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Original article

ST2 levels increased and were associated with changes in left ventricular systolic function during a three-year follow-up after adjuvant radiotherapy for breast cancer

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ABSTRACT

Objectives: To search for biomarkers of RT-induced cardiotoxicity, we studied the behavior of ST2 during RT and three years after RT, and the associations with echocardiographic changes.
Materials and methods: We measured soluble ST2 (ng/ml) in serum samples from 63 patients receiving RT for early breast cancer. Sampling and echocardiography were performed at baseline, after RT and at the three-year follow-up. Patients were grouped by >15% (group 1) and ≤15% (group 2) relative worsening in global longitudinal strain (GLS).
Results: ST2 levels tended to increase during RT, from a median (interquartile range; IQR) of 17.9 (12.4–22.4) at baseline to 18.2 (14.1–23.5) after RT ($p = 0.075$). By the three-year follow up, ST2 levels increased to 18.7 (15.8–24.2), $p = 0.018$. The increase in ST2 level was associated with worsening cardiac systolic function at three-year follow-up, GLS (rho = 0.272, $p = 0.034$) and left ventricular ejection fraction (LVEF) (rho = −0.343, $p = 0.006$). Group 1 ($n = 14$) had a significant increase in ST2 levels from 17.8 (12.3–22.5) at baseline to 18.4 (15.6–22.6) after RT, $p = 0.035$ and to 19.9 (16.0–25.1) three years after RT, $p = 0.005$. ST2 levels were stable in group 2 ($n = 47$): 17.8 (12.3–22.0) at baseline, 17.7 (12.6–23.5) after RT and 18.0 (15.5–22.4) at three years.
Conclusion: ST2 may be useful for determining which patients are at risk for long-term cardiovascular toxicity following adjuvant breast cancer RT, but prospective clinical studies are needed to confirm this hypothesis.

1. Introduction

Adjuvant radiotherapy (RT) reduces breast cancer (BCa) recurrence and mortality [1,2], but the increase in long-term cardiac morbidity and mortality caused by RT is of concern [3–9]. ST2 is released by cardiomyocytes in response to myocardial stress [10]. In heart failure patients and in population-based studies, elevated levels were associated with increased mortality [11–16]. No studies on the effect of RT alone exist, but radiation exposure was associated with increased ST2 levels in nuclear plant workers [17].

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Abbreviations

ACE	angiotensin converting enzyme inhibitor
AI	aromatase inhibitor
ARB	angiotensin II receptor blocker
ASA	acetylsalicylic acid
BCa	breast cancer
BMI	body mass index
CAD	coronary artery disease
DCIS	ductal carcinoma in situ
GLS	global longitudinal strain
IQR	interquartile range
LAD	left anterior descending coronary artery
proBNP	N-terminal pro-brain natriuretic peptide
Md	median
RT	radiotherapy
LV	left ventricle
LVEF	left ventricular ejection fraction
RV	right ventricle

To identify predictive markers for the detection of adjuvant RT-induced changes in left ventricular (LV) function in BCa patients, we evaluated the behavior of ST2 and its association with LV systolic function before RT, after RT and at the three-year follow-up.

2. Materials and methods

This prospective, observational, single center study included 63 chemo-naïve patients with early-stage BCa or ductal carcinoma in situ (DCIS) who received postoperative RT ± concurrent endocrine therapy. Fifty patients had left-sided and 13 patients had right-sided BCa. The key inclusion and exclusion criteria, and the RT procedure were described in detail previously [18,19]. The local ethics committee (R10160) approved the study and informed consent was obtained from all participants.

Sampling and echocardiography were performed, as described previously [20,21], at the start of RT (bRT), at the end of RT (eRT) and at the three-year follow-up (3yRT). The concentrations of ST2 were measured by enzyme-linked immunosorbent assay with reagents from R&D Systems Europe Ltd. (Abingdon, UK). The detection limit and interassay coefficient of variation were 7.8 pg/ml and 6.2%, respectively. N-terminal pro-brain natriuretic peptide (proBNP) was measured at an accredited laboratory [22].

2.1. Statistical analysis

The basic statistical testing was done as described previously [23]. Multivariable linear regression analyses were performed to model the change in GLS and in left ventricular ejection fraction (LVEF) over three years, adjusting the models with the change in ST2 over three years, age, body mass index (BMI), laterality of BCa, aromatase inhibitor (AI) use and hypertension. Additionally, patients were divided into two groups: >15 and ≤ 15% relative change in global longitudinal strain (GLS) [24], a clinically meaningful change [24,25]. Differences between these groups were tested using multivariable logistic regression analysis, adjusting the model with the change in ST2 over three years, AI use, age and the mean dose to the left anterior descending coronary artery (LAD). Statistical testing was performed utilizing IBM SPSS Statistics software, version 25 for Windows (Armonk, NY, USA). P-values less than 0.05 were considered significant.

3. Results

3.1. Changes in ST2 levels and correlations with age, BMI and proBNP

ST2 levels increased slightly from bRT to eRT and increased significantly from bRT to 3yRT (Table 1).

Age and the change in ST2 level during RT (Spearman's rho 0.281, $p = 0.025$), and BMI and the change in ST2 level during the follow-up (rho 0.309, $p = 0.014$) correlated. Furthermore, the change in ST2 and proBNP levels during the follow-up were correlated (rho 0.329, $p = 0.009$).

3.2. The change in ST2 level and baseline characteristics

The change in ST2 level was significantly greater patients with hypertension during RT, $p = 0.008$. Diabetic patients had higher median ST2 levels at bRT than non-diabetic patients, $p = 0.025$. There were no other significant differences according to other baseline characteristics.

3.3. ST2 levels and systolic echocardiographic measurements

A table of echocardiographic parameters at bRT, eRT and at 3yRT was published as a supplementary table in our previous publication [23]. The change in ST2 levels during RT correlated with GLS at 3yRT (rho = 0.287, $p = 0.025$). Furthermore, the change in ST2 level over the three years was correlated with GLS (rho = 0.272, $p = 0.034$) and LVEF (rho = −0.343, $p = 0.006$) at 3yRT.

In multivariable linear regression analyses, no variables significantly explained the decrease in LVEF, but AI use and left-sided BCa were associated with the impairment in GLS over the follow-up, $p = 0.042$ and $p = 0.013$, respectively. The change in ST2 level did not quite reach significance in the model, $p = 0.093$. The variables explained 24.3% of the variance.

3.4. Grouping according to >15% and ≤15% relative change in GLS over three years

Patients were grouped according to a clinically meaningful GLS change: 14 patients with >15% (group 1) and 47 patients with ≤15% (group 2) relative worsening in GLS. Group 1 had a significant worsening in GLS during RT, $p = 0.006$, and during the follow-up, $p < 0.001$ (Table 2). Group 2 had a stable GLS during RT, $p = 0.979$, and the follow-up, $p = 0.183$.

The baseline characteristics, cardiac doses, GLS measurements and ST2 levels are displayed in Table 2. The median ST2 level increased significantly only in group 1 during RT ($p = 0.035$) and the follow-up ($p = 0.005$). In group 2, the ST2 level remained stable, $p = 0.220$ during RT and $p = 0.500$ during the follow-up.

In multivariable binary logistic regression analysis, AI users (OR 5.61 [95% CI 1.25–25.10]) were more likely to be in group 1. Furthermore, increasing mean dose to LAD (OR 1.07 [95% CI 1.00–1.15]), greater increase in ST2 levels (OR 1.15 [95% CI 0.93–1.41]) and older age (OR 1.08 [95% CI 0.96–1.22]) nearly reached significance.

4. Discussion

We report a small, yet significant, increase in ST2, a possible marker of cardiotoxicity, three years after adjuvant RT for early BCa. One earlier study found no association between RT and ST2 levels, but the ST2 levels increased 6 months after chemotherapy, which could have masked the effect of RT [26].

Older age, BMI, hypertension and diabetes affected ST2 levels,

Table 1
ST2 levels at the different time points for the entire study population (n = 63).

	Baseline		After RT		3 years		p^1	p^2
	Md	(IQR)	Md	(IQR)	Md	(IQR)		
ST2 (ng/ml)	17.9	(12.4–22.4)	18.2	(14.1–23.5)	18.7	(15.8–24.2)	0.075	**0.018**

RT, radiotherapy; Md, median; IQR, interquartile range; p^1, change from baseline to after RT; p^2, change from baseline to the three-year follow-up.
Statistical significance is shown in bold ($p < 0.05$).

Table 2
Baseline characteristics, cardiac doses, GLS and ST2 levels compared according to the >15% (group 1) and ≤15% (group 2) relative change in GLS.

	Group 1 (n = 14)		Group 2 (n = 47)		p
Baseline characteristics					
Age, Md (IQR)	67.0	(59.0–73.5)	64.0	(58.0–66.0)	**0.049**
BMI, Md (IQR)	28.8	(24.8–30.7)	25.8	(23.9–27.7)	0.081
Left-sided BC, n (%)	14	(100.0)	35	(74.5)	0.052
AI, n (%)	9	(64.3)	11	(23.4)	**0.008**
Tam, n (%)	0	(0.0)	6	(12.8)	0.321
Hypertension, n (%)	5	(35.7)	18	(38.3)	1.000
ACE, n (%)	3	(21.4)	13	(27.7)	0.742
Beta-blockers, n (%)	4	(28.6)	7	(14.9)	0.256
ASA, n (%)	1	(7.1)	4	(8.5)	1.000
Statins, n (%)	2	(14.3)	10	(21.3)	0.715
CAD, n (%)	1	(7.1)	2	(4.3)	0.549
Diabetes, n (%), n = 14 and 44	1	(7.1)	3	(6.8)	1.000
Smoking, n (%)	1	(7.1)	5	(10.6)	1.000
Hypothyreosis, n (%)	4	(28.6)	6	(12.8)	0.245
Radiation doses to the heart					
Dmean heart ≥2 Gy, n (%)	11	(78.6)	23	(48.9)	0.068
Dmean heart (Gy); Md (IQR)	3.4	(2.0–4.0)	1.9	(1.0–3.8)	0.082
V20 Gy to heart (%); Md (IQR)	4.6	(1.5–5.3)	1.4	(0–4.5)	0.052
Dmean LV (Gy); Md (IQR)	4.6	(3.0–5.6)	2.7	(1.1–5.9)	0.148
V20 Gy to LV (%), Md (IQR)	6.8	(1.9–8.0)	1.8	(0–8.4)	0.150
Dmean RV (Gy), Md (IQR)	2.4	(1.7–3.0)	1.5	(1.0–2.9)	0.073
Dmean LAD (Gy), Md (IQR)	23.7	(10.5–28.9)	9.4	(1.4–24.8)	**0.012**
V20 GY to LAD (%), Md (IQR)	50.3	(14.7–71.9)	12.8	(0–55.0)	**0.015**
GLS at different time points					
GLS baseline (%), Md (IQR)	−20.0	(−23.3-–17.0)	−17.0	(−19.0-–15.0)	**0.036**
GLS after RT (%), Md (IQR)	−16.5	(−19.3-–14.8)	−17.0	(−20.0-–15.0)	0.704
GLS at 3 years (%), Md (IQR)	−14.0	(−16.3-–11.0)	−18.0	(−20.0-–16.0)	**<0.001**
ST2 levels					
ST2 baseline (ng/ml), Md (IQR)	17.8	(12.3–22.5)	17.8	(12.3–22.0)	0.803
ST2 after RT (ng/ml), Md (IQR)	18.4	(15.6–22.6)	17.7	(12.6–23.5)	0.561
ST2 at 3 years (ng/ml), Md (IQR)	19.9	(16.0–25.1)	18.0	(15.5–22.4)	0.383

GLS, global longitudinal strain; RT, radiotherapy; Md, median; IQR, interquartile range; BMI, body mass index; BC, breast cancer; AI, aromatase inhibitor; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, low dose acetylsalicylic acid; CAD, coronary artery disease; Diabetes, use of diabetes medication; Dmean; mean dose to the structure; V20, the percentage of volume of the structure receiving 20 Gy; LV, left ventricle; RV, right ventricle; LAD, left anterior descending coronary artery; p, p-value from the Mann-Whitney *U* test.
Statistical significance is shown in bold ($p < 0.05$).

possibly indicating that patients with underlying cardiac risk factors are at a greater risk for cardiotoxicity. These associations have been reported previously [16,27,28].

4.1. ST2 levels and changes in LV systolic function

The increase in the ST2 level during RT was associated with a higher, thus worse, GLS at the three-year follow-up. Additionally, the three-year change in the ST2 level correlated with a worsening in GLS and LVEF, both known prognostic factors for cardiovascular death [29]. The association between worsening GLS and increasing ST2 levels has been reported previously in patients with cardiac conditions [30,31]. In multivariable analysis, the worsening in GLS was predicted by AI use and left-sided BCa, an association we have reported previously [19,21]. The change in ST2 level was only suggestive in association with worsening GLS.

A significant increase in ST2 level was found in patients with a >15% relative worsening in GLS. In the multivariable analysis, only AI use significantly predicted the worsening of GLS. The associations between age, LAD radiation dose and the change in ST2 level during the follow-up and the change in GLS were hypothesis generating.

4.2. Limitations

The small sample size is a limitation of our study. Furthermore, the changes in LV systolic function and ST2 levels were subclinical and a longer follow-up is needed to determine whether these changes translate into clinically relevant cardiovascular risk.

5. Conclusion

We observed a small but significant increase in ST2 levels during adjuvant RT ± endocrine therapy for BCa and during the three-year follow-up. The increase was apparent in patients with a >15% worsening in GLS, which was also associated with AI use and higher radiation dose to the LAD. As it takes years for RT-induced heart disease to manifest, longer follow-up and larger prospective clinical

studies are needed to confirm whether ST2 levels provide additional value in cardiotoxicity risk evaluation.

Ethical approval

The study was approved by the Tampere University Hospital ethics committee (R10160), Tampere, Finland, and informed consent was obtained from all participants.

Declarations of competing interest

None.

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