Cardiac Surveillance Findings During Adjuvant and Palliative Trastuzumab Therapy in Patients with Breast Cancer

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Abstract. *Background/Aim: Trastuzumab therapy, the standard treatment for human epidermal growth factor receptor type-2 (HER2)-positive breast cancer, is associated with possible cardiotoxicity. We set out to retrospectively analyze the cardiac follow-up data of patients with breast cancer receiving trastuzumab treatment. Patients and Methods: The study involved 47 and 31 patients receiving adjuvant or palliative chemotherapy plus trastuzumab, respectively. Cardiovascular system assessments including echocardiography were regularly performed. Results: A significant heart abnormality was detected in 44.7% of the operable and 41.9% of metastatic cases. In the adjuvant setting, left ventricular ejection fraction changes occurred mostly during treatment and less frequently after its completion (40.4% vs. 19.4%), while in the palliative setting, 35.5% and 40% in the first and the second year of therapy. An asymptomatic atrial septum aneurysm was detected in 8.5% and 13% of the patients in the two groups. Conclusion: Trastuzumab-related cardiotoxicity is mostly manifested in an asymptomatic decrease in left ventricular ejection fraction; hypertension, a high body mass index and left-sided irradiation are its predictors.*

Breast cancer is the most common cancer in women in developed countries. The human epidermal growth factor receptor type-2 (HER2)/neu protein is a 185-kDa transmembrane cytoplasmic tyrosine kinase. Amplification of the *HER2* gene or overexpression of the HER2 protein occurs in 10-34% of breast cancer cases (1), and is associated with an adverse outcome (2). Trastuzumab (Herceptin®; Roche) is a recombinant humanized monoclonal antibody that inhibits tumor cell growth, differentiation and survival by binding with high affinity to the extracellular domain, and blocking the normal regulatory functions of the HER2 receptor (3).

The efficacy and safety of trastuzumab was first demonstrated in patients with HER2-overexpressing metastatic breast cancer (MBC) in different treatment lines, and in combination with standard chemotherapeutic regimens (4-7). In the adjuvant setting, the consistent outcome of several large multi-center randomized trials (8-14) led to the use of trastuzumab in HER2-positive breast cancer becoming a new standard (3, 12).

Retrospective analysis of the pivotal phase II and III trials revealed an increased incidence of cardiac dysfunction, usually manifested as congestive heart failure (CHF), a symptomatic or asymptomatic decrease of the left ventricular ejection fraction (LVEF) or, rarely, cardiac arrhythmias or ischemic heart disease (15). The incidence of cardiotoxicity in patients with MBC was found to be highest in those receiving concurrent trastuzumab and anthracyclines, but low when trastuzumab was administered in combination with paclitaxel or alone (16). The majority of these cases with a cardiac dysfunction were symptomatic, but standard treatment for CHF ameliorated the symptoms (17). In large studies in which the use of trastuzumab in early breast cancer was evaluated, the incidence of symptomatic cardiac dysfunction proved to be low (18), even after a long follow-up or radiotherapy (RT) (13, 14).

Unlike the case with anthracyclines, trastuzumab-related cardiac dysfunction constitutes an entity known as a type-2 chemotherapy-related cardiac dysfunction (CRCD), a reversible abnormality with no structural changes in the myocardium, not dose-dependent and which does not occur in all patients (19-21). The mechanism of type-2 CRCD has not been completely clarified and although several risk factors for trastuzumab-induced cardiotoxicity have been described, adverse cardiac events cannot be predicted (22). With the aim of identifying risk factors for cardiac morbidity

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Table I. *The chemotherapeutic regimens applied in patients receiving adjuvant trastuzumab treatment.*

Chemotherapeutic regimen	Number of patients receiving adjuvant trastuzumab treatment
CMF	7
CEF	10
AC-paclitaxel	14
AC-docetaxel	6
TAC	1
CMF-docetaxel	3
TEX	3
EC	1
Docetaxel-epirubicin	1
Paclitaxel-carboplatin	1

CMF=cyclophosphamide, methotrexate, 5-fluorouracil, CEF= cyclophosphamide, epirubicin, 5-fluorouracil, AC=adriamycin, cytoxan, TAC=taxotere, Adriamycin, cyclophosphamide, TEX=taxotere, epirubicin, Xeloda, EC=epirubicin, cyclophosphamide.

for our everyday practice, we set-out to perform a retrospective study of cardiac follow-up data on patients with breast cancer receiving trastuzumab in the adjuvant or palliative setting.

Patients and Methods

All the procedures followed were in full accordance with the ethical standards of the appropriate committees on human experimentation (institutional and national) and with the Helsinki declaration.

The retrospective analysis included patients with histologically confirmed, HER2-positive breast cancer who received adjuvant or palliative trastuzumab therapy. All the clinical and pathological data were extracted from the patient files.

The HER2 status was evaluated by immunohistochemical staining or with fluorescence *in situ* hybridization (23).

Trastuzumab therapy. Patients received either adjuvant or neoadjuvant chemotherapy with standard regimens (Table I). Trastuzumab was given for 12 months at the standard dose (an 8 mg/kg loading dose and a 6 mg/kg sustaining dose at 3-week intervals), usually after the chemotherapy, but in the case of the sequential use of taxane monotherapy, it was co-administered with either paclitaxel or docetaxel. After neoadjuvant chemotherapy, it was always used as monotherapy. In metastatic cases, trastuzumab was either co-administered with paclitaxel or was applied as monotherapy following it, continued until disease progression.

Heart function surveillance. Heart function surveillance was carried out in accordance with the internationally accepted guidelines (24). Electrocardiography (ECG) and echocardiography were performed prior to the initiation of trastuzumab therapy, at 3-month intervals during the therapy, and at 6-month intervals after its termination; this was carried out more frequently if any abnormality indicating a deteriorating heart function was detected.

The presence of risk factors such as the age, body mass index (BMI), baseline LVEF and echocardiography abnormalities, hypertension, ischemic heart disease, diabetes mellitus, a smoking history, the duration of trastuzumab therapy, the dose of anthracycline chemotherapy and the administration of RT in cases of left-sided breast cancer were extracted from the patient files.

Standard 2-dimensional transthoracic echocardiography was performed by two experienced cardiologists using a standard ultrasound machine (Toshiba PowerVision 8000 with a 2.0-3.8 MHz transducer; Toshiba, Tustin, CA, USA). The LV dimensions and volume parameters were obtained from standard parasternal and apical 4-chamber views. The LVEF was calculated by the modified Simpson's method, according to the guidelines of the American Society of Echocardiography (24).

Study end-points. The reduction of LVEF by an absolute value of 10% or more from the baseline or its decrease below the level of 50% indicated a significant abnormality. The development of other heart changes or heart failure was additionally analyzed. The discontinuation of trastuzumab therapy was decided on an individual basis, in accordance with the guidelines (25, 26).

Statistical analysis. Data are reported as mean±SE or median values. Comparison of the incidence of abnormal LVEF changes between groups was carried out with the χ^2 test or Fisher's exact test. The difference between the mean LVEF changes during the first and the second year was analyzed with the paired samples *t*-test. SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform the analysis. A *p*-value of less than 0.05 was considered significant.

Results

Adjuvant trastuzumab therapy. Between September 2006 and April 2012, 47 patients received adjuvant trastuzumab therapy; the median (range) duration of follow-up was 12 (3-36) months. The mean age (±SE) at diagnosis was 53.0±1.7 years. The tumor characteristics are shown in Table II. Two-thirds of the neoplasms were poorly-differentiated and about three-quarters of them were hormone receptor-negative. The average (±SE) number of chemotherapy cycles that the patients received before or during trastuzumab treatment was 5.62±0.27. Most patients completed the anthracycline-based chemotherapy, 18 patients (38.3%) received concomitant taxane and trastuzumab treatment, while 17 of those with left-sided breast cancer received RT (Table III). At least one of the patient-related risk factors for cardiovascular morbidity was present in 68% of the cases (Table IV).

Echocardiography findings are included in Table V. A total of 42 out of 47 patients completed a 1-year course of trastuzumab therapy, while in five cases, trastuzumab treatment was stopped after a mean duration of 5.2 (2.6-7) months (in four cases due to disease progression and in one due to a deterioration of cardiac function). The mean (±SE) duration of trastuzumab therapy was 10.8±0.4 months, with a median value of 11.9 months. The LVEF was normal at baseline in all cases, but decreased by 10% or more in 21 out of the 47 patients (44.7%). In 7/47 (14.9%) cases, these were

Table II. *Tumor characteristics in the patient population treated with adjuvant, and neoadjuvant chemotherapy and adjuvant trastuzumab.*

Tumor characteristics		Patients (N=47)	
		N	%
Histological type	Invasive ductal carcinoma	46	97.9
	Invasive lobular carcinoma	1	2.1
Grade	1	2	4.3
	2	16	34.0
	3	29	61.7
ER	Negative (≤10%)	33	70.2
	Positive (>10%)	14	29.8
PR	Negative (≤10%)	36	76.6
	Positive (>10%)	11	23.4
(y)pT	(y)pT1 (≤20 mm)	29	61.7
	(y)pT2 (>20 mm)	18	38.3
(y)pN	(y)pN0	20	42.5
	(y)pN1-2	27	57.5
Distribution			
	Unifocal	42	89.4
	Multifocal	5	10.6

N=Number, ER=estrogen receptor, PR=progesterone receptor, (y)pT=pathological tumor stage (after neoadjuvant treatment), (y)pN=pathological lymph node stage (after neoadjuvant treatment).

Table III. *Selected oncological therapies in the patient population treated with trastuzumab in the adjuvant and palliative settings.*

Previous/concomitant oncological therapy	Patients receiving adjuvant trastuzumab treatment (N=47)		Patients receiving palliative trastuzumab treatment (N=31)	
	N	%	N	%
Anthracycline chemotherapy before trastuzumab therapy	41	87.2	12	38.7
Irradiated left-sided breast cancer cases	17	36.2	11	35.5
Whole breast	8	17.0	5	16.1
Chest wall	9	19.1	6	19.4
Regional lymph nodes	9	19.1	9	29.0
Tumor bed boost	8	17.0	3	9.7
Endocrine therapy during trastuzumab monotherapy	14	29.8	0	0.0

N=Number.

merely isolated accidental findings during the treatment or the follow-up period. Abnormal LVEF changes occurred in 19/47 (40.4%) and 7/36 (19.4%) patients in the first and the second year, respectively. Among those who exhibited an LVEF decrease of 10% or more, the mean (±SE) changes were 10.58±1.82% (n=19) and 11.79±1.29% (n=7) in the first and the second year, respectively. None of the patients presented an LVEF <50% or symptoms of CHF. Four patients (8.5%) developed atrial septum aneurysm during the treatment or the follow-up period.

The presence of hypertension favored LVEF decrease by 10% or more (27.0% among those with hypertension *vs*. 12.4% among those without hypertension, p=0.004). Likewise, LVEF decrease was associated with the earlier delivery of left-sided RT (27.2% among those who received RT *vs*. 15.2% among those who did not, p=0.023). No statistically significant difference was found with regard to the presence of diabetes or ischemic heart disease; however, the numbers of such cases were low. With the median BMI taken as threshold, patients with a BMI >26.6 kg/m^2 demonstrated a higher incidence of abnormal LVEF changes than that for patients with a BMI less than this, at 28.0% *vs*. 10.5% (p=0.001). No association was found between abnormal LVEF reduction and treatment with anthracycline-based chemotherapy or its dose. An abnormal LVEF change during the first year correlated significantly with the presence of hypertension and BMI, but not with left-sided RT, while in the second (follow-up) year, only the association with left-sided RT remained significant (Table VI).

Palliative trastuzumab therapy. Between June 2003 and February 2012, 31 patients with MBC received chemotherapy and trastuzumab in the palliative setting, 25 patients in the first-line setting, and six in the second-line. Among them, nine patients were maintained on trastuzumab, while 12 received another oncological therapy throughout observation time. The median duration of follow-up was 12 (3-36) months. The mean age (±SE) of the patients was 54.7±2.2 years. Most of the carcinomas were poorly differentiated, and hormone receptor-negative (data not shown). The patients received an average (±SE) of 7.59±0.87 chemotherapy cycles before or during trastuzumab therapy; 12/31 patients (38.7%) were treated with anthracycline-based chemotherapy before trastuzumab, while 27 patients (87.1%) received concomitant taxane and trastuzumab therapy, and 11 patients left-sided RT (Table III). The mean (±SE) duration of trastuzumab therapy was 27.6±7.1 months. In five cases, trastuzumab monotherapy is ongoing.

Cardiovascular co-morbidities and risk factors were present in 80% of the patients (Table IV).

The initial mean (±SE) LVEF was 66.2±1.1%; a cardiac wall dysfunction was revealed in 5/31 patients (16.1%); mitral valve regurgitation and tricuspid valve insufficiency of grade 1 or 2 were the most common cardiac abnormalities

Table IV. *Patient-related risk factors for cardiac morbidity in patients with operable and metastatic breast cancer.*

Patient-related risk factors for cardiac morbidity	Patients receiving adjuvant trastuzumab treatment (N=47)		Patients receiving palliative trastuzumab treatment (N=31)	
	n	%	n	%
Hypertension	23	48.9	19	61.3
Diabetes mellitus	6	12.8	3	9.7
Ischemic heart disease	3	3.4	1	3.2
Smoking	15	31.9	4	11.0
Median BMI (kg/m^2)	26.6		29.5	
≥Median	24	51.1	16	51.6
<Median	23	48.9	15	48.4

N=Number, BMI=Body Mass index, kg=kilogram, m^2=quadratmeter.

Table V. *Heart function parameters at baseline in patients receiving adjuvant/palliative trastuzumab treatment.*

Heart function parameter at baseline	Population treated with trastuzumab in the adjuvant setting (N=47)	Population treated with trastuzumab in the palliative setting (N=31)
LVEF (mean±SE, %)	67.4±0.9	66.2±1.1
LVEF (median, %)	67.0	66.0
Wall dysfunction (N, %)	0 (0.0)	5 (16.1)
Mitral insufficiency (N, %)	20 (42.6)	26 (83.9)
Tricuspidal insufficiency (N, %)	14 (29.8)	14 (45.2)
Aortic valve abnormality (N %)	2 (4.3)	3 (9.7)
Pulmonary valve abnormality (N, %)	2 (4.3)	0 (0.0)

N=Number, SE=standard error.

(83.9% and 45.2%, respectively), while an aortic valve abnormality was reported in three patients (9.7%) (Table V). In the overall population, 31/133 (23.3%) follow-up echocardiographic tests showed an abnormal LVEF change. The mean (±SE) decrease in the LVEF was 7.85±2.11%. The development of an abnormal LVEF was observed at least once in 13/31 (41.9%) patients: in 11/31 (35.5%), in the first year of therapy and in 6/15 (40%), during the second year. However, in 4/31 (12.9%) cases this was merely an isolated accidental finding. The mean (±SE) decrease in the LVEF in the first year in these 11 patients was 8.7±2.3%. For the six patients who showed abnormal LVEF changes in the second year only, the mean (±SE) decrease was 8.1±2.9%. None of the patients developed symptomatic CHF. Three of the patients had an atrial septum aneurysm, while one patient exhibited pericardial fluid during the treatment.

More abnormal LVEF change was detected in patients with than in those without hypertension (Table VII). Likewise, there was a difference in the second year among those who had received RT and those who had not (Table VII). No difference was found concerning the presence of diabetes or ischemic heart disease, although the numbers of such cases were low. No association was detected between the incidence of abnormal LVEF findings and BMI, treatment with or the dose of anthracyclines, the lines or cycles of previous chemotherapies, nor the cumulative dose of trastuzumab.

Cardiac dysfunction detected during the second year was related to previous left-sided RT (Table VII).

Discussion

In our study, the incidence of asymptomatic cardiac dysfunction categorized as significant was higher than reported in large clinical trials (9-11, 27-35). None of our patients, however, developed symptomatic CHF, and approximately one-third of the cases in both groups exhibited merely an isolated accidental 'significant' LVEF decrease. The differences between our data and the published results may stem from the relatively high proportion of patients with risk factors for cardiovascular morbidity in our study. The data from the different trials are also not fully comparable as the assessment criteria, the definitions of cardiotoxicity and the testing methods sometimes differ somewhat; nonetheless, our methods did not differ in any fundamental way from those in the literature (9, 10, 29, 36).

Cardiac abnormalities not related to pumping function during trastuzumab therapy are under-reported. In our study, an asymptomatic atrial septum aneurysm was detected in 8.5% of the cases in the adjuvant group, and in 13.0% in the palliative group. Piotrowski *et al*. detected rare asymptomatic left and right bundle branch blocks and other ECG abnormalities (29). Olin *et al*. described newly-developed T-wave inversions (37). The most clearly established risk factors of trastuzumab-related cardiac events are the additive effect of concurrent trastuzumab and anthracycline treatment, previous anthracycline exposure and the cumulative dose of anthracyclines received (16). Trastuzumab seems to change the tertiary structure of the cardiac contractile apparatus reversibly by inhibiting the HER2 receptors of cardiomyocytes, and to lead to progressive mycocardial cell apoptosis and destruction (38). This potentiates the adverse effects of anthracyclines, *i.e*. the irreversible apoptosis of myocytes induced by reactive oxygen species (22). Hence, trastuzumab is administered following anthracycline treatment. Heavy alcohol abuse (39), co-existing diabetes (40) and older age (11, 32, 36), overweight and obesity, hypertension (11, 36), RT (41) or genetic factors (22) were suggested as predictors of trastuzumab-induced cardiac

Table VI. *Incidence of abnormal cardiac tests during and after adjuvant trastuzumab therapy in relation to selected risk factors.*

	First year		Second year	
	Number of patients with risk factors (N=47)	Number of abnormal findings/ number of measurements (N=179)	Number of patients with risk factors (N=36)	Number of abnormal findings/ number of measurements (N=53)
Hypertension				
Yes	23	27/88 (30.7%)	15	3/23 (13%)
No	24	9/91 (9.9%)	21	6/30 (20%)
p-Value		<0.001		0.387
BMI				
>26.6 kg/m^2	23	26/90 (28.9%)	18	7/28 (25%)
≤26.6 kg/m^2	24	10/89 (11.2%)	18	2/25 (8%)
p-Value		0.003		0.099
Left-sided RT				
Yes	17	15/60 (25%)	12	7/21 (33.3%)
No	30	21/119 (17.6%)	24	2/32 (6.3%)
p-Value		0.168		0.015

N=Number, BMI=Body Mass index, kg=kilogram, m^2=quadratmeter, RT=radiotherapy.

Table VII. *The incidence of abnormal cardiac tests during and after palliative trastuzumab therapy in relation to selected risk factors.*

	First year		Second year	
	Number of patients with risk factors (N=31)	Number of abnormal findings/ number of measurements (N=97)	Number of patients with risk factors (N=14)	Number of abnormal findings/ number of measurements (N=53)
Hypertension				
Yes	19	17/63 (27.0%)	12	9/28 (32.1%)
No	12	4/34 (11.8%)	2	1/8 (12.5%)
p-Value		0.066		0.269
Left-sided RT				
Yes	12	9/34 (26.5%)	5	7/15 (46.7%)
No	19	12/63 (19.0%)	9	3/21 (14.3%)
p-Value		0.275		0.039

N=Number, RT=radiotherapy.

adverse effects. In our study, among patients receiving adjuvant trastuzumab therapy, hypertension and high BMI proved to be significant risk factors during the first year, as did left-sided RT during the second year of observation. In the adjuvant setting, no association was found between trastuzumab-related cardiotoxicity and diabetes mellitus, ischemic heart disease or the use or dose of anthracyclines. In the metastatic group, only left-sided RT was a significant risk factor during the second year of treatment.

Since trastuzumab-related cardiotoxicity is progressive and initially asymptomatic, regular cardiac monitoring (using multiple-gated acquisition scans or echocardiography) is essential; the discontinuation of trastuzumab therapy and specific therapy are justified in rare cases (24, 25). Besides imaging methods, the measurement of plasma markers, such as N-terminal pro-B-type natriuretic peptide as a marker of myocardial strain, troponin-I as a sign of cardiac cell apoptosis and necrosis (42) or high-sensitivity C-reactive protein (43), may be used for the early detection of a cardiac dysfunction.

The limitations of our study include the small size of the population included and the short follow-up period.

In conclusion, given the substantial survival benefits of trastuzumab therapy that have been recorded in both early and MBC, the risk of cardiac complications (among which an LVEF decrease during trastuzumab treatment is the most common) can generally be justified. Our findings suggest that trastuzumab-related cardiac dysfunction is manageable, and largely reversible; it does not exclude patients from further treatment with trastuzumab. All patients should be evaluated for their cardiovascular status and risk factors for type-2 CRCD prior to the initiation of trastuzumab treatment, and cardiac surveillance should be routinely performed during treatment with trastuzumab.

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