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Clinical Research

Chronic Statin Administration May Attenuate Early Anthracycline-Associated Declines in Left Ventricular Ejection Function

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See editorial by Stone and Stone, pages 244-246 of this issue.

ABSTRACT

Background: Recent studies have shown an association between statin therapy and a reduced risk of heart failure among breast cancer survivors. Our goal was to evaluate whether statin therapy for prevention of cardiovascular (CV) disease would ameliorate declines in the left ventricular ejection fraction (LVEF) that is often observed during anthracycline-based chemotherapy (Anth-bC).

Methods: There were 51 participants (33 women and 18 men, aged 48 ± 2 years). We obtained cardiovascular magnetic resonance imaging (CMRI) measurements of LVEF before and 6 months after initiation of Anth-bC for patients with breast cancer, leukemia, or lymphoma. Fourteen individuals received statin therapy, and 37 patients received no statins. MR image analysts were blinded to participant identifiers.

Results: Individuals receiving statins were older and often had diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia (HLD). For

RÉSUMÉ

Introduction : Les récentes études ont montré une association entre le traitement par statines et la réduction du risque d'insuffisance cardiaque chez les survivants du cancer du sein. Notre but était d'évaluer si le traitement par statines pour prévenir la maladie cardiovasculaire (CV) pourrait améliorer les baisses de la fraction d'éjection ventriculaire gauche (FEVG) souvent observées durant la chimiothérapie par anthracyclines (C-Anth).

Méthodes : On comptait 51 participants (33 femmes et 18 hommes, de 48 ± 2 ans). Nous avons obtenu les mesures de l'imagerie cardiaque par résonance magnétique (ICRM) de la FEVG avant et 6 mois après l'introduction de la C-Anth chez les patients souffrant du cancer du sein, d'une leucémie ou d'un lymphome. Quatorze individus recevaient le traitement par statines, et 37 patients ne recevaient aucune statine. Les analystes de l'image de la RM procédaient à l'insu des identificateurs des participants.

Anthracycline-based chemotherapy (Anth-bC) is an important component of adjuvant chemotherapy for breast cancer and an essential element of curative combination chemotherapy for acute leukemia, Hodgkin disease, non-Hodgkin lymphoma, and many other solid tumours.[1,2] The cytotoxic antitumour effects from Anth-bC are related to their interactions with the enzyme topoisomerase IIα, production of double-strand DNA breaks, and the generation of intracellular cytotoxic free radicals.[3] Unfortunately, these cytotoxic free radicals promote oxidative and nitrosative stress in cardiomyocytes, which, in combination with other anthracycline-related effects (systemic inflammation and neurohormonal activation), promote LV dysfunction, myocardial replacement fibrosis, congestive heart failure, and cardiovascular (CV) events.[4-14] Strategies that could reduce Anth-bC–mediated myocellular oxidative/nitrosative stress could diminish LV dysfunction and possibly improve overall cancer-related survival.

Several lines of evidence suggest that generic inexpensive oral 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) may attenuate cardiomyocyte injury during

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those receiving statins, LVEF was 56.6% ± 1.4% at baseline and 54.1% ± 1.3% 6 months after initiating anthracycline treatment ($P = 0.15$). For those not receiving statins, LVEF was 57.5% ± 1.4% at baseline and decreased to 52.4% ± 1.2% over a similar 6-month interval ($P = 0.0003$). In a multivariable model accounting for age, sex, DM, HTN, HLD, and cumulative amount of anthracycline received, LVEF remained unchanged in participants receiving a statin (+1.1% ± 2.6%) vs a −6.5% ± 1.5% decline among those not receiving a statin ($P = 0.03$).

Conclusions: These data highlight the finding that individuals receiving statin therapy for prevention of cardiovascular disease may experience less deterioration in LVEF with early receipt of Anth-bC than individuals not receiving statins. Further studies with large numbers of participants are warranted to determine if statins protect against LVEF decline in patients receiving Anth-bC.

Résultats : Les individus recevant les statines étaient plus âgés et souvent souffraient de diabète, d'hypertension (HT) et d'hyperlipidémie (HL). Chez ceux recevant les statines, la FEVG était de 56,6 % ± 1,4 % au début et de 54,1 % ± 1,3 % 6 mois après l'introduction du traitement par anthracyclines ($P = 0,15$). Chez ceux ne recevant pas les statines, la FEVG était de 57,5 % ± 1,4 % au début et diminuait à 52,4 % ± 1,2 % au cours d'un intervalle similaire de 6 mois ($P = 0,0003$). Dans un modèle multivariable tenant compte de l'âge, du sexe, du diabète, de la HT, de la HL et de la quantité totale d'anthracyclines reçues, la FEVG demeurait inchangée chez les participants recevant une statine (+1,1 % ± 2,6 %) *vs* montrait une baisse de −6,5 % ± 1,5 % chez ceux ne recevant pas de statines ($P = 0,03$).

Conclusions : Ces données aboutissent à la conclusion que les individus recevant le traitement par statines pour prévenir la maladie cardiovasculaire subissent moins de détérioration de la FEVG lors d'un traitement précoce par C-Anth que les individus ne recevant pas de statines. D'autres études portant sur un grand nombre de participants sont justifiées pour déterminer si les statines protègent contre la baisse de la FEVG des patients recevant la C-Anth.

and after receipt of Anth-bC.[15] Although this class of drug is commonly used to treat hypercholesterolemia, these agents also reduce oxidative and nitrosative stress, inflammatory cytokines, and circulating neurohormones.[16,17] In a recent observational study, women receiving statins for primary or secondary prevention of CV events who also received adjuvant chemotherapy for breast cancer experienced fewer heart failure—related billing code events than did women receiving similar breast cancer therapy without concomitant statin use.[18]

Based on the preceding considerations, we hypothesized that participants receiving anthracycline chemotherapy who were also taking statin therapy for primary or secondary prevention of CV events may experience smaller decreases in left ventricular ejection fraction (LVEF) when compared with individuals not taking statins. To test this hypothesis, we measured LVEF with cardiovascular magnetic resonance imaging (CMRI) before and 6 months after initiation of Anth-bC in 51 participants with breast cancer, leukemia, or lymphoma.

Methods

Study population and design

The study was approved by the Institutional Review Board of the Wake Forest University School of Medicine, and all participants provided witnessed written informed consent. Between 2007 and 2010, we enrolled 51 consecutive participants who were recruited from the hematology and oncology outpatient and inpatient facilities of the Comprehensive Cancer Center at Wake Forest Health Sciences and were scheduled to receive Anth-bC. Of the cohort enrolled, we separated participants into 2 groups: 14 individuals who were receiving statins for primary or secondary prevention of CV events and 37 individuals who were not receiving statins.[19,20] Each participant was scheduled to receive a CMRI measurement of LVEF on 2 occasions: before receipt of their Anth-bC and 6 months after initiation of chemotherapy. All acquired images were transferred to workstations for determination of LVEF and mean midwall circumferential myocardial strain by personnel blinded to participant identifiers, study group, and the date or results of the other CMRI examination (a blinded unpaired read).

CMRI image acquisition analysis

Images were acquired with a 1.5T MAGNETOM Avanto (Siemens, Malvern, PA) whole body imaging system using a phased-array cardiac surface coil according to previously published techniques.[21,22] These sequences incorporated steady-state free-precession cine white blood cell imaging techniques in which a series of short axis slices were positioned across the LV apical 4-chamber view beginning at the base of the left ventricle and terminating at its apex. Imaging parameters included a 34-cm field of view, a 47.3-ms repetition time (TR), a 1.1-ms echo time (TE), an 80° flip angle (FA), an 8-mm—thick slice with a 2-mm interslice gap, and a 192 × 109 matrix. The measurements of LVEF were performed according to previously published techniques.[23,24]

Tagged CMRI images for calculation of myocardial strain were acquired in the middle LV short axis plane according to previously published methods using spatial modulation of magnetization (SPAMM).[25] Imaging parameters included a 36-cm field of view, a 42-ms TR, a 3.8-ms TE, a 12° FA, an 8-mm—thick slice, and a matrix size of 192 × 144. Mean midwall LV circumferential strain was measured in the midventricular short axis plane from the SPAMM grid tag deformations that occurred throughout the systolic frames according to previously published methods using harmonic phase (HARP) analysis (Diagnosoft, Raleigh, NC).[26]

Statistical analysis

Descriptive statistics were estimated for measures of interest, including means and standard errors for continuous measures and counts and percentages for categorical measures. For each continuous measure, a 2-sample t test was performed to compare the statin users with the non—statin users. For categorical measures, Fisher exact tests were performed to compare the 2 groups. Comparisons within the groups were made for changes in the LV function measures using paired t tests.