significance.

Results

In the EMBRACE-MRI trial, per our current study definition, 19 patients met the inclusion criteria. Among these 19 patients, 7 continued trastuzumab therapy and were thus matched to 7 patients in whom trastuzumab therapy was interrupted, resulting in a total of 14 patients being in this current study. Comparison of the interrupted and continued groups showed no substantial covariate imbalance in baseline characteristics (Table 1), time of onset of CTRCD from baseline (238 days [159-252] vs 242 days [200-250], $P = 0.67$), or LVEF at time of CTRCD (49% [48-50] vs 51% [49-52], $P = 0.63$). Maximal doses of beta-blockers and ACE inhibitors and/or ARB used to treat CTRCD in each group are summarized in Table 2.

All patients were followed similarly in our cardio-oncology program; 13 of 14 (93%) patients completed 17 cycles of trastuzumab, and 1 patient in the interrupted group received only 14 cycles. Trastuzumab therapy was interrupted for 1 cycle in 2 patients, 2 cycles in 4 patients, and 3 cycles in 1 patient. By the 2-year follow-up, 2 deaths had occurred in the interrupted group (both due to cancer progression), and none had occurred in the continued group. Post−trastuzumab therapy and at 2-year follow-up, none of the patients developed the primary outcome of CMR LVEF $< 40\%$ or clinical HF.

Temporal measures of secondary outcomes including LVEF, left ventricular volumes, T2 values, native T1 and extracellular volume fraction values pre−cancer therapy, at the time of CTRCD, at the post−trastuzumab therapy timepoint, and at 2-year follow-up are illustrated in Figure 1 for both groups. The trajectories of these measures were not statistically significantly different between the groups, in a comparison for the period from the time of CTRCD to the final follow-up.

No statistically significant differences were present in the post−trastuzumab therapy EQ-5D-3L Index score (1.0 [0.8-1.0] vs 1.0 [0.8-1.0], $P = 0.95$), the EQ-5D-3L visual analogue scale (VAS) score (80 [78-88] vs 80 [63-93], $P = 0.52$), the MLHFQ score (5.0 [1.0-13.0) vs 7.0 [3.5-19.0], $P = 0.77$), or the VO_{2peak} (17.8 mL O_2 kg^{-1} min^{-1} [16.5-19.7] vs 18.9 mL O_2 kg^{-1} min^{-1} [13.9-20.1] L/min, $P = 0.74$) in the interrupted and continued groups, respectively.

Discussion

In this exploratory matched cohort study of patients with HER2+ breast cancer who developed mild CTRCD and received HF therapy, we compared differences in CMR measures, QOL, and CRF in patients whose trastuzumab therapy was transiently interrupted vs those who continued therapy. Our primary findings were as follows: (i) none of the patients in either group developed LVEF $< 40\%$ or clinical HF during follow-up; (ii) no statistically significant between-group differences were present in CMR-measured ventricular

Table 2. Maximal doses of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blocker (ARB) and beta blockers used for treatment in groups who had interrupted vs continued trastuzumab therapy

	Trastuzumab therapy	
Doses	Interrupted (n = 7)	Continued (n = 7)
ACEs		
Ramipril, 2.5 mg	1	1
Ramipril, 5 mg	1	2
Ramipril, 10 mg	3	3
ARBs		
Candesartan, 8 mg	1	0
Candesartan, 16 mg	0	1
Candesartan, 32 mg	1	0
Beta-blockers		
Bisoprolol, 2.5 mg	2	2
Bisoprolol, 5 mg	1	1
Bisoprolol, 7.5 mg	0	1
Bisoprolol, 10 mg	4	3

The data are provided as number of patients.

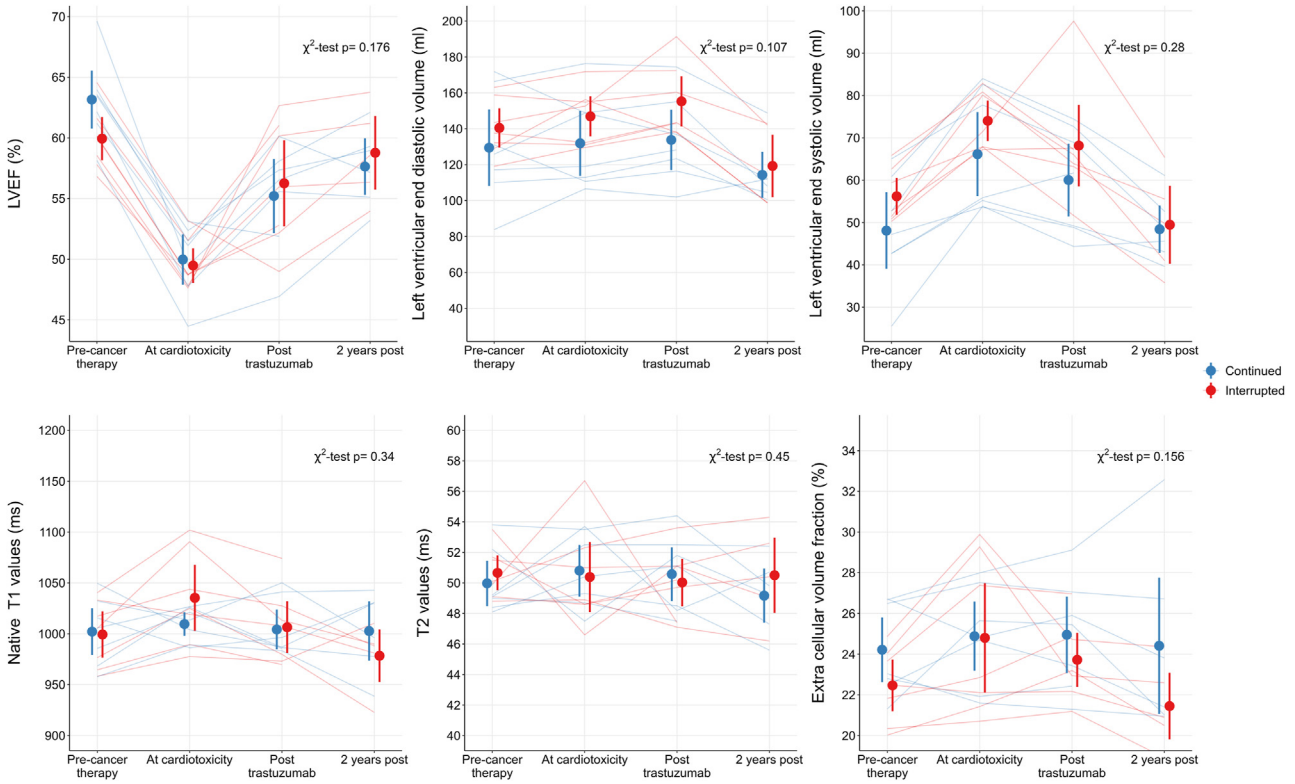

Figure 1. Individual patient trajectory and group-specific average and corresponding 95% confidence interval for interrupted and continued groups at each study time point. Data are presented for cardiac magnetic resonance imaging—measured left ventricular ejection fraction (LVEF) and volumes and tissue characterization measures (T2/T1 values, and extracellular volume fraction). *P* values are for comparison of between-group differences of changes over the 4 follow-up time periods.

volumes, LVEF, or markers of edema and fibrosis over follow-up; and (iii) no statistically significant between-group differences were present in QOL measures and VO_{2peak} post—trastuzumab completion. This exploratory study provides hypothesis-generating data indicating that in patients with mild CTRCD from sequential anthracyclines and trastuzumab therapy for breast cancer, who are started on HF therapy, continuation of trastuzumab therapy may be a consideration. Along with prior studies,[9,10] our study provides further impetus to support conducting larger clinical trials to help answer this clinically important question in the field of cardio-oncology.

Findings similar to ours have been demonstrated in 2 prior studies. The SCHOLAR study by Leong et al.[10] included 20 patients with HER2+ breast cancer, with mildly reduced LVEF of 40%-54% or a drop in ejection fraction of $\geq$ 15% from baseline to an LVEF $\geq$ 54% measured by echocardiography who were treated with an ACE inhibitor or ARB, and/or beta-blockers while continuing trastuzumab therapy. This study had no control group. Eighteen patients (90%) completed their planned trastuzumab therapy, whereas 2 (10%) developed severe CTRCD (LVEF drop to 28% and 26% with New York Heart Association class III-IV HF symptoms) requiring permanent cessation of trastuzumab therapy. However, these 2 patients improved their LVEF (56% and 47%, respectively) and HF symptoms (New York Heart Association class I) at subsequent follow-up. The SAFE-Heart study[9] included 30 patients with HER2+ breast cancer with LVEF 40%-49% measured by echocardiography and no HF symptoms, treated with ACE inhibitors or an ARB, and/or beta-blockers while continuing trastuzumab therapy. This study also had no control group. Twenty-seven of the patients (90%) completed trastuzumab therapy, 2 developed symptomatic HF, and 1 developed an asymptomatic LVEF decline to 32%.

Our study adds to the above studies in the following manner. First, we provide a control group in which treatment was continued as a comparison. Both the above-described studies used echocardiography-measured LVEF for the diagnosis of CTRCD and for subsequent follow-up to define safety. Echocardiography measures have significant intra-observer, interobserver, and temporal variability, especially in patients receiving cancer therapy,[11] potentially resulting in misclassification. We used the reference-standard technique for LVEF measurement to demonstrate more confidently that no statistically significant differences were present between the groups. Furthermore, given that patients may develop HF 1-2 years after completion of cancer therapy, we provide 2-year follow-up to ensure that the lack of difference in left ventricular volume and ejection fraction measures is sustained. We provide novel measures that were not available in the prior studies, including CMR-measured markers of myocardial edema and fibrosis, providing further suggestion that no differences were present in potential myocardial substrate for future HF.[12,13] We also provide novel data on CRF, which has been shown to be an important prognostic marker of poor

long-term outcomes in patients with cancer.[14,15] The lack of significant difference in VO_{2peak} post—trastuzumab therapy completion adds further confidence regarding the safety of the approach of continuing trastuzumab therapy for mild CTRCD. Finally, we examined patient-centric measures and found no significant differences in QOL measures between groups.

Despite the strengths outlined above, our study has limitations. We included 14 patients, which increases the likelihood of type II error in our statistical analysis. Furthermore, although nested within a prospective cohort study, the specific question addressed in this study was retrospective in nature and hence was subject to unmeasured confounders. Therefore, we consider our findings to be hypothesis-generating, and additive to prior studies, but not practice-changing. The small sample size reflects the fact that our study was nested within the EMBRACE-MRI study, in which only 19 patients received HF therapy for mild CTRCD. However, this approach provided us with the ability to use traditional and novel CMR measures to assess the safety of continuing trastuzumab therapy and helped us reduce potential bias, as all 14 patients received identical care. Despite the fact that all patients in the EMBRACE-MRI trial who developed CTRCD and received HF therapy would be candidates for transient trastuzumab therapy interruption,[5,6] the decision to continue or interrupt trastuzumab therapy was based on clinician and patient preference and not on randomization. Several reasons account for the difference between the recommendations and clinical practice. These reasons include patient reluctance to stop trastuzumab therapy due to concern about poor outcomes,[7,8] and newer data that suggest that unless the LVEF at time of CTRCD is $< 40\%$, the prognosis is excellent, resulting in physician reluctance to stop trastuzumab therapy for mild asymptomatic CTRCD.[16] Given that the decision to stop vs continue trastuzumab therapy may be a confounder, our findings should be interpreted within the context of this limitation.

As we wait for data from randomized controlled studies, such as **S**afety of **C**ontinuing **H**ER-2 Directed Therapy in **O**vert **L**eft Ventricul**ar** Dysfunction (SCHOLAR-2; NCT04680442), comparing the safety of trastuzumab continuation vs interruption in patients with mild CTRCD using echocardiography measures, our study adds to the existing literature regarding the potential safety of continuing trastuzumab therapy on the basis of additional prognostic measures. Overall, the data to date from the 2 prior studies[9,10] and the current study are encouraging, but these findings require robust validation before they should impact clinical practice.

Ethics Statement

The research study adheres to ethical guidelines.

Patient Consent

The authors confirm that a patient consent form(s) has been obtained for this article, as data used for this research article was part of the already collected data from the EMBRACE-MRI study.

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Disclosures

The authors have no conflicts of interest to disclose.

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