

Factors Affecting Long-Term Safety of Trastuzumab in Patients with Early HER2-Positive Breast Cancer

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Abstract

Background: Trastuzumab treatment is associated with cardiac dysfunction. We evaluated the incidence of cardiotoxicity during and long-term after trastuzumab treatment in an unselected early breast cancer population.

Methods: This study included a retrospective part, the chemotherapy- and trastuzumab treatment period and a prospective part, the period of data collection long-term after trastuzumab treatment. Cardiac evaluation included left ventricular ejection fraction (LVEF) changes and an evaluation of symptomatic cardiotoxicity. Cardiac events were defined as a decrease of 10 percentage points in LVEF compared with baseline and to an absolute LVEF of below 50%. Secondary outcomes included the evaluation of cardiac markers (B-type natriuretic peptide and troponins) and single nucleotide polymorphisms (SNPs) in the HER2 gene as parameters to detect or predict trastuzumab-related cardiotoxicity.

Results: Overall, 105 patients were evaluable for the primary endpoint. The 3-year cumulative incidence of cardiac events was 12% (95 CI, 4%-19%). All 8 patients with a cardiac event were pre-treated with anthracyclines and cyclophosphamide and 7 of them recovered partially or completely. Four patients experienced symptomatic cardiotoxicity, of who 2 recovered completely and the other 2 recovered partially. No statistically significant association was observed between cardiac events and cardiac markers or SNPs.

Conclusion: Trastuzumab treatment in combination with anthracycline-based chemotherapy is associated with significant and only partly reversible cardiac dysfunction. Baseline LVEF value is a prominent predictor for long-term LVEF especially, in patients who are not treated with anthracycline-based chemotherapy. These findings can be used to establish optimal monitoring strategies in trastuzumab treatment.

Keywords: Trastuzumab; Cardiotoxicity; Early breast cancer; Long-term safety

Background

Trastuzumab (Herceptin[®]) is a humanized monoclonal antibody that targets the extracellular domain of the human epidermal growth factor HER2 receptor protein and has resulted in clinical benefit in HER2 positive advanced breast cancer and improved disease-free and overall survival in HER2 positive primary breast cancer [1-4]. Although trastuzumab is generally well tolerated and not associated with adverse events that are commonly seen with chemotherapy, cardiac dysfunction is an important side-effect. Trastuzumab-associated cardiac dysfunction can result in asymptomatic decline in Left Ventricular Ejection Fraction (LVEF) and, even in symptomatic Congestive Heart Failure (CHF) [5-7]. Recently, a meta-analysis presented data from eight clinical trials that involved 11,991 women with HER2 positive early stage breast cancer who were treated with standard chemotherapy with or without trastuzumab [8]. Results of this analysis suggest that the risk of cardiac dysfunction is five times more likely for trastuzumab treated women than women receiving standard chemotherapy alone. The prevalence of trastuzumab-related cardiac dysfunction varies between studies and an indirect comparison between the clinical trials is hampered by differences in the applied definition of cardiac dysfunction. Although several peer reviewed articles outline the incidence and severity of trastuzumab-

related cardiac dysfunction, research to date has been limited largely to selected study patient populations in health care databases without the availability of covariates including risk factors for cardiac diseases, or to patients with short follow-up periods. Further research to establish the incidence of trastuzumab-related cardiac dysfunction in unselected patient populations, with long-term follow-up, and research on screening methods in trastuzumab-treated patients is needed to identify a risk profile for this patient population.

Preliminary data suggest that cardiac biomarkers such as troponins and the immunoreactive amino-terminal pro-Brain Natriuretic Peptide (NT-proBNP) are sensitive and specific markers to detect myocardial

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injury and to predict the development of future LVEF dysfunction and its severity [9-11]. Moreover, several Single Nucleotide Polymorphisms (SNPs) in the extracellular, transmembrane and intracellular region of HER2, have been studied to examine the impact of these polymorphisms on disease outcome and on trastuzumab-related toxicity [12,13]. To date, results of clinical trials are contradictory.

In this study we recruited breast cancer survivors after standard adjuvant trastuzumab treatment, to determine long-term tolerance cardiac safety and parameters to detect or predict trastuzumab-induced cardiotoxicity. We also analyzed variability in the *HER2* gene for identification of potential genetic factors predisposing patients to the development of trastuzumab-related cardiotoxicity.

Methods

Patients

Women with HER2-positive breast cancer who had received (neo-) adjuvant trastuzumab treatment were eligible. HER2-positive breast cancer was defined as an immunohistochemistry score of 3+ in the HercepTest® and/or gene amplification by Fluorescence in Situ Hybridization (FISH), or Chromogenic In Situ Hybridization (CISH). Other criteria for inclusion were: age 18 years or older; available LVEF values at baseline (i.e. before trastuzumab treatment); at least one LVEF value during trastuzumab treatment and written informed consent to participate in the study. Participants were excluded if they had advanced breast cancer; participated in clinical trials or were pregnant or breast feeding.

Trial design and procedures

The tolerability and safety of trastuzumab during treatment and long-term follow-up were evaluated. Patients were recruited at the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital (NKI-AVL). All trastuzumab treated patients who had received and finished trastuzumab treatment between 2005 and 2009 were identified through medical records and were informed of this study by letter. The study was approved by the medical ethics committee of the NKI-AVL. This study included retrospective data collection of the chemotherapy – and trastuzumab treatment period and data collection of the period long-term after the end of trastuzumab treatment. Medical records were reviewed for all demographic and treatment related data including type and dose of chemotherapy and endocrine therapy, side, dose and field of radiotherapy, dose, schedule and duration of trastuzumab treatment and the development of signs and symptoms of CHF. Prospective data collection was performed at two time-points. The first was immediately after informed consent procedure and the second was one year later. The following data were recorded: medical history, including risk factors for cardiac disease, other familiar predisposition for cardiac disease, New York Heart Association classification, smoking status and use of medication. Physical examination was performed and blood pressure, heart rate, performance status, body weight and height were determined at these occasions. An evaluation of cardiac abnormalities was performed by a 12-lead Electrocardiogram (ECG) and an identification of the left ventricular ejection fraction by Multiple-Gated Acquisition scanning (MUGA) scan, or echocardiography. For MUGA scans, 400 MBqTc-99m labelled autologous red blood cells were injected and acquisition was done in 6 min with a large-field-of-view gamma camera with a low energy all-purpose parallel-hole collimator. An independent cardiologist reviewed the ECGs of all eligible patients. The ECGs were reviewed for heart rate, QRS time, QT time and QTc. The QT time was corrected for heart rate (QTc) according to the method of Basset.

Laboratory

Laboratory tests were performed and included troponin T high sensitivity (cTnT_{hs}) and B-type natriuretic peptide (NT-proBNP). NT-proBNP levels were measured at baseline and long-term after trastuzumab treatment. cTnT_{hs} values were measured in samples taken at baseline and troponin T values long-term after trastuzumab treatment. The used assay details are outlined in the supplement (Appendix A).

Genotyping

In this study we determined genetic variability in the extracellular domain; FcγRIIIa-158 valine (V)/phenylalanine (F), FcγRIIIa-131 histidine (H)/arginine (R) and FcγRIIIa-232 isoleucine (I) threonine (T), in the transmembrane domain; Val654Ile, Val655Ile and in the intracellular domain; P1170A. Haplotype analysis was performed for HER2 I654V, I655V and A1170P SNPs. Genotyping was carried out using gene specific primers: Primer-Blast tool and commercially available Taqman SNP genotyping assays (Applied Biosystems). The used DNA primers, PCR conditions and genotyping assay details are outlined in the supplement (Appendix B).

Statistical methodology

The primary objective of the study was to analyze the change in LVEF long-term after trastuzumab treatment from baseline, i.e. start of trastuzumab treatment. Sample size was calculated to detect an effect size of 0.3 (difference of mean LVEF values divided by the standard deviation of the difference) with a two-tailed paired t-test at a significance level of 0.05. To obtain 85% power, 100 patients were targeted. Demographic and treatment characteristics were compared between the groups with and without anthracyclines prior to or concomitant with trastuzumab using the Chi-square or Fisher's exact test for categorical variables and the Kruskal Wallis, Mann-Whitney or t-test for continuous variables. LVEF values at baseline, during treatment and in follow-up were compared with the Kruskal Wallis or t-test after assessing normality of distributions. Follow-up time is the date of the first trastuzumab administration until the date of the last LVEF. Associations of change in LVEF with baseline characteristics and cardiac markers were tested with Wilcoxon's rank sum test or a linear-by-linear test (for ordered categories). Ordinary least squares regression was performed separately in the groups with and without anthracyclines, where the model R² was interpreted as the fraction of variance explained. Cumulative incidence-curves of cardiac events were made using the Kaplan-Meier method (there were no deaths) with the log-rank test assessing equality of distributions. Hazard ratio's for cardiac events comparing baseline groups and presence of SNPs were calculated using the Cox proportional hazards model. Analyses were performed employing SAS software, version 9.1 and R version 3.0.2.

Cardiac evaluation

Cardiac evaluation included LVEF values and an evaluation of symptomatic cardiotoxicity. An asymptomatic cardiac event was defined as follows: a decrease of 10 percentage points in LVEF compared with baseline and to an absolute value of below 50%. Complete recovery of asymptomatic cardiotoxicity was defined as a LVEF value equal to the baseline LVEF value with a margin of 5 absolute points. Partial (or total) recovery of asymptomatic cardiotoxicity was defined as two or more sequential LVEF values that did not meet the definition of an asymptomatic cardiac event. The severity of cardiotoxicity was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0. Symptomatic cardiotoxicity

was defined as: clinical signs and symptoms of CHF. A judgement of the degree of the patient's recovery was based on clinical findings, usage of cardiac medication and LVEF recovery. Complete recovery of symptomatic cardiotoxicity was defined as the disappearance of clinical findings and symptoms and a partial recovery was defined by continued but less severe signs and symptoms.

Results

Patients

In total 126 patients were informed of this study and 107 patients (85%) responded to participate (Figure 1). Overall, data of 105 patients were evaluable for analysis of the primary endpoint: 67 patients received anthracycline-based chemotherapy prior to or concomitant with trastuzumab treatment and 38 patients received trastuzumab treatment without anthracycline-based chemotherapy. The median follow-up was longer (51 months) in the anthracycline-based treatment group compared with the group of patients without

anthracycline treatment (37 months), $p < 0.0001$. There was no difference in demographic characteristics between the two treatment groups (Table 1). No patient in the non-anthracycline-based treatment group received cyclophosphamide in comparison with all patients in the anthracycline-based treatment group (Table 2).

Cardiac events

The mean difference between the most recent LVEF value before trastuzumab treatment and the LVEF value measured long-term after trastuzumab treatment was -0.3 points in the group of patients without anthracyclines and -3.3 points in the group with anthracyclines (two sample t-test $p = 0.01$). The fraction of the variance in long-term LVEF values explained by the baseline LVEF in the non-anthracycline treatment group was $R^2 = 0.574$ (95% CI, 0.387-0.762) and in the anthracycline treatment group $R^2 = 0.379$ (95% CI, 0.205-0.553) (Figure 2). The severity of cardiac toxicity during trastuzumab treatment was associated with anthracycline-based chemotherapy, $p = 0.002$ (Table 3). Eight patients experienced an asymptomatic cardiac event. These

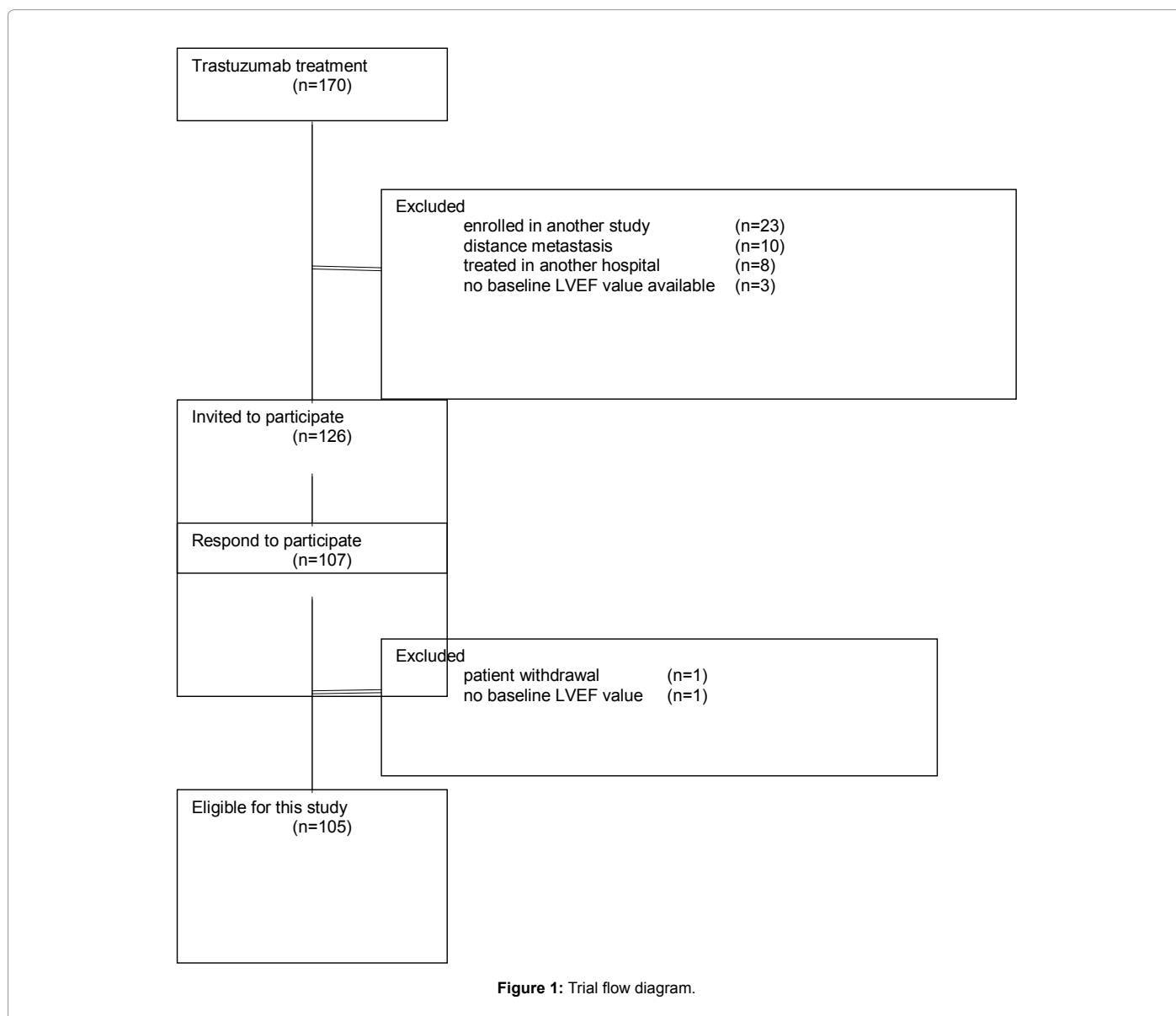


Figure 1: Trial flow diagram.

Characteristic			Anthracyclines	
			No N (%) 38	Yes N (%) 67
Age at baseline (years) (median, range)			50 (32-71)	50 (31-68)
Follow-up (months) (median, range)			37 (21-58)	51 (14-70)
Baseline LVEF value (median, range)			66 (53-79)	64 (38-80)
Last measured LVEF value (median, range)			67 (45-78)	61 (31-75)
Medical history	Hypertension	No	28 (74)	54 (81)
		Yes	10 (26)	13 (19)
	Hyperlipidemia	No	37 (97)	56 (84)
		Yes	1 (3)	11 (16)
	Diabetes mellitus, type I	No	38 (100)	67 (100)
		Yes	0	0
	Diabetes mellitus, type II	No	38 (100)	64 (96)
		Yes	0	3 (4)
	Asthma	No	34 (89)	63 (94)
		Yes	4 (11)	4 (6)
Family History	First members of cardiovascular disease by age <60 years		7 (18)	20 (30)
Cardiac co-medication at baseline	ACE inhibitors; diuretics; beta blockers; angiotensin blockers; calcium antagonists		3 (8)	10 (15)

Abbreviations: LVEF: Left Ventricular Ejection Fraction; N: Number

Table 1: Patient characteristics.

Characteristic			Anthracyclines	
			No N (%) 38 (36%)	Yes N (%) 67 (64%)
Chemotherapy	Cumulative dose anthracyclines (mg)	<430	0	30 (29)
		≥ 430	0	37 (35)
Interval between anthracyclines and trastuzumab (days) (median, IQR)			NA	21 (20-22)
Cyclophosphamide			0	67 (100)
Paclitaxel			37 (97.4)	57 (85.1)
Docetaxel			0	4 (6)
Radiotherapy	No		5 (13)	14 (21)
	Yes		33 (87)	53 (79)
Radiotherapy field	Axilla		15 (39.5)	16 (23.9)
	Parasternal		17 (44.7)	22 (32.8)
	Chest wall		15 (39.5)	11 (16.4)
	Side	Left	21 (55)	30 (45)
		Left and right	0	5 (7)
		Right	13 (34)	19 (28)
		Not available	4 (11)	13 (19)
Trastuzumab	Cumulative dose (mg) (median, IQR)		6960 (6097-7888)	6785 (5835-7570)
	Stop reason	According to standard one year of trastuzumab treatment	35 (92)	49 (73)
		Cardiac related	3 (7.9)	13 (19.4)
		Other	0	4 (6)
		Not available	0	1 (1)

Abbreviations: IQR: Interquartile Range; N: Number; NA: Not Applicable

Table 2: Treatment characteristics.

patients represented 7.6% of the study population and as they all had been pre-treated with an anthracycline they represented 12.1% of the latter group. The 3-year cumulative incidence of events was 12% (95% CI, 4-19%) (Figure 3). No potential risk factor for the development of cardiotoxicity (as measured by LVEF changes and cardiac events) could be identified (Tables 4 and 5).

Reversibility of cardiac events

Among the eight patients who experienced a cardiac event, the LVEF value recovered completely in six patients (75%), partially in one

patient (12.5%) and did not recover in another patient (12.5%).

Signs and symptoms of CHF

Four patients (3.8%) experienced signs and symptoms of CHF during trastuzumab treatment; these patients were previously treated with anthracyclines. Among these patients, one patient discontinued trastuzumab treatment temporarily and three patients discontinued trastuzumab treatment permanently. Two patients recovered completely after trastuzumab discontinuation. Two other patients recovered partially, and symptoms of CHF were less severe one year

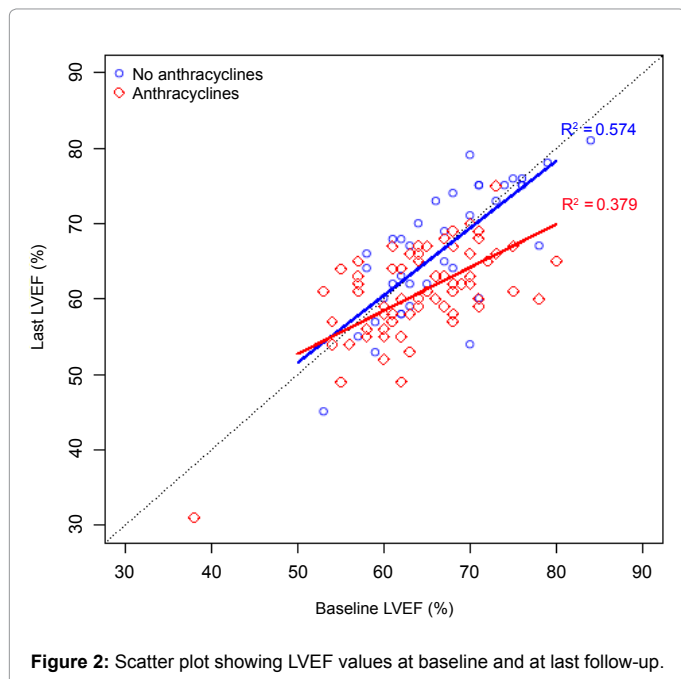


Figure 2: Scatter plot showing LVEF values at baseline and at last follow-up.

CTCAE grade	Anthracyclines		Linear-by-Linear Association Test p-value
	No N (%)	Yes N (%)	
Baseline LVEF value	No toxicity 38 (100%)	64 (96%)	0.22
	Grade II 0	2 (3)	
	Grade III 0	1 (1)	
LVEF value during trastuzumab treatment	No toxicity 30 (79%)	33 (45%)	0.002
	Grade II 8 (21%)	30 (45%)	
	Grade III 0	4 (6)	
Follow-up LVEF value	No toxicity 32 (84%)	49 (73%)	0.16
	Grade II 6 (16%)	17 (25%)	
	Grade III 0	1 (1)	

Abbreviations: CTCAE: National Cancer Institute Common Toxicity Criteria For Adverse Events Version 3.0; LVEF: Left Ventricular Ejection Fraction; N: Number

Table 3: LVEF toxicity.

after discontinuation of trastuzumab treatment, with use of ACE-inhibitors in one of these two patients. In total, 13 patients (12.4%) were suffering from physical symptoms such as dyspnea, effort, palpitations, fatigue and ankle edema long-term after trastuzumab treatment.

Cardiac markers and genotyping

Eighty-five patients (81%) were evaluable for analyses of the cardiac markers cTnT_{hs} and NT-proBNP at baseline and 104 patients (99%) long-term after trastuzumab treatment. Troponin levels did not change from baseline. NT-proBNP values were not statistically significantly associated with cardiac dysfunction (Figure 4). Measured SNPs and preliminary haplotype analysis did not show significant associations between the studied *Her2* genetic variability and the risk of a cardiac event (Table 6).

Electrocardiogram

In three patients there were ECG changes in comparison with the baseline ECG findings and in two of these patients the QTc time was prolonged (>440 msec) long-term after trastuzumab. These patients

were treated with anthracycline-based chemotherapy. These ECG findings were likely related with the adjuvant systemic therapy.

Discussion

Here we present long-term tolerance and cardiac safety data in an unselected trastuzumab treated early breast cancer population. After a median follow-up of 46 months, the incidence of cardiac events was 7.6% and 3.8% of the patients experienced signs and symptoms of CHF. All occurrences of cardiac events and CHF manifested during trastuzumab treatment and all patients had been treated with

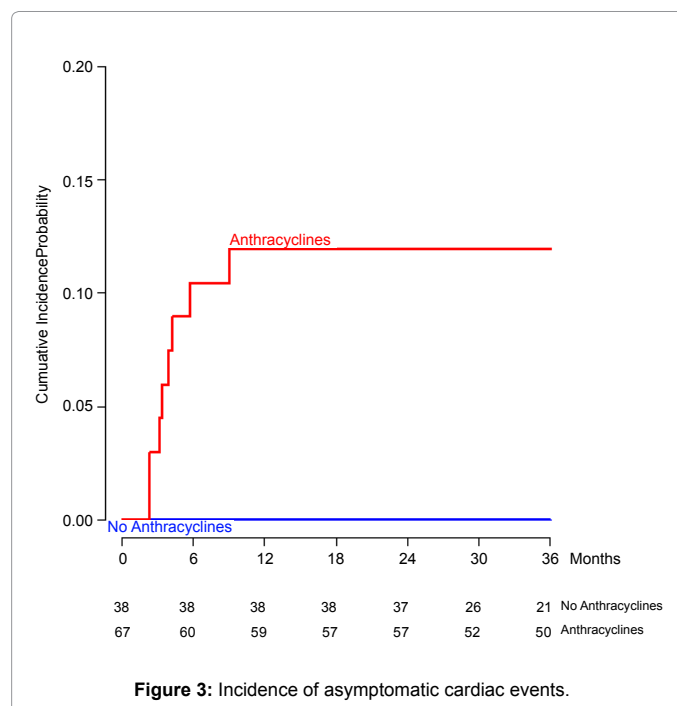


Figure 3: Incidence of asymptomatic cardiac events.

Characteristics	Number (%)	LVEF difference (IQR) (median)	p-value	
Age at baseline (years)	≤ 50	54 (51)	-2.5 (-7-1.75)	0.31
	>50	51 (49)	-2 (-5.5 -2)	
Body Mass Index (per kg/m ²)	<20	7 (7)	-4 (-6- -1)	0.82
	20-25	52 (50)	-1.5 (-7-3.25)	
	>25	46 (44)	-2 (-6-1)	
Smoking status	Never	32 (30)	-1 (-6.25-1.25)	0.3
	Past	57 (54)	-3 (-7-1)	
	Current	16 (15)	-2 (-4-6)	
Anthracyclines	No	38 (36)	0 (-3-4)	0.007
	Yes	67 (64)	-4 (-7-1)	
Anthracycline dose (mg)	<430	30 (29)	-2 (-5-2)	0.69
	≥ 430	37 (35)	-2 (-6.75-2)	
Duration trastuzumab (months)	≤ 6	7 (7)	-2 (-5-2)	0.87
	>6	98 (93)	-2 (-7-2)	
Radiotherapy	No	19 (18)	-2 (-6-0)	0.67
	Yes	86 (82)	-2 (-6.75-2)	
Baseline NT- proBNP (pmol/L)	<18	77 (73)	-2 (-6-1)	0.87
	≥ 18	8 (8)	-2.5 (-4.75-2.25)	
Baseline cTnT _{hs} (µg/L)	<0.05	81 (77)	-2 (-6-2)	0.8
	≥ 0.05	4 (4)	-2.5 (-4- -1.5)	

Abbreviations: IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; cTnT_{hs}: Troponin T High Sensitivity

Table 4: Univariable analysis of LVEF changes.

Characteristic		Patients (number)	Cardiac events	Hazard ratio (95% CI)	p-value
Age at baseline (years)	≤ 50	48	5	1	0.34
	>50	57	3	0.497 (0.12-2.08)	
Body Mass Index (kg/m ²)		105	8	0.85 (0.69-1.06)	0.15
LVEF at baseline (%-point)		105	8	0.93 (0.86-1.01)	0.09
History of hypertension	No	82	7	1	0.5229 (0.062-4.106)
	Yes	23	1	0.5 (0.06-4.10)	
Cumulative anthracycline dose (mg)		67	8	1 (0.99-1.00)	0.78
Interval between anthracyclines and trastuzumab (days) (excluding concomitant patients)		61	7	0.99 (0.94-1.04)	0.55
Paclitaxel treatment	No	11	1	1	0.84
	Yes	94	7	0.81 (0.10-6.56)	
Radiotherapy	No	19	3	1	0.14
	Yes	86	5	0.34 (0.08-1.43)	

Abbreviations: CI: Confidence Interval; LVEF: Left Ventricular Ejection Fraction

Table 5: Risk of cardiac event.

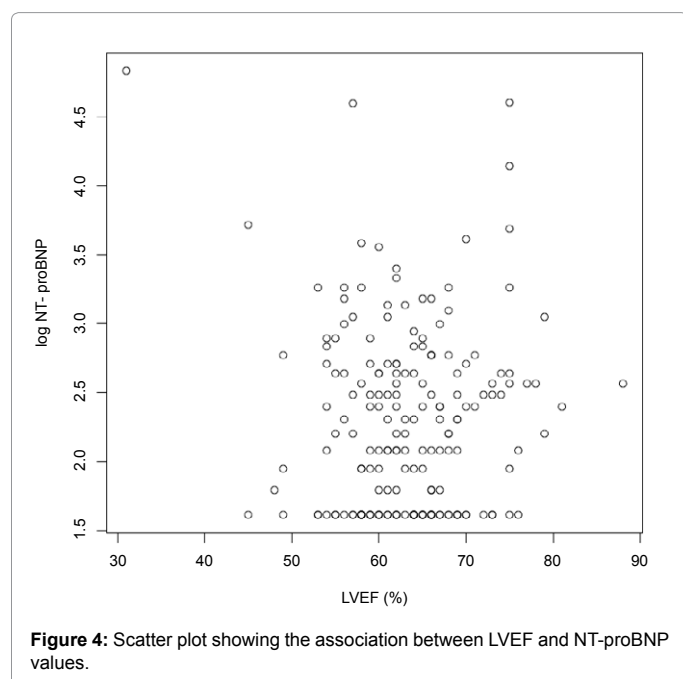


Figure 4: Scatter plot showing the association between LVEF and NT-proBNP values.

anthracyclines and cyclophosphamide prior to or concomitant with trastuzumab treatment. The results of this trial are in accordance with previous studies in which anthracyclines and trastuzumab have been studied. In these studies a higher incidence of cardiac dysfunction when trastuzumab is used in association with anthracyclines was described [14]. Investigators suggest that anthracyclines induce myocardial oxidative stress and trastuzumab blocks the *Her2* receptor, which is essential for cell survival pathways that modulate myocyte damage as result of oxidative stress and myocyte repair [15-17]. Withdrawal of trastuzumab allows recovery of *Her2* signaling and reversal of decline in LVEF [18-20]. Studies have shown that anthracycline-based chemotherapy is associated with acute decreases in LVEF [21]. In the present study, it is not possible to accurately determine which patients receiving anthracycline-based chemotherapy and trastuzumab treatment had LVEF changes due to anthracyclines. However, the study population of the North Central Cancer Treatment Group N9831 Intergroup Adjuvant trial (NCCTG N9831) and our study population are comparable in terms of patient and treatment characteristics.

In the NCCTG N9831 study, patients were treated with 4 cycles of doxorubicin and cyclophosphamide (AC)-based chemotherapy. Of the 1,576 eligible patients who completed AC treatment, 1,458 had pre- and post-AC LVEF measurements. Among these 1,458 patients, 37 patients (2.5%) had a LVEF decrease of more than 15% from baseline. In the present study, the 5-year incidence of asymptomatic cardiotoxicity was 8.1% (95% confidence interval 0.9% - 15%) according to definition of the NCCTG N9831 study. The higher rate of decline in LVEF might be explained by the addition of trastuzumab to anthracycline-based chemotherapy.

The incidence of asymptomatic cardiotoxicity was higher in this study compared with large adjuvant trastuzumab trials. Similarly, the rate of discontinuation of trastuzumab as a result of cardiac dysfunction was higher (15.4%) in our study in comparison with clinical trials (5.1%) [6]. The higher rate of decline in LVEF might be explained by lower baseline LVEF values. In clinical trials, patients with a LVEF value ≥ 50 or 55% were eligible, while in our study all trastuzumab treated patients were included, even patients with a baseline LVEF below 50%. Moreover, we found a significant relationship between baseline LVEF values and the variance in LVEF values long-term after trastuzumab treatment: 38% of the variance in long-term LVEF values could be explained by the baseline LVEF value in the anthracycline-based treatment group and 57% in the non-anthracycline group, respectively. These findings support that, potential predictors for trastuzumab-related cardiotoxicity might be different for patients who are or are not previously treated with anthracyclines. Hence, this finding may allow the design of specific monitoring strategies for both treatment groups. Seventy-five percent of the patients with a cardiac event and 50% of the patients with CHF recovered completely and 12.5% and 50% reached partial recovery, respectively. Despite the reassuring results that all cardiac events and CHF occurred during trastuzumab treatment and the high percentage of reversibility, longer follow-up of cardiac safety is required for more definitive conclusions about cardiac safety at long-term. This is even more relevant, as we keep in mind that all the patients with a cardiac event or CHF had been treated with trastuzumab and anthracyclines, and anthracyclin-related cardiac events can become manifest even 10 years after the initial exposure. Furthermore, upon relapse of HER2 positive disease re-introduction of trastuzumab might be hindered by pre-existing reductions in LVEF. In our study, we found no evidence that baseline risk factors for cardiac dysfunction have important associations with the incidence or severity of cardiac events in trastuzumab treated breast cancer patients.

Dominant model for Cardiac Failure* (Val/Val versus Ile/Ile and Ile/Val)									
	Subjects	Genotype distribution			Missing	Cox PH model		Logistic model	
		Ile/Ile	Ile/Val	Val/Val		HR (95%CI)	P-value	OR (95%)	P-value
Ile654Val									
No cardiac failure	99	94	2	0	3	6.63 (0.81-53.99)	0.08	6.71 (0.54-83.47)	0.14
Cardiac failure	8	7	1	0	0				
Ile655Val									
No cardiac failure	99	51	39	6	3	1.15 (0.29-4.61)	0.84	1.13 (0.27-4.80)	0.86
Cardiac failure	8	4	4	0	0				
Ala1170Pro									
No cardiac failure	99	34	52	10	3	1.60 (0.32-7.91)	0.57	1.65 (0.31-8.60)	0.56
Cardiac failure	8	2	5	1	0				
FCGR2A 166His									
No cardiac failure	99	28	50	18	3	0.67 (0.16-2.82)	0.59	0.69 (0.15-13.07)	0.62
Cardiac failure	8	3	2	3	0				
FcgR2B Ile232Thr									
No cardiac failure	99	71	16	6	6	0.49 (0.06- 3.95)	0.5	0.46 (0.05-3.95)	0.48
Cardiac failure	8	7	1	0	0				
FcgR3A 158Phe/Val									
No cardiac failure	99	13	42	40	4	1.10 (0.14-8.94)	0.93	1.11 (0.13-9.77)	0.93
Cardiac failure	8	1	3	4	0				

Table 6: The distribution of ERBB2 polymorphisms among the study population.

Although our study is considered representative for estimating the incidence of trastuzumab-related cardiotoxicity in clinical practice, our findings may have been different if we had studied a larger group of patients. In this study, we found no statistically significant association between changes in NT-proBNP values, troponin values and changes in LVEF values. Several clinical studies, with only a few exceptions, demonstrated that the increase in NT-proBNP levels is predictive for the development of cardiac dysfunction in chemotherapy treated patients [9,22-24]. Cardinal et al. [11] reported that the measurement of troponin I predicted the development of cardiac dysfunction and enabled identification of patients who were less likely to recover from trastuzumab-related cardiotoxicity. Although these data suggest that cardiac markers may be useful tools for assessing cardiac risk in trastuzumab treated patients, more clinical evidence is needed to establish the value of these markers as predictors of trastuzumab-related cardiotoxicity in clinical practice. We found no evidence that the SNPs, FcγRIIIa-158 valine (V)/phenylalanine (F), FcγRIIIa-131 histidine (H)/arginine (R), FcγRIIIa-232 isoleucine (I) threonine (T), Val654Ile, Val655Ile and P1170A were associated with trastuzumab-related cardiotoxicity. Beaclair et al. found a relationship between the Val655Ile polymorphism and trastuzumab-related cardiotoxicity, defined as a ≥ 20% reduction in LVEF, in advanced breast cancer patients [12]. Recently, two published abstracts reported no association between Ile655Val polymorphism and trastuzumab-related cardiotoxicity [25,26]. The results of clinical trials on the association between SNPs and trastuzumab-related cardiotoxicity are contradictory [13]. Although we observed no significant relationship between these SNPs and trastuzumab-related cardiotoxicity, the limited number of events might have underestimated the value of these SNPs as predisposing factor for trastuzumab-associated cardiac dysfunction.

Conclusion

In conclusion, cardiac dysfunction is an important side-effect of trastuzumab treatment, especially in women who are previously treated with anthracycline-based chemotherapy. Cardiac dysfunction is only partly reversible. Based on current data, the cardiac markers

troponins and NT-proBNP are not predicting for trastuzumab-related cardiac dysfunction. Baseline LVEF values are prominent predictors for LVEF after completion of trastuzumab treatment, especially in patients who were not treated with anthracycline-based chemotherapy. Our findings may be relevant for optimizing cardiac monitoring strategies in trastuzumab treated patients.

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