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Risk factors for developing cardiotoxicity of trastuzumab in breast cancer patients: An observational single-centre study

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Abstract

Background: Trastuzumab is a recombinant humanized monoclonal antibody used to treat human epidermal growth factor receptor 2 positive breast cancer, with recognized associated cardiotoxicity. In this retrospective observational study, we investigated associated cardiotoxicity on clinical outcomes using trastuzumab in women referred to our clinic.
Materials and methods: The study was made up of 111 women with human epidermal growth factor receptor 2-overexpressing breast cancer who received trastuzumab in the Medical Oncology Department, between 2010 and 2013.
Results: A > 10% reduction of the baseline fraction of the left ventricular ejection fraction was observed in 18 (16.21%) women. Two individuals (1.8%) suffered from symptomatic heart failure, seven women showed cardiac symptoms and nine women showed asymptomatic decline of left ventricular ejection fraction. Risk factors for cardiotoxicity in the group included: postmenopausal status ($p = 0.01$), hypertension ($p = 0.002$), obesity ($p = 0.0001$), previously diagnosed coronary artery disease ($p = 0.0001$) and smoking ($p = 0.03$).
Conclusion: The aforementioned factors pose a risk for cardiotoxicity. We found postmenopausal status, hypertension, obesity, previous coronary artery disease and smoking to be associated with an increased risk of cardiac dysfunction in women using trastuzumab. While administering trastuzumab to women who have these conditions, one must be aware of the risk of cardiotoxicity of trastuzumab.

Keywords

Trastuzumab, breast cancer, cardiotoxicity, onco-pharmacology, risk factors

Introduction

Breast cancer (BC) is the most common type of cancer and the most common cause of cancer-related mortality among women worldwide.[1] Human epidermal growth factor receptor 2 (HER2) positivity is present in 20%–25% of invasive BC and correlates to an unfavourable prognosis.[2,3] Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of HER2.[4]

Important studies of trastuzumab in adjuvant treatment show that the addition of trastuzumab to adjuvant therapy significantly extends disease-free survival and overall survival.[5–7] Because of the prevalent use of trastuzumab in treating BC, candidates are carefully selected and are closely monitored in order to ascertain any likely difficulty that may arise during treatment. Cardiotoxicity is a side effect that must be carefully supervised in trastuzumab treatment. It is often revealed as heart failure along with a decline in left ventricular ejection fraction (LVEF) or an asymptomatic reduction in LVEF. While receiving trastuzumab

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monotherapy, approximately 4%–7% of women suffer from myocardial dysfunction, and 3% suffer from grade 3 and 4 toxicity.[8,9]

The purpose of this study was to assess the rate of cardiotoxicity related to trastuzumab treatment in clinical practice in our centre, and to determine its potential associated risk factors.

Patients and methods

This was a retrospective institutional study conducted at the Department of Medical Oncology, in the Cukurova University Medical School Adana, Turkey from January 2010 to May 2013. Treatment of trastuzumab was given for one year in adjuvant therapy while it was only given until progression in metastatic BC. The study respected the ethical rules for medical research involving human subjects as stipulated by the World Medical Association in the Declaration of Helsinki. The local ethical committee approved this study. Women gave their consent prior to treatment.

Cardiotoxicity was defined as a decrease in LVEF below normal values (50%) or an absolute decrease of >10 points below the baseline value or any indication of heart failure. The following factors were investigated to determine their potential impact on the evolution of cardiac side effects: age at disease onset, menopausal status, history of smoking, hormone receptor status, stage of BC, previous chemotherapy containing anthracyclines, previous radiotherapy on the left side of the chest, comorbidities (diabetes, hypertension, obesity, stable ischaemic heart disease, hyperlipidemia), family history of coronary artery disease (CAD) and baseline LVEF.

The information was recorded in an Excel database and analysed using NCSS (Number Cruncher Statistical System), version 2007 statistical software (Utah, USA). To assess baseline characteristics, categorical variables were compared using the chi-squared test or Fisher's exact test while continuous variables were analysed using the Mann–Whitney *U*-test whenever appropriate. Logistic regression analysis was conducted to obtain unadjusted odds ratios (OR) and revealed as OR, 95% confidence interval, *p* value in comparison of both LVEF normal and LVEF decreased groups. Statistical inference was based on the *p* value determined using a one-sided test and 95% confidence intervals at a power of 80%. Differences were considered statistically significant if the *p* value was <0.05.

Eligibility criteria

BC women who had been verified pathologically and HER2 (+) status determined by immunohistochemistry (3+) or fluorescent in situ hybridization (+) were enrolled in this study. These women received trastuzumab treatment, and their measured LVEF was ≥50% on an echocardiography. There were no cases of uncontrolled hypertension, uncontrolled diabetes or unstable ischaemic heart disease. Echocardiography was performed every three months during trastuzumab therapy and also before and after treatment with anthracyclines. Cardiac side effects were assessed according to the NYHA (New York Heart Association) classification and on the CTCAE scale (ver. 4.0).[8] A reduced LVEF, abnormalities of right ventricular contractility, ventricular dilation and abnormalities of left ventricular contractility were the earliest indications of myocardial damage diagnosed by an echocardiography.

Results

A total of 111 Turkish women were enrolled in the study. All BC patients admitted to our medical oncology department used trastuzumab for BC. These women were not specifically chosen for this study. The median age at diagnosis was 49 years (range: 33–72). The baseline characteristics of the women and the treatment details are presented in Tables 1 and 2.

Table 1. Characteristics of patients.

		n	%
Age	<55	77	69.37
	≥55	34	30.63
Stage	I	6	5.41
	II	44	39.64
	III	31	27.93
	IV	30	27.03
Radiotherapy		66	59.46
Chemotherapy	Others	9	8.11
	Doxorubicin	56	50.45
	Epirubicin	42	37.84
	Doxo + epirubicin	4	3.60
Menopause	Pre-	45	40.5
	Post-	40	36
Diabetes mellitus		16	14.41
Hypertension		25	22.52
Hyperlipidemia		25	22.52
CAD		17	15.32
BMI	<30	64	57.66
	≥30	47	42.34
History of familial CAD		40	36.04
History of Smoking		27	24.32
Hormone receptor status		45	63.38

Table 2. Frequency of the LVEF status in patients with cardiotoxicity ($n = 18$).

	n	Median age	SS	Minimum	Maximum
Normal LVEF	93	48.62	9.36	33	72
Decreased LVEF	18	54.67	8.44	41	70
All groups	111	49.60	9.45	33	72

SS: standard deviation.

Table 3. Characteristics of the LVEF decrease in patients with cardiotoxicity ($n = 18$).

Cardiotoxicity criteria	*n*	%
LVEF decreased to 40%–45%	2	1.8
LVEF decreased to 45%–50%	7	6.3
LVEF decreased to 50%–55%	9	8.1

The studied group contained 81 (72.98%) non-metastatic BC patients and 30 (27.03%) metastatic patients. A total of 81 (72.98%) women were treated with adjuvant chemotherapy concurrent with trastuzumab, and 66 (59.46%) women were treated with radiotherapy. The women treated with chemotherapy ($n = 56$) were involved in four cycles of AC (adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every three weeks) followed by taxane (paclitaxel or docetaxel) along with trastuzumab (6 mg/kg) every three weeks. They ($n = 42$) were also treated with chemotherapy involving four cycles of epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2, followed by taxane (paclitaxel and docetaxel) with trastuzumab (6 mg/kg) every three weeks. Trastuzumab was given with non-anthracyclines and continued to be administered three weeks after last anthracycline dose. Doxorubicin was replaced by epirubicin due to an allergic reaction to doxorubicin in four women. There were no differences in the incidence of cardiac side effects between the type of cytotoxic chemotherapy agents ($p = 0.74$). Twenty-eight (42.42%) women received radiotherapy on the left side of the chest. There was no vast difference found between women who received radiotherapy on the left side of the chest and women who received radiotherapy on the right side of the chest ($p = 0.74$).

In 18 women (16.21%), a decrease of greater than 10% of the baseline fraction of the LVEF was observed. Decompensated heart failure manifesting as a considerable limitation of physical activity, dyspnea and tachicardia developed in two women, while generalized hypokinesia occurred in seven women in whom the LVEF was reduced to 45%–50%. Two women did not improve with medical treatment (angiotensin converting enzyme-ACE inhibitors); these patients had both heart failure and LVEF 40%–45%, whereas seven women did improve with medical treatment with (ACE inhibitors). In nine women, the LVEF was 50%–53% and increased to 58%–60% during follow-up without medical treatment. In seven women, appropriate cardiac treatment improved the cardiac status, normalized LVEF >55%, and allowed trastuzumab to be reintroduced. No improvement in cardiac status was achieved in the remaining two women who required premature discontinuation of trastuzumab (Table 3).

In our study of women treated with trastuzumab, an asymptomatic decline in LVEF was observed in 8% of women. Symptoms of decompensated heart failure were seen in 1.8% of women; symptoms of compensated heart failure were seen in 4.5%.

There was no statistically significant difference in relation to cardiac side effects when comparing non-metastatic disease and metastatic disease ($p = 0.216$).

No link was established between the prospect of cardiotoxicity in trastuzumab treatment and the presence of risk factors such as diabetes ($p = 0.76$), hyperlipidemia ($p = 0.06$), hormone receptor positive status (estrogen and/or progesterone) ($p = 0.58$), CAD in family history ($p = 0.78$) or age ($p = 0.09$).

A reduction in the LVEF was observed as a significant statistic in postmenopausal women ($p = 0.013$), obese women (body mass index (BMI) > 30) ($p = 0.0001$), those with hypertension (using antihypertensive agent) ($p = 0.002$), previously stable CAD (0.0001) and smokers (current smokers and/or previous smokers) ($p = 0.03$) (Table 4).

Discussion

In our study of women treated with trastuzumab, an asymptomatic decline in LVEF was observed in 10% of women. Symptoms of decompensated heart failure were seen in 1.8% of women; symptoms of compensated heart failure were seen in 4.5%. There was no association between increasing age and cardiac toxicity. We compared a low dose of doxorubicin (<240 mg/m^2) trastuzumab with a low dose of epirubicin (<500 mg/m^2) trastuzumab, and we found no difference in the risk of trastuzumab-induced cardiotoxicity. We found no association between left-sided irradiation and trastuzumab-induced cardiotoxicity. We found a relationship between postmenopausal women and trastuzumab-induced cardiotoxicity. A reduction in LVEF was observed in obese women (BMI > 30), those with hypertension, in women with a previous history of CAD and in smokers. There was no meaningful association created between diabetes, hyperlipidemia, radiotherapy on the left side of the chest, a decline in LVEF, or hormone receptor positive status.

Table 4. A comparison of parameters of LVEF decrease.

		LVEF normal		LVEF decreased		
		n	%	n	(%)	*p* value
Age	<55/≥55	68/25	73.12/26.88	9/9	50/50	0.091
Metastatic status	Non-metastatic	70	75.3	11	61.1	0.216
	Metastatic	23	24.73	7	38.9	
Radiotherapy		53	56.99	13	72.22	0.228
Anthracycline		86	92.47	16	88.89	0.610
Chemotherapy	Others	7	7.53	2	11.11	0.744
	Doxorubicin	46	49.46	10	55.56	
	Epirubicin	36	38.71	6	33.33	
	Doxo + epirubicin	4	4.30	0	0.00	
Menopause status	Pre/post	41/28	59.42/40.58	4/12	25/75	0.013 OR: 4.39 CI: 1.28–15.02
Diabetes mellitus		13	13.98	3	16.67	0.766
Hypertension		16	17.20	9	50.00	0.002 OR: 4.81 CI: 1.65–14.02
Hyperlipidemia		18	19.35	7	38.89	0.069
CAD		2	2.15	15	83.33	0.0001 OR: 8.22 CI: 2.23–30.26
BMI	<30/≥30	62/31	66.67/33.33	2/16	11.11/88.89	0.0001 OR: 16 CI: 3.45–74.03
History of familial CAD		33	35.48	7	38.89	0.783
History of smoking		19	20.43	8	44.44	0.03 OR: 3.11 CI: 1.08–8.97
Hormone receptor status		37	64.91	8	57.14	0.589
Priori left-sided radiotherapy	Right/left	69/24	74.20/25.80	14/4	77.80/22.2	0.749

For women with HER2(+) BC, treatment using trastuzumab is the norm. It can be used along with chemotherapy or on its own. Although several mechanisms have been proposed to detail anticancer agent-associated cardiotoxicity, risk factors are not yet fully understood.[4,10] While the most common side effect of cardiotoxicity seen with trastuzumab is an asymptomatic decline in LVEF, symptoms of heart failure can occur. These symptoms can include exercise intolerance, dyspnea and tachycardia. The conditions of most women who suffered from cardiac dysfunction improved significantly by terminating trastuzumab therapy and beginning cardiac therapy.[8,11,12] In the HERA and NSABP B31 trials with trastuzumab, an asymptomatic decline in LVEF was observed in 7.1% and 14.2% of women, and symptoms of heart failure were seen in 1.7% and 4.7%,[5,7] respectively. Our findings are consistent with these trials.

Age > 50 years was found to be a risk factor for cardiac toxicity.[7,13] In contrast, in other trials, older age had no obvious impact on cardiac side effects.[6,11] In our study, there was no association between age >55 years and cardiac toxicity, although age was high in those who developed a decrease of LVEF.

Trastuzumab combined with anthracycline-containing chemotherapy regimens elevated the frequency of cardiac side effects to 27%.[9] The addition of trastuzumab to anthracycline-containing chemotherapy was related to a greater rate of heart failure (NYHA III–IV) compared with trastuzumab combined with anthracycline-free chemotherapy in another trial.[6] In a study, a previous cumulative dose >240 mg/m^2 of doxorubicin or >500 mg/m^2 of epirubicin increased the risk of trastuzumab-induced cardiotoxicity compared with lower doses.[14] In the HERA trial, a higher cumulative dose of anthracycline (over 287 mg/m^2) proved to be a significant risk factor for cardiotoxicity.[5] We found no difference in the risk of trastuzumab-induced cardiotoxicity. Although there is a difference proportionally between a low cumulative dose of doxorubicin and a low cumulative dose of epirubicin with a decline of LVEF, there is no significant statistical link between doxorubicin and epirubicin with a decline of LVEF.

While one study reported that left-sided irradiation was associated with an increased cardiac toxicity following the use of concurrent trastuzumab,[15] in another study, a history of radiotherapy to the left side of the chest was not found to have any cardiological side effects. However, women receiving radiotherapy were more likely to develop cardiotoxicity if they were older.[16] We found no association between left-sided irradiation and trastuzumab-induced cardiotoxicity.

A comparison of non-metastatic and metastatic disease revealed no statistically significant difference in terms of cardiac side effects.[4] Our results are consistent with this study.

CAD was associated with trastuzumab-induced cardiotoxicity in postmenopausal women in a recent study. The increased risk of cardiovascular disease in the postmenopausal period can be attributed to elevated levels of lipids and increased systolic blood pressure, regardless of the effects of advanced age or BMI.[17,18] We found a relationship between postmenopausal women and trastuzumab-induced cardiotoxicity.

Obesity, hypertension and diabetes are other conditions raising the risk of cardiac side effects.[9,17] The HERA trial found that a lower baseline LVEF (55%–60%), high BMI (>25) and hyperlipidemia were significant risk factors for cardiotoxicity.[5] On the other hand in other studies, diabetes, a history of cardiac diseases and hypertension had no powerful effect on the development of cardiotoxicity.[4,11,19] A reduction in LVEF was observed in obese women, those with hypertension, in women with a previous history of CAD and in smokers. There was no meaningful association created between diabetes, hyperlipidemia, radiotherapy on the left side of the chest, a decline in LVEF, or hormone receptor positive status.

There were limitations to our study. Our study was limited by the small trial group. This could affect the statistics. The fact that this study was retrospective also has limitations in that we did not continue to follow up with women after trastuzumab therapy. Moreover, we did not calculate the cumulative dose of trastuzumab. This should be calculated in further trials. In addition to echocardiography, other techniques to detect cardiac issues can be used, such as radyonuclide methods, serum biomarkers (B-type natriuretic peptide, troponin-T) to determine cardiac dysfuntion.

In conclusion, in light of BC's high survival rates, it will be important in the future to test the indications for anthracyclines with and without trastuzumab with other combination therapies that may be less cardiotoxic. This could determine factors that predict responses to anthracyclines and potential cardiotoxicities. This information could be used to put together more tailor-made treatments. Finally, we suggest that women who are postmenopausal, or have hypertension, CAD, are obese, or smoke should be closely monitored when treated with trastuzumab for BC.

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Conflict of interest

None declared.

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