

Aim of the study: The aim of this study was to present our own experiences concerning risk factors for cardiac side effects in the study group.

Material and methods: The study was performed in 120 patients with HER2-overexpressing breast cancer who received immunotherapy in the Clinical and Experimental Oncology Department, between 2006 and 2011.

Results: LVEF reduction > 10% of the baseline fraction was observed in 10 (8%) patients. Symptomatic heart failure occurred in two individuals. Due to persistent cardiotoxicity five patients (4%) had to discontinue therapy prematurely. Risk factors for cardiac toxicity in the analyzed group included: previous radiotherapy to the left side of the chest ($p = 0.05$), higher BMI ($p = 0.05$), negative steroid receptor status ($p = 0.045$) and low baseline LVEF ($p < 0.001$). Patients receiving radiotherapy were more likely to develop cardiotoxicity if presenting older age ($p = 0.0003$).

Conclusions: Previous radiotherapy to the left side of the chest, negative steroid receptor status, high BMI and low baseline LVEF were associated with increased risk of cardiac dysfunction. There was no difference between patients receiving adjuvant therapy and those treated due to metastatic disease.

Key words: trastuzumab, cardiotoxicity, risk factors, breast cancer.

Cardiac side effects of trastuzumab in breast cancer patients – single center experiences

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Introduction

Trastuzumab is a humanized monoclonal antibody, selectively targeted at the extracellular domain of human epidermal growth factor receptor 2 (HER-2). Overexpression of HER2 or amplification of the *HER2* gene occurs in about 20% of breast cancer patients [1]. Due to the widespread use of trastuzumab in breast cancer therapy, special caution in the qualification for treatment is necessary and also careful monitoring during patients' treatment to detect potential complications. One of the most common side effects of trastuzumab treatment is cardiotoxicity manifested as heart failure, accompanied by a decrease in left ventricular ejection fraction (LVEF) or an asymptomatic decrease in LVEF. The incidence of myocardial dysfunction during trastuzumab monotherapy is estimated at about 4–7%, including about 3% for toxicity grade 3 and 4 according to CTCAE (Common Terminology Criteria for Adverse Events) [2, 3]. Cardiotoxicity in treatment regimens containing anthracyclines can even reach 27% [3]. As opposed to the risk of cardiac side effects developing as a consequence of anthracycline treatment, the risk of trastuzumab-induced cardiomyopathy does not depend on the total dose of the drug [4]. The mechanism underlying trastuzumab-induced cardiomyopathy is not entirely clear. Some authors believe that it may be linked to the presence of the HER2 receptor on the surface of cardiomyocytes. Human epidermal growth factor receptor 2 is a receptor which plays an important role in cardiogenesis and myocardial protection against harmful factors such as ischaemia or adrenergic stimulation. Trastuzumab blocks the HER2 receptor by binding to its extracellular domain. Suppression of signal transduction inhibits repair mechanisms and promotes cardiomyocyte apoptosis [5]. Prior use of anthracyclines reduces the number of receptors on the surface of myocardial cells, which then are additionally blocked by trastuzumab [6]. Echocardiography is a routine method for monitoring cardiac side effects. Assessment includes measurement of parameters for systolic and diastolic function as well as anatomical cardiac dimensions. Simpson's method is recommended for assessment of ejection fraction [7–9]. Abnormalities of right ventricular contractility, ventricular dilation and abnormalities of left ventricular contractility are the earliest manifestations of myocardial damage diagnosed by echocardiography. In case of clinical symptoms of heart failure, therapy must be stopped as well. Patients with an asymptomatic decrease in LVEF by 15% (or by 10%, if the acceptable lower LVEF limit is assumed as 50%) also require discontinuation of trastuzumab therapy [10]. Both scenarios require cardiac treatment. After normalization of LVEF or resolution of clinical symptoms, the decision to treat with trastuzumab is based on careful risk-benefit analysis for an individual patient. Major risk factors for cardiac side effects are: age over 65 years, prior anthracycline therapy, history of radiotherapy to the left side of the chest, obesity (BMI > 25 kg/m²), diabetes and hypertension. The study outlines the

authors' own experience in a risk assessment of cardiac side effects in a group of trastuzumab-treated breast cancer patients.

Material and methods

The retrospective study was conducted on a group of 120 women treated in the Clinical and Experimental Oncology Department of the Oncology Centre – Maria Skłodowska-Curie Memorial Institute (Gliwice Branch), between the years 2006 and 2011. The study group comprised breast cancer patients with HER2 receptor overexpression or *HER2* gene amplification. Human epidermal growth factor receptor 2 overexpression was assessed using an immunohistochemical method (IHM) in postoperative specimens or in samples obtained by thick needle biopsy. *HER2* gene amplification was additionally assessed by FISH in 8 patients. Inclusion criteria were: baseline LVEF > 50% and medical history without major pathologies, such as unstable ischaemic heart disease, valvular heart disease, chronic hypertension with cardiovascular problems or uncontrolled diabetes (uncontrolled diabetes was classified as a random blood glucose level \geq 11.0 mmol/l in diabetic patients). Patients' characteristics are shown in Table 1.

Echocardiography was performed every 3 months during trastuzumab therapy and also before and after the anthracyclines. Cardiac side effects were assessed according to the NYHA (New York Heart Association) classification and on the CTCAE scale (ver. 4.0). Left ventricular ejection fraction decrease, abnormalities of right ventricular contractility, ventricular dilation and abnormalities of left ventricular contractility were the earliest manifestations of myocardial damage diagnosed by echocardiography.

The following factors were analyzed to determine their potential impact on the development of cardiac side effects: age at disease onset, menopausal status, smoking, hormone receptor status, previous chemotherapy containing anthracyclines, previous radiotherapy to the left side of the chest, comorbidities (diabetes, hypertension, obesity) and baseline LVEF.

Statistical analysis was performed using STATISTICA 7 (StatSoft). Univariate Cox analysis was conducted to assess the impact of risk factors on the development of cardiac side effects. Statistical inference was based on the *p* value determined using a one-sided test and 95% confidence intervals. Differences were considered as statistically significant if the *p* value was < 0.05. Confounding and effect-modifying variables were studied by multivariate analysis.

Results

The median age was 54 \pm 10.4 years (range: 24–71 years). Twenty percent of patients were older than 60 years. Surgery was performed on 100 (83%) patients (of whom 20 patients underwent BCT). In 20 (17%) patients operation was impossible due to advanced stage of disease. The studied group contained 74 (62%) early breast cancer patients and 46 (38%) metastatic patients. Adjuvant chemotherapy was given to 113 (94%) patients and adjuvant radiotherapy to 91 (76%) patients. FAC (5-fluorouracil 500 mg/m², adriamycin 50 mg/m², cyclophosphamide 500 mg/m²) was the most com-

mon chemotherapy regimen. The other used regimens were AC (adriamycin 60 mg/m², cyclophosphamide 600 mg/m²), AT (adriamycin 50 mg/m², docetaxel 75 mg/m²) and TAC (docetaxel 75 mg/m², adriamycin 50 mg/m², cyclophosphamide 500 mg/m²). Estrogen receptor expression was identified in 66 (55%) patients and progesterone receptor expression in 55 (45%) patients. Both steroid receptors were negative in 48 (40%) women. Trastuzumab was used for adjuvant therapy in 74 (62%) patients, and for the treatment of metastatic disease in 46 patients (38%), including 15 patients who underwent immunotherapy in second-line systemic treatment. Adjuvant trastuzumab was given after anthracyclines to 74 (62%) patients and simultaneously with taxanes to 46 (38%) patients. Adjuvant therapy consisted of 18 infusions of trastuzumab. Patients treated for metastatic disease received between 2 and 118 infusions (median number: 23).

During trastuzumab therapy, a total of 56 patients (47%) had reduced LVEF in comparison with baseline values. The LVEF reduction observed in the majority of patients (46 individuals, 39%) was clinically insignificant, not

Table 1. Patient characteristics

	No. of patients	%
Age, years		
< 65 years	108	90
> 65 years	12	10
Menopausal status		
pre-menopause	31	26
post-menopause	89	74
Early breast cancer	74	62
Metastatic breast cancer	46	38
History of smoking		
yes	37	31
no	83	69
Hormonal receptor status		
positive	48	40
negative	72	60
ER		
ER+	66	55
ER–	54	45
PR		
PR+	55	45
PR–	65	54
Radiotherapy		
yes	91	76
no	29	24
Priori left-sided radiotherapy	49	54
Hormone therapy		
yes	71	60
no	48	40
Anthracycline exposure		
yes	109	91
no	11	9
cumulative dose >300 mg/m ²	10	8
Diabetes mellitus	4	3.4
Hypertension	11	9
BMI > 25 (obesity)	22	18

exceeding 10% of the baseline value. In ten women (8%), the LVEF reduction exceeded 10% of the baseline. In five patients the LVEF decrease did not exceed 15% and in the remaining five it was higher than 15% of the baseline value. Two patients had an accumulation of fluid in the pericardium. Decompensated heart failure manifesting as a considerable limitation of physical activity, heart palpitations and dyspnea developed in two patients, while abnormal contractility (generalized hypokinesia) occurred in five patients. Among patients requiring cardiac treatment only one woman was older than 65 years. Four patients received trastuzumab for metastatic disease (9% of all patients with metastatic diseases) and six patients in adjuvant treatment (8% of all patients receiving adjuvant treatment). 109 (91%) women were previously treated with chemotherapy containing anthracyclines and 49 (54%) of them received radiotherapy to the left side of the chest. Furthermore, no steroid receptor expression (either ER or PR) in tumor was detected in any of those patients. Appropriate cardiac treatment improved the cardiac status and normalized LVEF in five patients and it allowed immunotherapy to be reintroduced. No cardiac status improvement was achieved in the remaining five patients who required premature discontinuation of immunotherapy. Univariate Cox analysis demonstrated cardiac side effects in 4.2% of patients previously treated with radiotherapy applied to the left side of the chest, and in 3.3% of patients who did not have radiotherapy to that area of the body ($p = 0.05$). In the multivariate analysis patients receiving radiotherapy were more likely to develop cardiotoxicity if they were older ($p = 0.0003$). In the analyzed group patients had baseline LVEF ranging between 50% and 70%. Left ventricular ejection fraction values between 50% and 60% were noted in 77 patients (64%) and between 60% and 70% in 43 women (36%). Cardiac side effects occurred in nine patients with baseline LVEF between 50% and 60%, and in one patient whose LVEF was 70% ($p < 0.001$). No relationship was confirmed between the number of trastuzumab infusions and LVEF decrease. A decrease of LVEF was frequently observed in patients with higher BMI ($p = 0.05$). A full description of LVEF changes during trastuzumab therapy is included in Table 2.

Cardiac side effects, including symptomatic heart failure, developed in four patients who were previously treated with chemotherapy containing anthracyclines at a dose exceeding 300 mg/m² and in six patients who were treated with anthracyclines at doses lower than 300 mg/m² ($p = 0.084$). Negative receptor status (either ER or PR) was detected in ten patients (8%) with symptoms of cardiac side effects. Evidence of cardiac side effects was noted in 25% of patients with negative ER or PR tumors in comparison with 72 (60%) patients with positive receptor status and without cardiotoxicity symptoms ($p = 0.045$). Univariate analysis showed a correlation between cardiac side effects and negative steroid receptor status (ER/PR) compared to positive receptor status (6% vs. 3%) ($p = 0.00005$). In the multivariate analysis ER/PR negative, HER 2 overexpressing breast cancer patients were significantly more prone to develop asymptomatic or symptomatic cardiac events during treatment with trastuzumab if presenting with baseline LVEF between 50% and 60% ($p = 0.0001$). No relationship was identified in the study group between cardiotoxicity risk in trastuzumab treatment and the presence of such risk factors as age ($p = 0.465$), menopausal status ($p = 0.728$), obesity ($p = 0.977$), hypertension ($p = 0.685$), diabetes ($p = 0.537$) and use of stimulants ($p = 0.891$).

Sixty-two percent of women in the study group were given trastuzumab in adjuvant treatment and 38% for metastatic disease of breast cancer. In the group of patients receiving adjuvant therapy, cardiotoxicity occurred in 6.6% of patients and in patients treated for metastatic disease in 8.7% of cases, $p = 0.710$. Among patients receiving adjuvant treatment a decrease in LVEF was noted in three patients in the initial stage of therapy (4–8 infusions) and in two patients at the end of therapy. As for treatment implemented in metastatic disease, a decrease in LVEF was mainly observed after 20 infusions. In the group treated for metastatic disease there was an insignificantly higher incidence of contractility abnormalities compared with the group receiving adjuvant treatment (8.7% vs. 1.4%, $p = 0.141$). Also, there was not significantly higher incidence of fluid accumulation in the pericardial cavity (2.2% vs. 1.4%, $p = 0.739$). There were no differences between the groups in terms of LVEF reduction

Table 2. Symptomatic and asymptomatic cardiac events

Cardiotoxicity	NYHA criteria	No. of risk factors	LVEF before trastuzumab (%)	Lowest LVEF value (%)	Trastuzumab continuation	LVEF after completion of therapy (%)
asymptomatic	II	2	52	45	yes	55
symptomatic	III	3	59	39	no	41
asymptomatic	II	1	55	43	yes	53
symptomatic	IV	1	58	35	no	38
asymptomatic	II	2	60	40	no	45
asymptomatic	II	3	50	35	no	40
asymptomatic	I	2	56	46	yes	51
asymptomatic	I	0	58	45	no	48
asymptomatic	I	1	70	55	yes	60
asymptomatic	I	1	55	45	yes	56

Table 3. A comparison of adjuvant therapy with treatment of metastatic disease

Parameter	Trastuzumab in adjuvant treatment (n = 74)		Trastuzumab in metastatic disease (n = 46)		p
	N	%	N	%	
age > 60 years	13	17.6	8	17.4	0.941
hormonal receptor status (ER/PR-)	26	35.1	22	47.8	0.167
radiotherapy	57	77.0	34	73.9	0.698
hormone therapy	48	64.9	23	50.0	0.088
anthracycline exposure	66	89.2	43	93.5	0.428
cardiotoxicity	5	6.6	4	8.7	0.710
decrease in LVEF	6	8.1	4	8.7	0.852
cardiac arrhythmias	1	1.4	4	8.7	0.141
changes of pericarditis	1	1.4	1	2.2	0.739
adverse events	2	2.7	1	2.2	0.656

(8.7% vs. 8.1%) or symptomatic heart failure (2.2% vs. 2.1%) (Table 3).

Discussion

Trastuzumab is the standard care for patients with HER2 (+) breast cancer both for adjuvant therapy and treatment of metastatic disease. Trastuzumab can be combined with chemotherapy regimens containing anthracyclines and taxanes or used in monotherapy. Four major studies of trastuzumab in adjuvant treatment (HERA, NSABP B31, FinHER, and BCIRG 006) showed that the addition of trastuzumab to adjuvant therapy significantly extended disease-free survival (DFS) and overall survival (OS) without a significant effect on toxicity with the exception of cardiotoxicity in trastuzumab-treated patients [11–16]. The HERA trial demonstrated that trastuzumab in adjuvant treatment significantly increased 4-year OS rates (89% vs. 87%) and 4-year DFS rates (78% vs. 72%) in comparison with trastuzumab-free therapy [11]. The NSABP B31 and N9831 trials demonstrated that addition of trastuzumab to chemotherapy regimen (paclitaxel following AC) reduces disease recurrence by 52% and risk of death by 33% compared with chemotherapy alone [16, 17]. In the PACS04 study, which was a randomized phase III trial of women with node positive early breast cancer, the results contrast with the above-mentioned trials. The results of this study showed that patients who received trastuzumab had a non-significant, 14% reduction in the risk of relapse [18].

Some of the patients experiencing cardiac side effects exhibit typical symptoms of heart failure including reduced exercise tolerance, dyspnea on exertion, tachycardia or signs of fluid retention. But the most common cardiotoxicity seen with trastuzumab is asymptomatic decline in LVEF. In most patients cardiac dysfunction was reversible on discontinuation of trastuzumab therapy and introduction of cardiac therapy [2, 13]. In the HERA trial asymptomatic decline in LVEF was observed in 7.1% of patients and symptoms of heart failure were seen in 1.7% of trastuzumab treated patients [11]. Similarly, in the NSABP B31 and N9831 trials 14.2% of patients discontinued trastuzumab therapy because of

asymptomatic decline in LVEF and only 4.7% of patients discontinued therapy due to heart failure [16, 17]. In a study by Serrano *et al.*, performed in elderly patients (age > 70) who were given trastuzumab both in adjuvant therapy and for treatment of metastatic disease, cardiac side effects triggered by trastuzumab developed in 26.7% of patients, including symptoms of heart failure in 8.9% [19]. In the study group an asymptomatic decrease in LVEF was noted in 37% of patients. Cardiotoxicity occurred in 8% of women, including 2% of patients with heart failure symptoms. Cardiac side effects developed in nine patients with baseline LVEF between 50% and 60%, and in just one patient whose baseline LVEF was 70% ($p < 0.001$). The increase of LVEF was frequently observed in patients with higher BMI ($p = 0.05$).

Patient age and prior anthracycline therapy are recognized independent risk factors for trastuzumab-induced cardiotoxicity [4, 20]. Age > 60 years was found to be a risk factor in the NSABP B31 trial [16]. An association between increasing age and cardiac toxicity was also observed in the NCTG N9831 trial, in which 15% of patients were aged ≥ 60 . In contrast, in the BCIRG 006 trial an influence of older age on cardiac side effects was not reported [13]. In this studied group, older age and history of cardiac diseases had no significant impact on the development of cardiotoxicity. Only patients receiving radiotherapy were more likely to develop cardiotoxicity if they were older ($p = 0.0003$). Trastuzumab combination with anthracycline-containing chemotherapy regimens increased the incidence of cardiac side effects even to 27% [3]. The risk of cardiac dysfunction increases after a cumulative dose of doxorubicin exceeding 300 mg/m² [20]. The addition of trastuzumab to anthracycline-containing chemotherapy was associated with a higher incidence of heart failure (NYHA III–IV) compared with the combination of trastuzumab with anthracycline-free chemotherapy (BCIRG trial) [13]. In this study 90% of patients received anthracycline-containing therapy, including 23% who received anthracycline doses exceeding 300 mg/m². The HERCULES multicenter, phase I to II trial was conducted to evaluate the cardiac safety of epirubicin/cyclophosphamide plus trastuzumab reg-

imen as first line therapy for HER2-positive metastatic breast cancer patients. In this regimen the incidence of dose-limiting cardiotoxicity was lower in comparison with trastuzumab and doxorubicin [22]. Prior anthracycline treatment was not an independent risk factor for trastuzumab-induced cardiotoxicity in the current study. The small size of the sample may have impacted these results.

Other factors elevating the risk of cardiac side effects are: obesity, hypertension, diabetes and previous radiotherapy to the left side of the chest [3, 21]. In the HERA trial, lower baseline LVEF (55–60%), high BMI (> 25), hyperlipidemia and higher cumulative dose of anthracycline (over 287 mg/m²) proved to be significant risk factors for cardiotoxicity. On the other hand, diabetes, history of cardiac diseases or hypertension had no significant effect on the development of cardiotoxicity [11, 20]. In a study by Serrano *et al.*, history of cardiac diseases and diabetes also had a major effect on the development of cardiotoxicity in the elderly patient population. Hypertension, trastuzumab dose, history of radiotherapy to the left side of the chest and use of stimulants were not found to have any effect on cardiac side effects [19]. The discrepancies in study results may arise from differences in endpoints, inclusion criteria and therapeutic regimens. Statistically significant risk factors for cardiac toxicity in the analyzed group of patients included: lower (50–60%) baseline LVEF ($p < 0.001$), high BMI (> 25), negative steroid receptor status (ER/PR) ($p = 0.045$) and history of radiotherapy applied to the left side of the chest ($p = 0.05$). ER/PR negative, HER2 overexpressing breast cancer patients were significantly more likely to develop cardiac events during treatment with trastuzumab if presenting with baseline LVEF between 50% and 60% ($p = 0.0001$). The myocardium is a target tissue for estrogen, which plays an important role in the pathogenesis of cardiovascular disease. Myocytes contain functional receptors (ERs) ER α and ER β . A study with ER knockout animals showed that ERs are required for cardioprotection in myocardial ischemia and pressure overload left ventricular hypertrophy [23]. The influence of negative steroid receptor status on cardiac toxicity may be connected with the lack of cardioprotective effects of estrogens.

A comparison of adjuvant therapy with treatment for metastatic disease revealed no statistically significant difference between two patient groups in terms of cardiac side effects including contractility disorders, pericardial abnormalities (fluid accumulation in the pericardium), LVEF decrease or symptomatic heart failure. Differences in the number of patients in both groups may also be responsible for the lack of significant correlation between cardiotoxicity and anthracycline-containing chemotherapy ($p = 0.08$). Baseline LVEF > 55%, longer interval between anthracycline-containing chemotherapy, radiotherapy and immunotherapy, and more frequent cardiac assessment by echocardiography are associated with lower cardiotoxicity of treatment [20, 24].

Summary

In the analyzed group of patients, risk factors for cardiac toxicity included: previous radiotherapy to the left side of the chest ($p = 0.05$), high BMI, low baseline LVEF ($p < 0.001$) and negative steroid receptor status ($p = 0.045$). The impact of

anthracycline-containing chemotherapy was not significant ($p = 0.08$). Patients receiving radiotherapy were more prone to develop cardiotoxicity if they were older ($p = 0.0003$). Factors such as diabetes, hypertension, menopausal status, use of stimulants or age of the patients did not affect the development of cardiotoxicity. Moreover, cancer advancement was not found to have any prognostic value for cardiac side effects. There was no significant difference between patients receiving adjuvant therapy and patients treated for metastatic disease.

The authors declare no conflict of interest.

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Submitted: 23.07.2012

Accepted: 22.10.2012