Effect of Statins on Early Anthracycline Cardiotoxicity

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Abstract

Background: Anthracycline-induced cardiotoxicity is driven by oxidative stress, endothelial dysfunction, and DNA damage, often leading to ventricular remodeling. Emerging data suggest that the right ventricle (RV) may be affected earlier than the left. The TAPSE/PAPs ratio is a validated noninvasive index of RV–RV-pulmonary arterial (PA) coupling and may serve as a sensitive marker for early dysfunction. Statins, through inhibition of Rho GTPases and antioxidant effects, could mitigate anthracycline-related myocardial and vascular injury.
Aim: To evaluate whether rosuvastatin preserves RV–PA coupling and attenuates early cardiotoxicity in patients with breast cancer receiving anthracycline-based chemotherapy.
Methods: A total of 226 consecutive breast cancer patients (mean age 52 ± 10 years) were screened prior to anthracycline treatment. 28 asymptomatic patients with low HFA/ICOS risk before therapy and -with decreased TAPSE/PAPs (<0.40 mmHg) and elevated Nt-pro-BNP (median 225 pg/mL) but normal ejection fraction after cycle 6-were randomized 1:1 to standard cardioprotective therapy with ACE inhibitors + beta-blockers (statin−, n = 14) or the same regimen plus rosuvastatin 20 mg daily (statin+, n = 14) for 12 months. Echocardiography and NT-proBNP were assessed at baseline, after chemotherapy, and during follow-up.
Results:After 12 months, patients receiving rosuvastatin demonstrated a trend toward higher TAPSE/PAPs ratios and improvement in RV function compared with the statin- group. Nt-pro-BNP levels decreased and mitral regurgitation grade improved in the statin+ group, while ejection fraction remained stable in both. No adverse drug effects were reported.
Conclusions: A decline in TAPSE/PAPs ratio may identify early anthracycline-induced cardiotoxicity despite preserved LV function. Rosuvastatin added to standard therapy was associated with improved RV–PA coupling and biomarker profile, suggesting potential benefit as an adjunctive cardioprotective strategy. Larger trials are needed to confirm these findings.
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Keywords: Anthracycline, Cardiotoxicity, Rosuvastatin, Right ventricle, TAPSE/PAPs, RV–PA coupling, Cardio-oncology

Introduction

It is generally believed that anthracycline-induced reactive oxygen species (resulting from the intracellular metabolism of anthracyclines), which lead to oxidative stress, DNA damage, and apoptosis, mediated by anthracycline-induced inhibition of topoisomerase II, are the key mechanisms responsible for anthracycline-induced cardiotoxicity (1,2). Accumulating evidence has suggested a role of the small Ras homolog GTPase in DNA damage response(3). Statins are anti-inflammatory and anti-oxidative drugs and inhibitors of small Ras homolog GTPases, which are a major factor in the development of oxidative stress (4,5).

Several studies have suggested that the RV may be more vulnerable to injury from anthracyclines, and early RV dysfunction may predict anthracycline-induced cardiotoxicity (6)

It was shown that the TAPSE/PAPs index measured on echocardiography strongly correlated with the invasive assessment of RV-PA coupling and unmasked the early occurrence of symptoms and an initial depression in the RV functional reserve(7)

Till now, there has been no research on the pharmacological effects of RV-PA coupling(8)Our objective was to investigate the effect of rosuvastatin on cardiotoxicity in

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patients with breast cancer receiving a standard anthracycline-based regimen by the dynamic of coupling between right ventricular (RV) contractile function and pulmonary artery systolic pressure (RV-PA coupling) assessed with TAPSE/PAPs index.

Methods

226 consecutive patients with breast cancer, over 5 years, mean age 52 ±10, with newly diagnosed breast cancer, with informed consent, were recruited for a 16-month follow-up before and after the completion of anthracycline therapy (median cumulative dose of anthracycline was 250 mg/m^2). Clinical assessment was combined with Nt-pro-BNP and transthoracic echocardiography. The median follow-up period was 16 months. Echocardiography and Nt-pro-BNP were performed at list 4-fold: at baseline, after cycle 6, and at 3 and 12 months post-completion of treatment.

Baseline echocardiography and Nt-pro-BNP were normal.

28 clinically asymptomatic patients with low HFA/ICOS and low SCORE 2 before standard anthracycline-based regimen therapy and with decreased TAPSE/PAPs index (<0.40 mm/mmHg, median 0.37.Table 1), and elevated Nt-pro-BNP (median 225, Table 2) after cycle 6 were identified (HF, Stage B). EF was in the normal range. Mitral valve regurgitation more than mild was diagnosed in 19 patients.

28 patients were randomized 1:1 to conventional therapy with ACI and β-blockers (- statin group,14 p.) and therapy with ACI and β-blockers and rosuvastatin 20 mg. (+ statin group,14 p)-for 12 months. Echocardiography was performed using a GE Vivid 7 ultrasound system according to the ASE's recommendations. Patients were investigated by the TAPSE/PAPs index. A Student's T-test, which is particularly useful for small samples, was used to perform statistical analysis. P< 0,001 was considered statistically significant. All procedures were conducted in accordance with the ethical standards of the Helsinki Declaration.

Results and discussion

RV-PA coupling assessed by the TAPSE/PAPs index was higher and Nt-pro-BNP was lower in the +statin group by trend (Table 3,4). Improvements in RV function, mitral regurgitation, and Nt-pro-BNP after 12 months of cardioprotective treatment with statin, ACI, and β-blocker were observed in this study.

Anthracycline cardiotoxicity is traditionally characterized by left-ventricular systolic dysfunction, yet accumulating evidence indicates that the right ventricle (RV) may demonstrate subclinical impairment even earlier(9). The RV is particularly susceptible to oxidative and metabolic stress, presumably because of its thinner wall, lower coronary perfusion pressure, and dependence on longitudinal fiber shortening. The TAPSE/PAPs ratio—a non-invasive surrogate of RV–RV-pulmonary arterial (PA) coupling (10). The TAPSE/PAPs index allows emphasis the right ventricular function in terms of afterload (7) . In this study, the TAPSE/PAPs ratio proved sensitive to early anthracycline-related injury, preceding reductions in ejection fraction and the onset of symptoms. Our results show that rosuvastatin, when added to standard cardioprotective therapy, tended to preserve or improve TAPSE/PAPs compared with control. Although the sample size was modest, the consistent direction of change (p<0,001) and accompanying reductions in Nt-pro-BNP (p<001) suggest a biologically plausible effect. Statins exert pleiotropic cardioprotective actions independent of lipid-lowering (11): inhibition of Rho and Rac GTPases, attenuation of NADPH-oxidase-mediated reactive oxygen species generation, and up-regulation of endothelial nitric oxide synthase(12). Through these mechanisms, rosuvastatin may mitigate microvascular dysfunction and oxidative DNA damage induced by anthracyclines, improving RV contractile–afterload matching. Previous investigations have linked anthracycline therapy with increased systemic and pulmonary vascular stiffness(13), which elevates RV afterload even in the absence of overt pulmonary hypertension. Although no prior study has specifically evaluated statins' impact on RV–PA coupling, our findings align with data demonstrating statins' cardioprotective role in chemotherapy-induced endothelial dysfunction and LV strain reduction(14). Previous research has shown that anthracyclines increase both systemic and pulmonary vascular stiffness, resulting in elevated RV afterload and impaired coupling (9). The improvement in TAPSE/PAPs among statin-treated patients in our study may therefore reflect not only direct myocardial protection but also favorable modulation of pulmonary vascular compliance. These observations are consistent with preclinical data demonstrating reduced pulmonary vascular resistance and enhanced endothelial function under statin therapy(14) .The findings support TAPSE/PAPs as a sensitive, reproducible, and noninvasive biomarker for early anthracycline-induced RV dysfunction. Identifying subclinical RV–PA uncoupling may enable earlier intervention, potentially before irreversible myocardial injury occurs. Incorporation of statin therapy into cardioprotective regimens could represent a low-risk strategy to preserve biventricular function in susceptible patients. This study was performed with a limited sample size (n=28 in randomized groups), which constrained statistical power and precluded multivariable analysis. Quantitative assessment of pulmonary vascular stiffness and RV strain imaging was not performed. Future investigations should integrate TAPSE/PAPs assessment with advanced imaging modalities such as RV strain and cardiac MRI to refine early detection of anthracycline cardiotoxicity.

While the study was not powered to detect small intergroup differences, the observed trends support further exploration of statins as adjuncts in cardio-oncology prophylaxis. Incorporating RV-PA coupling indices into longitudinal echocardiographic follow-up may enhance early detection of cardiotoxicity and refine patient selection for cardioprotective therapy.

Conclusion

In patients receiving anthracycline-based chemotherapy, a decline in the TAPSE/PAPs ratio may represent an early marker of subclinical right-ventricular dysfunction. The addition of rosuvastatin to standard cardioprotective ther-

apy appeared to preserve RV–PA coupling and improve functional parameters. These findings highlight the potential of statin therapy as a strategy for early cardioprotection and warrant confirmation in larger prospective studies.

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