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Clinical Research

Cardioprotective Effect of Statins in Patients With HER2-Positive Breast Cancer Receiving Trastuzumab Therapy

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See editorial by Davis and Virani, pages 142–144 of this issue.

ABSTRACT

Background: Statins can reduce the risk of anthracycline-induced cardiotoxicity. Whether such cardioprotective effects can be seen in trastuzumab-treated patients has not been explored.

Methods: Consecutive women with HER2+ breast cancer who received trastuzumab with or without anthracyclines were identified retrospectively. Patients receiving statins before and during cancer treatment were matched with 2 patients of the same age (± 2 years) and anthracycline exposure status but without statin treatment. The primary outcome was final left ventricular ejection fraction (LVEF). Analysis of covariance (ANCOVA) was used to assess the relationship between statin exposure and the final LVEF. A logistic regression model was constructed to assess the relationship between statin exposure and cardiotoxicity (secondary outcome).

Results: Included were 129 patients (62 ± 9 years). Forty-three received statins during cancer treatment. The median trastuzumab exposure time was 11.8 (interquartile range [IQR] 11 to 12) months.

RÉSUMÉ

Contexte : Les statines peuvent réduire le risque de cardiotoxicité des anthracyclines. La question de savoir si de tels effets cardioprotecteurs peuvent être observés chez les patients traités par le trastuzumab n'avait pas encore été explorée.

Méthodologie : Des patientes consécutives atteintes de cancer du sein HER2+ qui avaient été traitées par le trastuzumab avec ou sans anthracyclines ont été repérées rétrospectivement. Les patientes qui recevaient une statine avant ou pendant le traitement de leur cancer ont été appariées à 2 patientes ayant le même âge (± 2 ans) et le même statut quant à l'exposition à l'anthracycline, mais ne prenant pas de statine. Le critère d'évaluation principal était la fraction d'éjection ventriculaire gauche (FEVG) finale. L'analyse de la covariance (ANCOVA) a été utilisée pour évaluer la relation entre l'exposition à la statine et la FEVG finale. Un modèle de régression logistique a été élaboré pour évaluer la relation entre l'exposition à la statine et la cardiotoxicité (critère d'évaluation secondaire).

Anthracyclines and trastuzumab are 2 effective drugs that are used to treat women with human epidermal growth factor receptor 2-positive (HER2+) breast cancer. However, these drugs are associated with a risk of cancer treatment-related cardiac dysfunction (CTRCD).[1,2] Strategies to mitigate CTRCD have included primary prevention with cardioprotective medications or cardiac surveillance to detect subclinical cardiac injury followed by intervention. For primary prevention, renin-angiotensin system inhibitors and β-blockers are the most common therapies studied.[3] However, these drugs can reduce heart rate and blood pressure and contribute to fatigue. As a consequence, they are often poorly tolerated in patients receiving cancer therapy who are already fatigued from the cancer, its treatment, or anemia and are intravascularly volume depleted because of poor oral intake, vomiting, and diarrhea. This prompted clinicians to consider alternate cardioprotective medications. Statins are

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Seventy-two (56%) patients received anthracyclines. Compared with controls, patients treated with statins were more likely to have diabetes (37.2% vs 4.7%, $P < 0.001$), hypertension (58.1% vs 22.1%, $P < 0.001$), and coronary artery disease (11.6% vs 2.3%, $P = 0.04$). Within a median cardiac follow-up duration of 11 (IQR 9 to 18) months, the adjusted final LVEF was lower in the control group (61.2% vs 64.6%, $P = 0.034$). A significant change in LVEF was observed in the control group (median −6%, IQR −10% to −1% $P < 0.001$) but not in the statin group (median 0%, IQR −5% to +3%, $P = 0.27$). Upon adjusted analysis, statin treatment was independently associated with a lower risk of cardiotoxicity (odds ratio [OR] 0.32, 95% confidence interval [CI], 0.10-0.99, $P = 0.049$).

Conclusions: In women with HER2+ breast cancer receiving trastuzumab-based therapy with or without anthracyclines, concomitant use of statins was associated with a lower risk of cardiotoxicity.

Résultats : L'étude portait sur 129 patientes (62 ± 9 ans). Quarante-trois patientes ont reçu des statines durant le traitement de leur cancer. La durée médiane d'exposition au trastuzumab était de 11,8 (écart interquartile [EIQ] de 11 à 12) mois. Soixante-douze (56 %) patientes avaient reçu des anthracyclines. Comparativement aux témoins, les patientes traitées par une statine étaient plus susceptibles de souffrir de diabète (37,2 % vs 4,7 %, $p < 0,001$), d'hypertension (58,1 % vs 22,1 %, $p < 0,001$) et de coronaropathie (11,6 % vs 2,3 %, $p = 0,04$). À l'intérieur d'une période de suivi cardiaque d'une durée médiane de 11 (EIQ de 9 à 18) mois, la FEVG finale ajustée était moins élevée dans le groupe témoin (61,2 % vs 64,6 %, $p = 0,034$). Une variation significative de la FEVG a été observée dans le groupe témoin (médian -6 %, EIQ de -10 % à -1 %, $p < 0,001$), mais pas dans le groupe ayant reçu une statine (médian 0 %, EIQ de -5 % à +3 %, $p = 0,27$). Après l'analyse ajustée, le traitement par la statine était associé de façon indépendante à un risque de cardiotoxicité plus faible (rapport des cotes [RC] 0,32, intervalle de confiance [IC] à 95 %, 0,10-0,99, $p = 0,049$).

Conclusions : Chez les femmes atteintes de cancer du sein HER2+ ayant reçu un traitement à base de trastuzumab avec ou sans anthracyclines, la prise concomitante d'une statine était associée à un risque de cardiotoxicité plus faible.

hypothesized to have pleiotropic effects, including anticancer, antioxidative, and anti-inflammatory effects.[4,5] In fact, animal models and small clinical studies have shown that statins could provide cardioprotection during anthracycline treatment.[6-9] Whether statins also confer cardioprotective effects in trastuzumab-treated patients has not yet been studied.

Our objective was to assess whether statin exposure during trastuzumab treatment (with or without anthracyclines) in women with HER2+ breast cancer is associated with cardioprotective effect. We hypothesized that trastuzumab-treated patients who were exposed to statins during their treatment would have a lower decline in left ventricular ejection fraction (LVEF) and lower incidence of cardiotoxicity compared with those who were not exposed to statins.

Material and Methods

Patients

This is a retrospective case-control study based on electronic chart review of consecutive women with HER2+ breast cancer treated with trastuzumab-based therapy at Princess Margaret Cancer Center (Toronto, ON) between 2002 and 2013. Patients were included if they received a pretherapy multigated acquisition (MUGA) scan and ≥ 2 subsequent follow-up scans during the course of their treatment. We identified patients who were receiving any statin (regardless of clinical indication) before and during cancer treatment. Each statin-treated patient was randomly matched with 2 patients of the same age (± 2 years) and anthracycline exposure status but without statin treatment before or during cancer treatment. The LVEF data were not available at the time of matching. The study complies with the Declaration of Helsinki; it was approved by the University Health Network (UHN) Research Ethics Board; and, given its retrospective nature, the Research Ethics Board waived the need for informed consent.

Through electronic patient records, baseline characteristics were collected, including cardiovascular risk factors, cardiac disease history, cardiovascular medications, cancer-related variables (disease stage, estrogen-receptor status, progesterone-receptor status) and cancer-treatment history. For each patient, we calculated the cardiac risk score generated from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 study.[10] Trastuzumab exposure time was defined as the period (months) between the first and the last trastuzumab dose in each patient. Cardiac follow-up was defined as the time (months) between the first and the last MUGA scans.

Outcomes

The primary outcome was the final LVEF, defined as the last LVEF value within follow-up period closest to the last trastuzumab treatment. We also assessed the following secondary outcomes: (1) change in LVEF, defined as the difference between the final LVEF and the LVEF on the pretreatment scans (baseline LVEF); (2) incidence of cardiotoxicity, defined as the proportion of patients meeting the Cardiac Review and Evaluation Committee (CREC) definition for cardiotoxicity (LVEF decline ≥ 10% to < 55% without symptoms of heart failure or ≥ 5% drop to < 55% with symptoms[11]) in at least 1 MUGA scan; and (3) the incidence of trastuzumab interruption (at least 1 cycle interruption attributed to LVEF reduction). The median number of MUGA scans between groups was compared to assess for ascertainment bias.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Two sample Students' *t*-tests or Mann−Whitney U test were used to compare the means of continuous variables between patients and controls based on the data distribution. Categorical variables were expressed as

frequencies and percentages and were analyzed using Fisher's exact test. Wilcoxon signed-rank test was used to compare the change in LVEF (as defined above) within each group. Analysis of covariance (ANCOVA) was used to assess the relationship between statin exposure status and the primary outcome after adjustment for the baseline LVEF and the following covariates: age, body mass index (BMI), cardiovascular risk factors (diabetes, hypertension, coronary artery disease), cardiovascular medications (angiotensin-converting enzyme inhibitors [ACEi], angiotensin II receptor blockers [ARBs], β-blockers), cancer stage (early or metastasic), and anthracycline therapy. Given the established atherosclerosis-related benefits of statins in patients with coronary artery disease or diabetes, we included interaction terms for diabetes and coronary artery disease with statins as covariates in the ANCOVA models. A logistic regression model was constructed using cardiotoxicity (as defined above) as the outcome, treatment with statins as the predictor, and anthracycline exposure, number of cardiovascular risk factors (diabetes, hypertension, coronary artery disease, smoking), and the NSABP-31 cardiac risk score[10] as confounders. Analyses were performed using SPSS v.20 (IBM Corp, Armonk, NY). Statistical tests were 2-sided, and statistical significance was defined as $P < 0.05$.

Results

Patients

We identified 525 consecutive women with HER2+ breast cancer receiving trastuzumab therapy between 2002 and 2013. Forty-three patients received statins (statin group) before and during cancer treatment; they were matched to 86 statin-unexposed controls. Mean age at cancer diagnosis was 62 ± 9 years. Statin types and median doses used are summarized in Table 1. The majority (81.4%) of the patients were on moderate- to high-intensity statin therapy.[12] Anthracyclines were used in 72 (56%) patients prior to trastuzumab exposure. The median trastuzumab exposure time for the whole cohort was 11.8 (IQR 11 to 12) months with no significant difference between statin-treated patients and controls. With the exception of tamoxifen use, cancer treatments did not differ between the groups. The median doxorubicin equivalent dose was 201.5 mg/m^2 in the statin arm and 202.7 mg/m^2 in the control group ($P = 0.24$).

Patients in the statin group had a larger BMI and were more likely to have diabetes, hypertension, dyslipidemia, and coronary artery disease than controls. This higher cardiovascular risk profile was reflected in the higher frequency of other cardiovascular medications such as ACEi, ARBs, β-blockers, mineralocorticoid-receptor antagonists, and calcium-channel blockers (Table 1). Mean baseline LVEF was similar between the 2 groups (66.7 ± 5.4% vs 66.0 ± 7.0% in control and statin groups, respectively, $P = 0.57$).

Follow-up

During a median cardiac follow-up of 11 (IQR, 9 to 18) months, a median of 5 MUGA scans were performed in each group ($P = 0.35$). There was no significant difference in the number of trastuzumab cycles (Table 1) or cardiac follow-up duration between controls (12 months, IQR 10 to 20 months) and statin-treated patients (11 months, IQR 9 to 14 months; $P = 0.15$).

Outcomes

The mean final LVEF was significantly lower in the control group (61.1 ± 8.1% vs 64.4 ± 6.5%, $P = 0.026$). The median absolute change in LVEF in the statin group was 0% (IQR −5% to +3%; $P = 0.27$), compared with an absolute decline of 6% (IQR −10% to −1% $P < 0.001$) in the control group. After adjustment for baseline LVEF and potential confounders (age, cardiovascular risk factors, cardiovascular medications, BMI, cancer stage, and anthracycline exposure), the difference observed in final LVEF between the 2 groups remained statistically significant (Table 2). No interaction was noted between the presence of coronary artery disease or diabetes and statin use on the differences in LVEF (Table 2). There was a higher incidence of cardiotoxicity (LVEF decline ≥ 10% to < 55% without symptoms or ≥ 5% drop to < 55% with symptoms) in the control group (21/86, 24.4%) compared with the statin group (5/43, 11.6%), but this did not reach statistical significance in unadjusted analysis ($P = 0.1$). However, upon adjusted analysis, statin treatment was independently associated with a lower risk of cardiotoxicity (odds ratio [OR] 0.32, 95% CI, 0.10-0.99, $P = 0.049$) although with wide confidence intervals (Table 3). Trastuzumab interruption was almost twice as frequent in the control patients (9.3%) than in patients treated with statins (4.7%), but this was not statistically significant ($P = 0.49$). Adjusted analysis was not performed owing to the limited number of events.

Subgroup analysis by anthracycline exposure is summarized in Figure 1). The benefit of statins in preventing a reduction in LVEF was similar in those who did and did not receive anthracycline treatment.

Discussion

We demonstrate that statin exposure (moderate- to high-intensity doses) is associated with lower declines in LVEF in women receiving trastuzumab therapy for HER2+ breast cancer. Patients who were on statins during cancer therapy had higher LVEF at end of treatment and smaller change in LVEF during treatment. This benefit persisted after adjusting for confounders including the use of anthracyclines and other known potentially protective cardiac medications. The magnitude of benefit was similar in patients who did and did not receive anthracycline therapy before trastuzumab. Although the difference in final LVEF between statin-treated and nontreated groups was modest, the magnitude of benefit was similar to that shown with other primary prevention studies in patients receiving cardiotoxic cancer therapies.[9,13,14] Furthermore, statin-treated patients had a lower risk for cardiotoxicity as defined by CREC; however, the confidence interval around the OR was wide.

Mechanism of cardioprotection

The mechanism by which statins protect against trastuzumab-induced cardiotoxicity is unknown. However, oxidative stress and endothelial dysfunction are hypothesized

Table 1. Baseline characteristics

	All patients N = 129	Control N = 86	Statins N = 43	*P* value
Mean age, years ± SD	62.0 ± 9.0	62.0 ± 9.0	62.0 ± 9.1	-
Body mass index, kg/m^2 ± SD	27.6 ± 5.3	26.9 ± 5.2	28.9 ± 5.2	0.04
Postmenopausal, n (%)	108 (83.7)	71 (82.6)	37 (86.0)	0.80
Diabetes, n (%)	20 (15.5)	4 (4.7)	16 (37.2)	< 0.001
Hypertension, n (%)	44 (34.1)	19 (22.1)	25 (58.1)	< 0.001
Dyslipidemia, n (%)	52 (40.3)	9 (10.5)	43 (100)	< 0.001
Smoking history, n (%)	39 (30.2)	26 (30.2)	13 (30.2)	1.0
Coronary artery disease, n (%)	7 (5.4)	2 (2.3)	5 (11.6)	0.04
Heart failure, n (%)	3 (2.3)	1 (1.2)	2 (4.7)	0.26
Valvular heart disease, n (%)	5 (3.9)	3 (3.5)	2 (4.7)	1.0
Atrial fibrillation, n (%)	7 (5.4)	4 (4.7)	3 (7)	0.69
Median statin dose, mg (range, % within statin group)				
Atorvastatin	20 (10-40, 55.8%)			
Rosuvastatin	10 (5-20, 25.6%)			
Simvastatin	20 (10-40, 11.6%)			
Pravastatin	20 (10-20, 7.0%)			
Previous medications, n (%)				
ACEi	15 (11.6)	5 (5.8)	10 (23.3)	0.007
β-Blocker	11 (8.5)	5 (5.8)	6 (14)	0.18
ARB	17 (13.2)	6 (7)	11 (25.6)	0.005
MRA	2 (1.6)	0 (0)	2 (4.7)	0.11
CCB	12 (9.3)	3 (3.5)	9 (20.9)	0.002
Early breast cancer	105 (81.4)	66 (76.7)	39 (90.7)	0.06
ER positive, n (%)	80 (62)	50 (58.1)	30 (69.8)	0.25
PR positive, n (%)	51 (39.5)	32 (37.2)	19 (44.2)	0.45
Surgery, n (%)	114 (88.4)	73 (84.9)	41 (95.3)	0.14
Anthracyclines, n (%)	72 (55.8)	48 (55.8)	24 (55.8)	-
Median doxorubicin equivalent dose, mg/m^2 (IQR)	202.3 (199-238)	202.7 (200-238)	201.5 (182-232)	0.24
Cyclophosphamide, n (%)	83 (64.3)	53 (61.6)	30 (69.8)	0.44
Taxane, n (%)	116 (89.9)	75 (87.2)	41 (95.3)	0.22
5-FU, n (%)	47 (36.4)	30 (34.9)	17 (39.5)	0.70
Tamoxifen, n (%)	63 (48.8)	36 (41.9)	27 (62.8)	0.04
Radiotherapy, n (%)	93 (72.1)	60 (69.8)	33 (76.7)	0.53
Median Herceptin exposure, months (IQR)	11.8 (11-12)	11.9 (11-12)	11.6 (11-12)	0.58
Median Herceptin cycles (IQR)	17.0 (17-18)	17.0 (17-18)	17.0 (17-18)	0.85
Mean baseline LVEF, % ± SD	66.4 ± 6.0	66.7 ± 5.4	66.0 ± 7.0	0.57
Median number of MUGAs (IQR)	5.0 (4-6)	5.0 (4-6)	5.0 (4-5)	0.35
Mean cardiac risk score ± SD	59.6 ± 15.3	59.1± 15.2	60.6 ± 15.8	0.60

5-FU, fluorouracil; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ER, estrogen receptor; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MUGA, multigated acquisition scan; PR, progesterone receptor; SD, standard deviation.

to play an important role in the pathophysiology of trastuzumab-induced cardiotoxicity.[15,16] Neuregulin (NRG-1) is a protein released by coronary microvasculature and myocardial endothelial cells in response to stress. It binds to the transmembrane HER4, which, in turn, dimerizes with HER2 to activate critical cell-survival pathways. The inhibition of HER2 signalling by trastuzumab results in accumulation of reactive oxygen species (ROS) within cardiomyocytes, which leads to apoptosis and myocardial dysfunction.[16] Moreover, NRG-1/ErbB2 signalling regulates myocyte-myocyte and myocyte-matrix interactions, which are essential for maintenance of sarcomeric structure.[17]

Table 2. Adjusted final LVEF and LVEF change

	Control N = 86	Statins N = 43	Mean difference (95% CI)	*P* value
Mean final LVEF, % (95% CI)	61.2 (59.6-62.8)	64.6 (62.2-67.1)	−3.4 (−6.6 to −0.3)	0.034
LVEF change (95% CI)	−5.4 (−7.2 to −3.7)	−1.3 (−3.9 to +1.3)	−4.1 (−7.5 to −0.8)	0.016

The estimates and *P* value were derived from analysis of covariance with adjustment for baseline LVEF (only for final LVEF), age, body mass index, cardiovascular risk factors (diabetes, hypertension, coronary artery disease), cancer stage (early or metastatic), cardiovascular medications (angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, β-blocker), and anthracycline-based therapy. When interaction terms for coronary artery disease, diabetes, and statins were include the magnitude of difference for mean final LVEF and LVEF change remained similar and statistically significant. The interaction terms were not significant. For mean final LVEF: coronary artery disease*statin, $P = 0.14$; diabetes*statin, $P = 0.69$. For LVEF change: coronary artery disease*statin, $P = 0.20$; diabetes*statin, $P = 0.88$.

CI, confidence interval; LVEF, left ventricular ejection fraction.

Table 3. Multivariable logistic regression model (cardiotoxicity as dependent variable)

Variable	OR (95% CI)	*P* value
Statin treatment	0.32 (0.10-0.99)	0.049
Anthracycline Exposure	2.46 (0.94-6.45)	0.07
Number of cardiovascular risk factors*	1.25 (0.78-1.99)	0.35
Cardiac risk score (NSABP-B31)	1.03 (0.99-1.06)	0.07

CI, confidence interval; OR, odds ratio.
*Diabetes, hypertension, coronary artery disease, and smoking.

Inhibition of these pathways through trastuzumab results in alterations in mechanical coupling, aggravated by imbalance in calcium (Ca^{2+}) homeostasis, causing impaired contractility and relaxation and subsequent cardiac dysfunction.[18] Accordingly, the attenuation of these effects by statins might be the basis for the observed outcomes in our study. In support of this hypothesis, a recent study of rats treated with doxorubicin and trastuzumab demonstrated worsened LV function and greater ROS and glutathione production compared with treatment with doxorubicin alone.[19] The worsening of LV function and ROS and glutathione production were blunted by rosuvastatin. Therefore, we postulate that the pleiotropic effects of HMG-CoA reductase inhibitors may account for our observed results but acknowledge that further mechanistic studies are needed.

Trastuzumab cardiotoxicity

The cardiotoxicity risk of 20.2% based on the CREC definition seen in our study is similar to the incidence that has been reported in other studies and is not surprising given the high cardiovascular risk profile of our study population.[20-22] We have demonstrated recently that in patients with at least 1 cardiovascular risk factor (age $\geq$ 60 years, hypertension, diabetes, coronary artery disease, or atrial fibrillation), the 5-year cumulative incidence of a major adverse cardiac event (heart failure [HF] hospitalization, HF diagnosis, or cardiovascular death) can be as high as 8.2% in patients receiving nonanthracycline, trastuzumab-based chemotherapy and 11.3% in patients exposed to anthracyclines followed by trastuzumab.[2] Thus, the potential use of primary prevention strategies in such high-risk patients receiving trastuzumab therapy is clinically relevant.

Primary prevention with statins

Although other studies have shown a similar cardioprotective effect of statins in patients treated with anthracyclines,[7,8] our study is the first to demonstrate this effect in trastuzumab-treated patients. Although more than half of our patients also received anthracyclines prior to trastuzumab therapy, the effect remained significant after adjustment for anthracycline use, and the magnitude of effect of statins was similar in those who did and did not receive anthracycline therapy.

The fact that substantial cardioprotective effect was observed in the statin group despite a presumed higher cardiovascular risk due to higher prevalence of traditional cardiovascular risk factors is an important finding. This may reflect the fact that these traditional risk factors may increase the risk of heart failure in the mid- to long-term follow-up but be less relevant

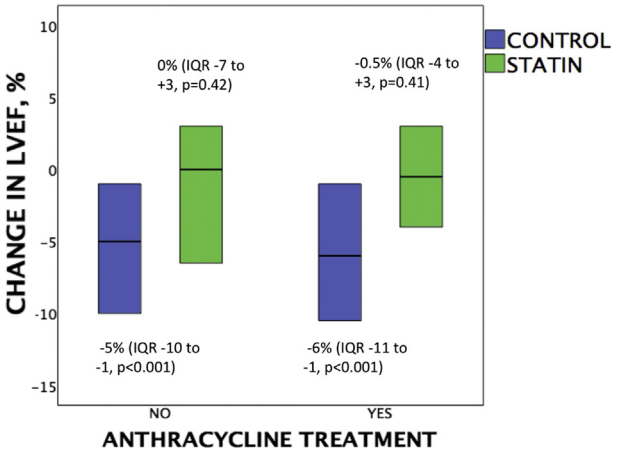

Figure 1. Subgroup analysis comparing the benefit of concomitant use of statins in patients who did and did not receive anthracyclines prior to trastuzumab therapy.

for LVEF changes that occur during cancer therapy, as has been demonstrated in previous studies.[23,24] Also, the patients in the statin group were more likely to be treated with renin-angiotensin system inhibitors and β-blockers than the control group owing to their cardiovascular comorbidities. Even though the use of these medications can be viewed as a potential confounder, the protective effect with statins was maintained even after adjustment for exposure to these therapies. Moreover, modern cardio-oncology trials have not uniformly supported the cardioprotective effects of β-blockers and ACE inhibitors in patients similar to ours.[13,25] The cardioprotective benefit of statins despite higher risk of cardiovascular disease (CVD) has also been reported in a prospective observational study in which 14 patients treated with statins had a smaller change in cardiac magnetic resonance image (MRI)-measured LVEF after anthracycline treatment than 37 controls, despite a higher cardiovascular risk and lower baseline LVEF.[9] Here, we extend these findings to patients receiving trastuzumab therapy.

We also identified a lower incidence of CREC-defined cardiotoxicity in statin-treated patients in our adjusted analysis. However, given the wide confidence interval around the odds ratio and the borderline *P* value, we consider this to be only hypothesis generating. Furthermore, trastuzumab interruption was lower in the statin-treated patients, although the difference did not meet statistical significance. We were unable to perform adjusted analysis because of the small number of events. Larger studies are required to further assess the impact of statin therapy in preventing cardiotoxicity and interruption of trastuzumab treatment in women with HER2+ breast cancer.

Limitations

Our study is limited by its retrospective and observational design. Accordingly, we cannot establish that the relationship between statin exposure and preservation of LVEF is causal. We matched on age and anthracycline exposure, then performed an adjusted analysis to demonstrate that statin use remained independently associated with LVEF decrement. However, residual confounding cannot be ruled out, as we

were unable to adjust for other factors that may influence LVEF measurements such as blood pressure, volume status, and anemia. However, we have no reason to believe that these changes would have occurred differentially in statin-treated patients vs controls. Moreover, we had to rely on clinical notes to determine patients' statin exposure status. Therefore, it was not possible to confirm adherence during cancer therapy or to explore the impact of the duration of statin use prior to cancer therapy on preventing LVEF decrement. Furthermore, as patients receiving statin treatment had a higher prevalence of cardiovascular comorbidities, it is possible that they were more likely to have been followed by cardiologists, which may hypothetically reduce the risk of cardiotoxicity.

Echocardiography (specifically 3D echocardiography) is currently considered the preferred imaging modality for surveillance during cancer treatment.[26] However, in our patients treated between 2002 and 2013, MUGA scans were still the most commonly used modality. Although the temporal reproducibility of LVEF measurements with MUGA in patients receiving cancer therapy is not well established, it still remains widely used in routine clinical practice.[2,21] Also, previous work has demonstrated that MUGA-measured LVEF has similar agreement with MRI measurements as 3D echocardiography in patients receiving breast cancer therapy.[27] Furthermore, as the same imaging modality was used in our statin-treated and control groups, the intergroup comparisons are still valid.

There was a higher proportion of patients with metastatic cancer in the control group; however, after adjustment for this variable, the overall effect persisted. Specific cardiovascular outcomes, such as cardiovascular death or cardiovascular disease hospital admission, were not recorded and likely warrant further exploration in longer-term follow-up studies. The number of confounders included in our logistic model was limited by the total number of cardiotoxicity events; however, we included the most important confounders in our model with 1 variable for every 6 to 7 events.[28] Given the wide confidence interval around the odds ratio for statins in the multivariable logistic model, we consider this finding to only be hypothesis generating. We used the cardiac risk score from the NSABP B-31 study as a confounder in the logistic model. This risk score was created in patients who were treated with anthracyclines followed by trastuzumab, which constituted only 56% of our cohort. However, as this was a secondary analysis, and the score incorporates 2 important confounders (age and baseline LVEF), we decided to include this score in the model, considering the low number of cardiotoxicity events. Finally, a relatively small sample size from a single centre is a limitation that can be addressed by validating these results prospectively in large multicentre studies.

Conclusions

The concomitant use of statins in women with HER2-positive breast cancer receiving trastuzumab therapy was associated with a lower magnitude of reduction in LVEF during treatment compared with those not receiving statin therapy. The benefit was seen in those who did and did not receive previous anthracycline therapy. Furthermore, the attenuation of LVEF decline in the statin group occurred despite a higher baseline cardiovascular risk profile than the non-statin users. Prospective clinical studies are warranted to confirm our findings and to determine whether concomitant administration of statins can prevent cardiotoxicity in trastuzumab-treated patients.

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Disclosures

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