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Research Article

Evaluation of Changes in Left and Right Ventricular Volumes in Women with Breast Cancer Treated with Adjuvant Trastuzumab

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Keywords

- Trastuzumab
- Herceptin
- Left ventricle ejection fraction
- Right ventricle ejection fraction

Abstract

Aim: To evaluate the changes in left and right ventricular volumes during adjuvant treatment with trastuzumab in women with HER2 positive breast cancer.

Methods: 115 women with HER2 positive primary breast cancer treated with trastuzumab after anthracycline therapy in the adjuvant setting were included. Patients had a routine multigated radionuclide angiography (MUGA) before the initiation of trastuzumab as well as every third month during treatment.

Results: After 270 days of trastuzumab mean left ventricular end diastolic and end systolic volumes increased from 86.8 ml to 96.5 ml and from 30.4 ml to 39.3 ml, respectively ($p = 9^{*}10^{-9}$ and $2^{*}10^{-10}$). Simultaneously, mean left ventricular ejection fraction (LVEF) decreased from 66.3 (± 9.3) to 60.7 (± 9.7) ($p = 6^{*}10^{-10}$). An LVEF decrease ≥ 10 percentage points (pp) from baseline to 270 days was found in 37 women and 16 experienced a decrease of ≥ 15 pp, while 22 women experienced a decrease in LVEF to ≤ 50%. Significant changes in mean blood pressure (120/73 to 125/75, p = 0.007) and heart rate (72 to 67 bpm, $p = 4^{*}10^{-5}$) were observed, but changes were not substantial enough to account for the changes in ejection fraction and left ventricular volumes. Though right ventricular volumes increased (mean end diastolic from 114 to 131 ml, mean end systolic from 63.3 to 73.3ml) no significant changes in right ventricular ejection fraction (RVEF) were found.

Conclusion: Mean LVEF decreased significantly during treatment with trastuzumab, while right ventricular ejection fraction was apparently not affected to the same extent.

INTRODUCTION

Trastuzumab in combination with chemotherapy is standard of care of HER2 positive breast cancer in both early and advanced disease and has improved the prognosis significantly [1]. However, trastuzumab is associated with a small to modest risk of cardiotoxicity leading to a decline in left ventricular ejection fraction (LVEF) or (rarely) to manifest clinical symptoms of heart failure [1-3]. The cardiotoxic effect of trastuzumab is not related to cumulative dose and can be reverted by pausing treatment and does not necessarily reappear when resuming therapy. Nevertheless, women receiving chemotherapy in combination with trastuzumab for early breast cancer have a fivefold increase in risk of congestive heart failure and a twofold increase in risk of significant LVEF reduction compared to women receiving only chemotherapy [1].

Left ventricular function during potentially cardiotoxic treatments has traditionally been monitored using echocardiography, magnetic resonance imaging (MRI) or multigated radionuclide angiography (MUGA). MUGA is regarded as a good method for monitoring cardiotoxicity of potentially cardiotoxic anticancer treatments, due to its applicability, high reproducibility, and low inter-observer variation when compared to echocardiography, as well as its low cost and high availability when compared to MRI [4]. The latest type of dedicated cardiac single photon emission computed tomography (SPECT) gamma camera with Cadmium Zinc Telluride (CZT) detectors provide highly reproducible assessments of both left and right ventricular volumes and ejection fractions [5].

The present study evaluates whether changes in right and left ventricular volumes can be detected using CZT detector based MUGA as well as whether volume changes are more predominant in patients treated for cardiotoxicity.

MATERIALS AND METHODS

All patients receiving adjuvant treatment with anthracycline (epirubicin), cyclophosphamide and trastuzumab for HER2

positive breast cancer at the Department of Oncology at Herlev and Gentofte University Hospital, Denmark, between October 2012 and April 2016 were evaluated for inclusion in the present study.

Patients received three cycles of anthracycline (epirubicin 90 mg/m^2) and cyclophosphamide (1000 mg/m^2) followed by 3 cycles of taxanes (docetaxel or paclitaxel). Trastuzumab was administered concomitant with taxane and intravenously as an 8mg/kg loading dose followed by either 6 mg/kg every three weeks or 600 mg sc. every three weeks for a total of one year. Patients underwent routine MUGA before initiation of trastuzumab as well as every third month during treatment. Initial MUGA was performed when practically possible, i.e. before or after the third and final dose of anthracycline and cyclophosphamide.

Ventricular function was evaluated with steady state ^{99m}Tc-HSA planar gated equilibrium radionuclide angiography with a SPECT camera with CZT-detectors GE Discovery 530c (GE Healthcare, Milwaukee, WI, USA). Each patient received 550 MBq ^{99m}Tc-labelled human serum albumin (HSA) intravenously. Assessment of the left ventricular function was performed including volume estimations of end diastolic volume (EDV) and end systolic volume (ESV) with Cedars-Sinai QBS processing software (revision 2009.0) and Xeleris 3 Imaging workstation reorientation software (version no. 3.0562). The reconstruction algorithm and filtering were generic. Matrix size was 74x74 resized to 64x64. A multiple gated acquisition was applied, using 16 bins and 600 accepted beats. A 20% energy window centered on 140 keV was used for all acquisitions [5,6].

Regions of interest (ROI) around the left and right ventricles were automatically generated by the Cedars-Sinai QBS processing software and each acquisition was processed by two technologists who were blinded. If the two resulting LVEFs differed more than 2 percentage points (pp), results were revised by a chief consultant (a senior medical doctor) to ensure that the ROI were visually correct and in accordance with the illustrations and instructions proposed by Daou et al [7].

The following variables were recorded: Left ventricular end systolic and end diastolic volumes (LVESV and LVEDV), left ventricular ejection fraction (LVEF), right ventricular end systolic and end diastolic volumes (RVESV and RVEDV) and right ventricular ejection fraction (RVEF). A reduction in LVEF of ≥ 10 pp or a reduction to ≤ 50% as compared to baseline values was considered significant during treatment [8]. Furthermore, in the present paper, a reduction in LVEF of ≥ 15 pp were used. Data on height, weight, heart rate and blood pressure was registered at the time of inclusion and at each following MUGA scan.

Paired t-tests were used to assess change from baseline. P-values ≤ 0.05 were considered significant.

RESULTS

A total of 156 women with breast cancer were assessed for eligibility at Department of Oncology at Herlev and Gentofte Hospital, Denmark. See Figure A for exclusion criteria and details. A total of 115 women with primary HER2 positive breast cancer treated with trastuzumab following adjuvant anthracycline were included. Baseline characteristics are summarized in Table 1.

The MUGA scan after 360 days was missed by 77 women (67%). Most likely, as this was the final scan, and had no consequence for further treatment, it was easily overlooked. Only 18 women (16%) completed the MUGA scan after 360 days of treatment. In total, 92 women (80%) completed the MUGA scan after 270 days, and as such, results from the first 270 days were considered representative. Observations at baseline as well as 90, 180, 270 and 360 days are listed in Table 2 and portrayed in Figures B and C.

Heart rate and blood pressure

Mean heart rate increased from 72 beats per minute (bpm) at baseline to 74 bpm after 90 days (p = 0.05), however, after 180 and 270 days, a reduction below the baseline rate was recorded (68 and 67 bpm respectively, p = 0.0002 and $4^{*}10^{-5}$ respectively). Blood pressure increased significantly after 270 days when compared to baseline, i.e. from 120/73 to 125/75 (p = 0.004 (systolic) and 0.008 (diastolic)).

Baseline values demonstrated a lower systolic BP (p = 0.042) among the group of women who later developed an LVEF decrease to ≤ 50% than those who did not. Though statistically significant, these changes were hardly clinically relevant.

Left ventricle changes

Mean baseline LVEF before initial trastuzumab dose was 66.3

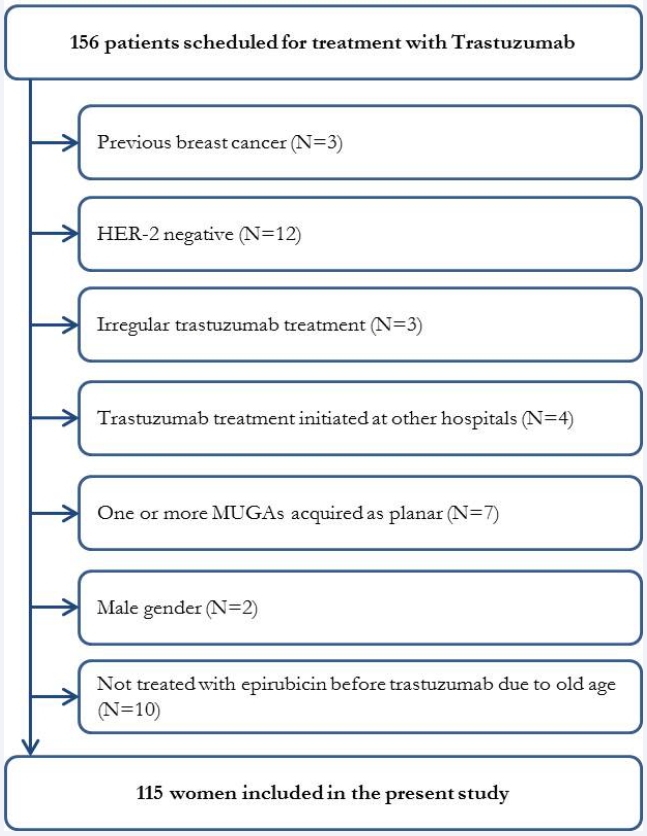

Figure 1 Flowchart of patient inclusion/exclusion criteria. 115 women were found eligible and included in criteria.

Table 1: Baseline characteristics (n = 115).		
	Mean (SD)	**N (%)**
Age (years)	57.2 (11.3)	
Height (cm)	166.7 (6.7)	
Weight (kg)	69.0 (12.8)	
Atrial fibrillation		2 (1.7)
Ischemic heart disease		2 (1.7)
Hypertension		15 (13)
Hypercholesterolemia		12 (10)
Diabetes		4 (3.5)
Smoking (current or previous)		50 (44)

± 9.3%. Mean LVEF decreased significantly to 62.1 ± 9.7% after 90 days ($p = 4^{*}10^{-8}$) after which no further significant changes were observed (Figure B).

A decrease in LVEF *either* to ≤ 50 % *or* by ≥ 15 pp compared to baseline was developed by 40 women in total (13 women after 90 days, 18 women after 180 days, 7 women after 270 days, and 2 women after 360 days, respectively). Of these 40, 11 women received treatment for left ventricular dysfunction with ACE-inhibitors. A decrease in LVEF to ≤ 50% *and* by ≥ 15 pp compared to baseline was observed in 8 women (2, 1, 5, and 0 women after 90, 180, 270, and 360 days, respectively).

Baseline values demonstrated a higher LVESV ($p = 0.0004$), lower LVEF and RVEF ($p = 6*10^{-6}$ and 0.016, respectively) among the group of women who later developed an LVEF decrease to ≤ 50% than those who did not. These differences in baseline values were still present after exclusion of patients with known hypertension (15 patients) (Table 3).

The group of women who later developed an LVEF decrease of ≥ 15 pp compared to baseline, had a higher baseline-LVEF ($p = 4^{*}10^{-7}$) and lower baseline-LVESV ($p = 0.0002$) than those women who had no significant LVEF decease. Even after excluding women with known hypertension, the difference persists ($p = 1^{*}10^{-5}$ and $9^{*}10^{-7}$, respectively). Furthermore, a slightly lower baseline-LVEDV ($p = 0.039$) was seen.

Right ventricle changes

Mean right ventricle volumes increased significantly after 90 days. No further changes were found after 180, 270 or 360 days. No significant changes in mean RVEF were proven (all p-values > 0.09) (Figure C). RVEF at baseline was significantly lower in the group of women who's LVEF dropped to ≤ 50% (39.8% and 45.7%, respectively; $p = 0.006$)

Treatment for left ventricular dysfunction

Eleven women were treated for left ventricular dysfunction with ACE-inhibitor. In this patient group, mean baseline LVEF before initial trastuzumab dose was 53 ± 12.2 %. Mean LVEF decreased significantly to 50 ± 7.2% after 90 days ($p = 0.036$). After 270 days, only 2 patients remained in trastuzumab treatment (Table 4).

At all tests, including baseline, LVEF was significantly lower in this group compared to the group of women who were not treated for left ventricular dysfunction with ACE-inhibitor (Table 5).

A decrease to ≤ 50% was found in all eleven of these women. All but two had a decrease of ≥ 10 pp compared to baseline, in five cases by ≥ 15 pp compared to baseline. After treatment LVEF increased to > 50% in six women. No further decrease was observed after restarting treatment with trastuzumab. One woman was excluded from trastuzumab after an LVEF decrease from 86 % to only 32 %.

At the time of LVEF decrease, one woman had an RVEF *increase* of 18 pp compared to baseline (at baseline her RVEF was only 14%). All other women had changes < 10 pp compared to baseline at the time of LVEF decrease. Two women had RVEF decrease of ≥ 10 pp (14 and 16 pp, respectively) succeeding the LVEF decrease.

Not surprising, women who are later treated for left ventricular dysfunction had significantly lower baseline-LVEDV and LVEF (p-values 0.037 and 0.024, respectively). However, these women also displayed a lower baseline-RVEDV ($p = 0.042$) and significantly higher baseline heart rate (80 ± 10 bpm vs. 71 ± 12 bpm, $p = 0.025$) than women who did not develop left ventricular dysfunction (Table 6 and Figure D).

If we exclude all women without an LVEF decrease to ≤ 50%, the women who were later treated for left ventricular dysfunction still had a significantly higher baseline heart rate than those *with* an LVEF decrease but *without* left ventricular dysfunction (80 ± 10 bpm and 69 ± 9 bpm, respectively; $p = 0.006$) (Figure E). The same was found to be true in the group of women who's LVEF decrease by ≥ 15 pp. Again, the women treated for left ventricular dysfunction have a significantly higher heartrate at baseline (87 ± 7 bpm and 72 ± 12 bpm respectively, $p = 0.017$) (Table 5). No significant differences in baseline BP was found in either group.

DISCUSSION

The present study demonstrated an increase in left ventricular volumes and a decrease in LVEF during treatment with trastuzumab. After excluding the 11 women treated for left ventricular dysfunction, this decrease persisted.

To our knowledge, this is the first study to show a trastuzumab-related increase in left ventricular volumes estimated by MUGA. The SPECT camera with CZT-detectors has previously been shown to have an excellent intra- and inter observer variation which makes detecting even minor changes in ventricular volumes possible [5,9].

Trastuzumab-related increase in left ventricular volumes estimated by echocardiography or cardiovascular magnetic resonance imaging (MRI) has previously been demonstrated, as abbreviated in Table 7 [10-12]. Together, they provide a deeper insight in the pathophysiological mechanisms behind trastuzumab cardiotoxicity.

In a population of chemotherapy naïve patients, SPECT CZT MUGA has been used to show an age-related decrease in left ventricular volumes, resulting in an age related LVEF increase. This effect was particularly seen in women and assumed to be cause by creasing fibrosis, a decreasing number

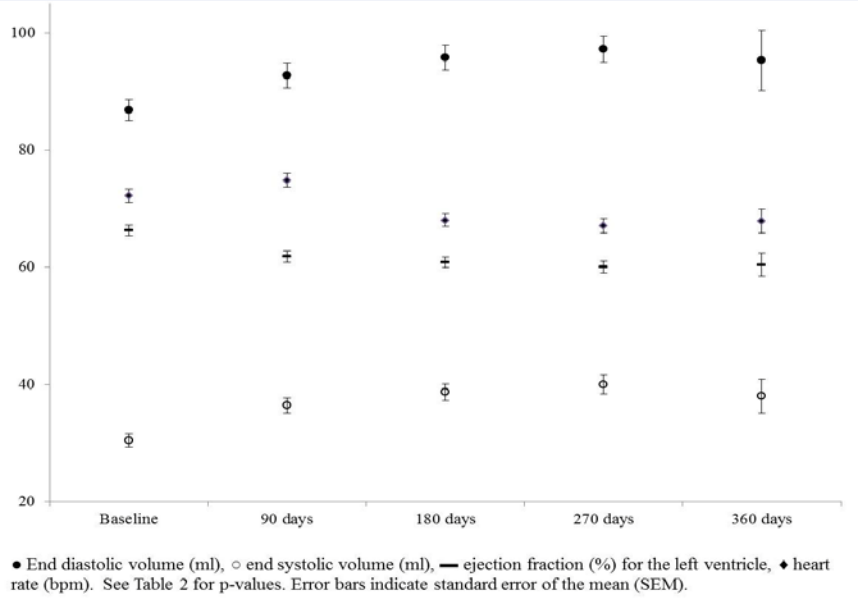

Figure 2 Changes in left ventricle parameters over one year.

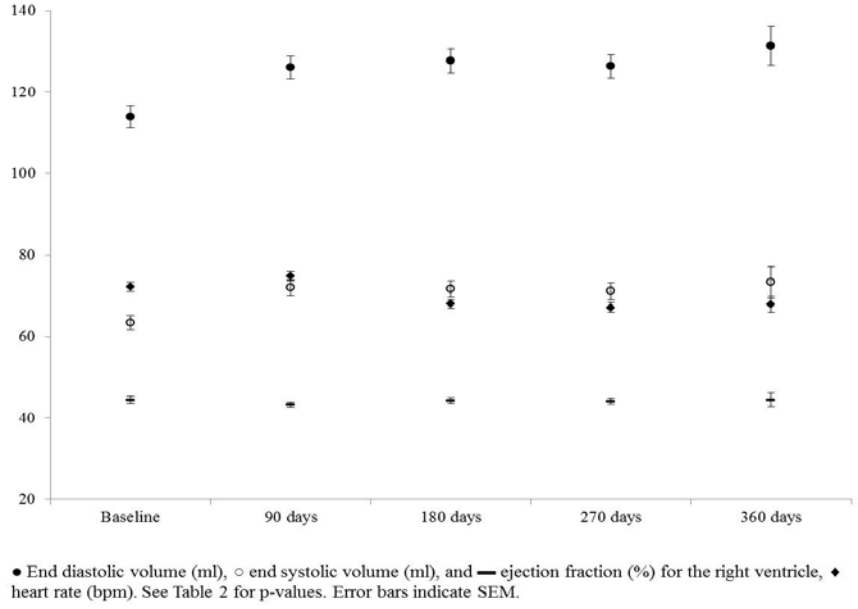

Figure 3 Changes in right ventricle parameters over one year.

of myocytes and increasing size of each singular myocyte [6]. The pathophysiological mechanism behind trastuzumab cardiotoxicity is unknown, but may even be more pronounced if adjusted for age [6]. Nonetheless, the cardiotoxicity of trastuzumab appears to be controllable by sufficient monitoring and readily available intervention with proper medical treatment.

The slight changes in blood pressure and heart rate during treatment are hardly clinically relevant and cannot explain the changes seen in left ventricular volumes and LVEF.

The present study aims to identify trastuzumab induced changes in left ventricular volumes. However, as patients receive anthracycline prior to trastuzumab, certain differentiation between cardiotoxicity induced by trastuzumab and cardiotoxicity induced by anthracycline is difficult.

Adjustments for potential confounders such as known ischemic heart disease, left breast radiation therapy, smoking or whether the initial MUGA was performed before/after the final anthracycline dose have not been made. Compared to previous studies on trastuzumab, a relatively high number of patients have

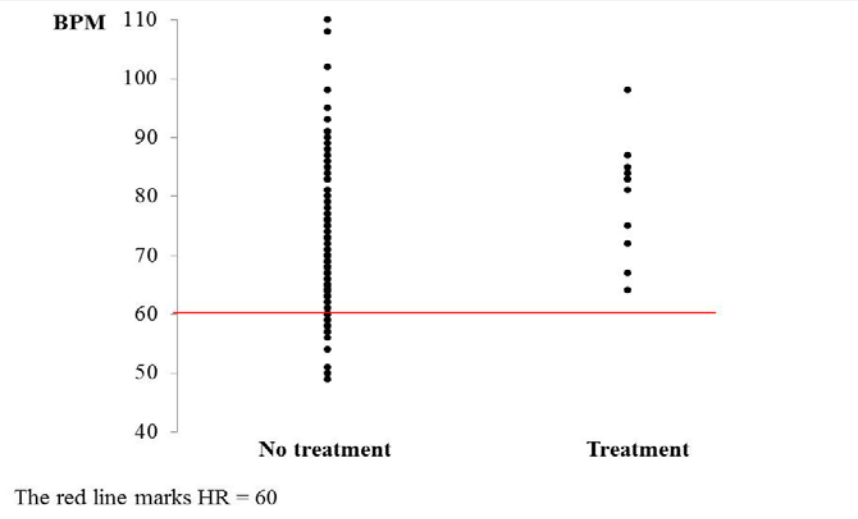

Figure 4 Baseline hear rate, according to treatment for cardiotoxicity.

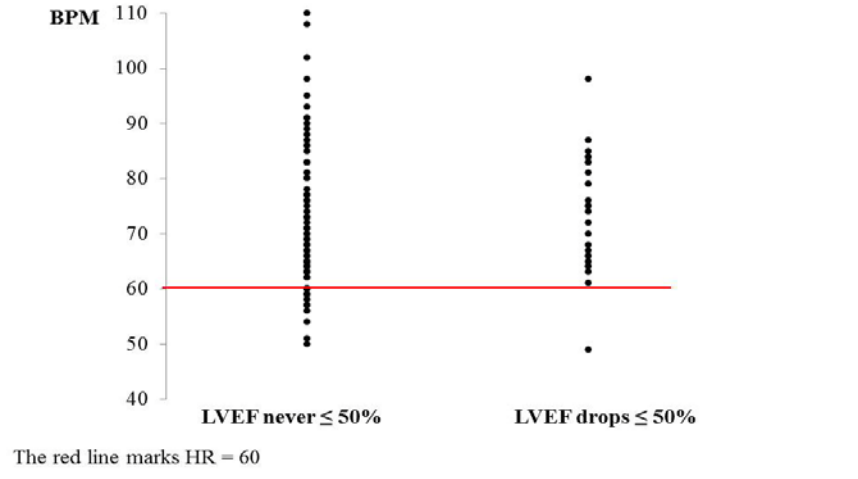

Figure 5 Baseline heartrate according to left ventricle ejection fraction decrease ≤ 50% or no.

Table 2: Observations during 360 days of treatment with adjuvant trastuzumab in 115 women with breast cancer.

	Baseline	90 days		180 days		270 days		360 days	
	Mean (SD)	Mean (SD)	p-value*	Mean (SD)	p-value*	Mean (SD)	p-value*	Mean (SD)	p-value*
N	115	103		104		92		18	
LVEDV (ml)	86.8 (19.4)	92.5 (21.3)	$4*10^{-5}$	95.6 (22.0)	$3*10^{-9}$	96.5 (20.8)	$9*10^{-9}$	94.9 (21.3)	0.02
LVESV (ml)	30.4 (11.8)	36.2 (13.3)	$2*10^{-10}$	38.3 (14.5)	$2*10^{-13}$	39.3 (15.3)	$2*10^{-10}$	37.6 (11.9)	0.003
LVEF (%)	66.3 (9.3)	62.1 (9.7)	$4*10^{-8}$	61.3 (9.3)	$7*10^{-11}$	60.7 (9.7)	$6*10^{-10}$	60.5 (8.1)	0.003
RVEDV (ml)	114.0 (28.1)	126.1 (28.6)	$4*10^{-9}$	127.7 (30.2)	$8*10^{-10}$	126.3 (27.6)	$8*10^{-7}$	131.3 (20.3)	$6*10^{-6}$
RVESV (ml)	63.3 (18.7)	71.9 (19.5)	$8*10^{-12}$	71.7 (20.2)	$2*10^{-9}$	71.1 (19.7)	$1*10^{-7}$	73.3 (16.5)	0.089
RVEF (%)	44.4 (9.4)	43.2 (6.8)	0.09	44.3 (6.9)	0.46	44.1 (7.5)	0.22	44.4 (7.3)	0.42
Systolic BP (mmHg)	120 (17)	120 (16)	0.82	122 (15)	0.33	125 (16)	0.004	118 (16)	0.28

Diastolic BP (mmHg)	73 (10)	72 (9)	0.76	74 (10)	0.1	75 (9)	0.008	74 (7)	0.74
Heart rate (bpm)	72 (12)	74 (12)	0.05	68 (11)	0.0002	67 (11)	$4*10^{-5}$	68 (9)	0.49
Paused trastuzumab N (%)	0 (0.0)	4 (3.9)		1 (1.0)		1 (1.1)		0 (0.0)	
Treated for heart failure N (%)	1 (0.9)	6 (5.8)		4 (3.8)		2 (2.2)		0 (0.0)	
Scheduled MUGA not performed N (%)	0 (0.0)	11 (9.6)		0 (0.0)		6 (6.1)		77 (81.1)	
Pneumonitis N (%)	0 (0.0)	0 (0.0)		1 (1.0)		0 (0.0)		0 (0.0)	

Left and right end diastolic volumes (LVEDV and RVEDV), left and right end systolic volumes (LVESV and RVESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), systolic and diastolic blood pressure (BP), heart rate, paused trastuzumab, treatment for heart failure, scheduled MUGA not performed and adverse events other than heart failure (pneumonitis) at baseline as well as 90, 180, 270 and 360 days.
* As compared to baseline using paired t-tests

Table 3: Baseline characteristics in women with LVEF decrease ≤ 50 % vs. those without and women with decrease ≥ 15 % vs. those without

	LVEF decrease to ≤ 50%					LVEF decrease by ≥ 15 pp				
	Decrease		No decrease		p-values	Decrease		No decrease		p-values
	Mean	(SD)	Mean	(SD)		Mean	(SD)	Mean	(SD)	
N	25		90			29		86		
LVEDV (ml)	88.8	-19.3	86.2	-19.5	0.559	81.3	-18.4	88.7	-19.5	0.078
LVESV (ml)	37.6	-12.6	28.4	-10.8	0.0004	22.6	-9.6	33	-11.3	0.0002
LVEF (%)	58.8	-10	68.4	-7.9	0.000001	73.5	-7.8	63.9	-8.4	0.0000004
RVEDV (ml)	108.3	-25.6	115.5	-28.7	0.259	116	-28.4	113.3	-28.1	0.652
RVESV (ml)	64.5	-15.2	63	-19.6	0.728	61	-16.2	64.1	-19.5	0.444
RVEF (%)	39.8	-9.7	45.7	-9	0.006	47	-8	43.6	-9.8	0.095
Systolic BP (mmHg)	113.3	-13.8	122.1	-17.2	0.02	123.7	-16.1	119	-17	0.188
Diastolic BP (mmHg)	69.6	-8	73.9	-10.4	0.055	72.9	-10.6	73	-10	0.945
Heart rate (bpm)	73.6	-10.7	71.8	-12.5	0.521	74.7	-12.6	71.3	-11.9	0.191

Left and right end diastolic volumes (LVEDV and RVEDV), left and right end systolic volumes (LVESV and RVESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), systolic and diastolic blood pressure (BP) and heart rate at baseline.

Table 4: Changes in LVEF according to cardiotoxicity.

	Cardiotoxicity treatment			No cardiotoxicity treatment			p-values
	N	Mean	(SD)	N	Mean	(SD)	
Baseline	11	53	(12.2)	104	67	(8.7)	0.023
90 days	9	50	(7.2)	94	63	(8.1)	$3*10^{-6}$
180 days	7	48	(5.2)	97	61	(8.1)	$2*10^{-5}$
270 days	2	34	(2.1)	89	59	(7.7)	$4*10^{-6}$
360 days	0	-	-	18	59	(7.9)	-

LVEF: Left ventricle ejection fraction

Table 5: Baseline characteristics in women receiving treatment for cardiotoxicity vs. those who do not in the groups of women with LVEF decrease ≤ 50 % and women with decrease ≥ 15 %.

	LVEF decrease to ≤ 50 %					LVEF decrease by ≥ 15 pp				
	Treatment		No treatment		p-values	Treatment		No treatment		p-values
	Mean	(SD)	Mean	(SD)		Mean	(SD)	Mean	(SD)	
N	11		14			5		24		
Height	167.0	7.0	164.9	7.0	0.470	167.6	7.2	167.1	6.8	0.889
Weight	65.8	11.7	68.0	13.4	0.664	66.6	14.4	71.0	12.8	0.503
Age	58.5	11.7	52.6	13.0	0.252	65.6	5.3	59.3	11.5	0.247
LVEDV (ml)	78.7	11.5	96.8	20.9	0.017	72.4	8.5	83.2	19.5	0.241
LVESV (ml)	32.6	11.9	41.6	12.1	0.075	22.6	9.9	22.5	9.7	0.990

LVEF (%)	60.4	12.2	57.5	8.1	0.488	70.4	11.8	74.2	6.9	0.336
RVEDV (ml)	97.6	23.0	116.7	25.2	0.063	98.9	24.4	119.6	28.3	0.142
RVESV (ml)	56.7	14.3	70.6	13.4	0.020	51.00	12.9	63.1	16.2	0.130
RVEF (%)	40.8	14.0	39.1	4.4	0.692*	47.6	12.8	46.8	7.0	0.843
Systolic BP (mmHg)	113.4	17.8	113.2	10.5	0.797	118.2	24.2	124.9	14.4	0.409*
Diastolic BP (mmHg)	69.7	9.5	69.4	6.9	0.928	72.0	11.4	73.0	10.7	0.846
Heart rate (bpm)	79.9	9.7	68.6	8.7	0.006	86.6	6.7	72.3	12.2	0.017

Left and right end diastolic volumes (LVEDV and RVEDV), left and right end systolic volumes (LVESV and RVESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), systolic and diastolic blood pressure (BP) and heart rate at baseline.
* Equal variances not assumed according to Levene's Test for Equality of Variances

Table 6: Baseline characteristics in women receiving treatment for cardiotoxicity vs. those who do not.

	Treatment		No treatment		p-values
	Mean	(SD)	Mean	(SD)	
N	11		104		
Height	167.0	7.0	166.7	6.7	0.878
Weight	65.8	11.70	69.3	12.9	0.395
Age	58.5	11.7	57.1	11.3	0.682
LVEDV (ml)	78.7	11.5	87.7	19.9	0.037*
LVESV (ml)	32.6	11.9	30.2	11.8	0.525
LVEF (%)	60.4	12.2	67.0	8.7	0.024
RVEDV (ml)	97.6	23.0	115.7	28.1	0.042
RVESV (ml)	56.7	14.3	64.0	19.0	0.219
RVEF (%)	40.8	14.0	44.8	8.8	0.189
Systolic BP (mmHg)	113.4	17.8	120.9	16.7	0.160
Diastolic BP (mmHg)	69.7	9.5	73.3	10.1	0.263
Heart rate (bpm)	79.9	9.7	71.4	12.1	0.025

Left and right end diastolic volumes (LVEDV and RVEDV), left and right end systolic volumes (LVESV and RVESV), left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), systolic and diastolic blood pressure (BP) and heart rate at baseline.
* Equal variances not assumed according to Levene's Test for Equality of Variances

Table 7: Four studies of trastuzumab induced changes in ventricular volumes.

	Present study	Grover et al(10)	Tan et al(11)	Fei et al(12)
Method	**CZT MUGA**	**MRI**	**Echocardiography**	**Echocardiography**
N	115	46¤	29	95
Months of observation	12	12	15	17
Baseline performed	Before TRZ	Before AC and/or TRZ	Before AC	Before AC
LVEF change (pp)	5.8	6.2	5	p< 0.0001#
RVEF change (pp)	0.0	-	-	-
LVEDV change	8.5 ml	6.3 ml/m2 (11.3 ml*)	6 ml/m^2 (10.8 ml*)	p< 0.0001#
LVESV change	7.6 ml	6.1 ml/m^2 (11.0 ml*)	4 ml/m^2 (7.2 ml*)	p< 0.0001#

TRZ trastuzumab; AC anthracycline
value not specified
* Calculated using body surface area = 1.8 m^2
- not presented
pp: percentage points
¤ 46 patients were included, 31 received Anthracycline and 15 received Trastuzumab

been included in the present study [10-12]. However, the low number of women who underwent final MUGA after 360 days makes statistical analysis at this point difficult and data after 270 must be considered more representative.

The present study finds, that a large group of patients (40 of 115, 51%) have an LVEF decrease to ≤ 50% or by ≥ 15 pp, but only 11 need treatment for left ventricular dysfunction with ACE-inhibitor.

The present study assessed not only left ventricular volumes, but also right ventricular volumes and as such not only corroborated previous findings but also offered new findings on the cardiotoxic effects of trastuzumab. We found a significant increase in left ventricular volumes leading to a significant decrease in left ventricular ejection fraction during treatment with trastuzumab. Though a similar increase in right ventricular volumes was found, this seems to be balanced, leaving right ventricular ejection fraction unchanged.

We found, that women who developed a need to be treatment for left ventricular dysfunction had a significantly higher heart rate at baseline than those without left ventricular dysfunction. Even when only examining women who developed a significant LVEF decrease, the difference in baseline heart rate is significant (Table 5).

CONCLUSION

During treatment with Trastuzumab, LVEF decreased significantly from baseline to 90 days after initiated treatment, after which no further LVEF-changes are seen. Comparably, while an increase in right ventricle volumes after 90 days was proven, no significant RVEF were found.

CONTRIBUTION OF AUTHORS

All authors had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: BZ. Acquisition of data: JWC, BZ, AP, DN. Analysis and interpretation of data: All authors. Statistical analysis: JWC, CH and BZ. Drafting of the manuscript: JWC and CH. Critical revision of the manuscript: All authors

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