HeSMO • 7(2) • 2016 • 1–6
DOI: 10.1515/fco-2016-0007

DE GRUYTER OPEN

Forum of Clinical **Oncology**

Cardiotoxicity of the adjuvant trastuzumab in a Saudi population: clinical experience of a single institution

Rasha Hamdy Hamed[1]*, Khalid Salim[2], Abdullah Alzahrani[3], Shereef Elsamany[3]

[1]*Clinical Oncology and Nuclear Medicine , Faculty of Medicine , Mansoura University, Egypt, Mansoura, Egypt*

[2]*Cardiology , King Abdulla Medical City Makkah , Kingdom of Saudi Arabia*

[3] *Medical Oncology, Oncology Center of King Abdulla Medical City (KAMC), Makkah , Kingdom of Saudi Arabia*

Received 23 February 2016; Accepted 14 October 2016

Abstract: **Purpose:** Adjuvant trastuzumab is currently an internationally standard for the treatment of localised breast cancer that over express HER2 with the most adverse effect being cardiotoxicity. We conducted this study to evaluate the cardiac safety of trastuzumab in clinical practice.

Methods: This study is a retrospective observational single institutional study conducted in the Oncology Center of King Abdulla Medical City (KAMC), Makkah, Saudi Arabia, from June 2011 to January 2014. We evaluated the incidence of cardio toxicity and associated risk factors during adjuvant trastuzumab treatment.

Results: Of 57 patients, 20 patients (35%) exhibited cardiotoxicity. About 14% of patients had drop of left ventricular ejection fraction (LVEF) below 50%, whilst 10% and 15% drop of LVEF below their baseline levels were found in 30% and 5% of patients, respectively. About 98.3% of our patients have completed treatment, of whom 21% had a provisional interruption because of a fall in LVEF. A definitive trastuzumab discontinuation has been made in 1.75% of cases because of a nonregressive reduction in LVEF. Analysis of risk factors related to trastuzumab cardio toxicity found that patients older than 40 years were more likely to develop cardio toxicity compared to those younger than 40 years. This difference was statistically significant ($p = 0.042$).

Conclusion: In our study, the cardiac safety seems comparable with the literature data. Trastuzumab-related cardiotoxicity is manifested by an asymptomatic decrease in the LVEF and less commonly by clinical heart failure. Most instances are transient, asymptomatic and reversible.

Keywords: *Cardiotoxicity • Adjuvant trastuzumabin • Breast cancer*

© De Gruyter Open

Introduction

Breast cancer is the most common malignant disease and amongst the most frequent causes of cancer mortality in females worldwide [1,2]. Amplification and/or overexpression of human epidermal growth factor receptor type 2 (HER2) occurs in about 15-20% of invasive breast cancers. HER2 positive breast tumours are more aggressive and more susceptible to recurrence than HER2 normal tumours [3,4]. Trastuzumab is a humanised monoclonal antibody that binds to the extracellular domain of HER2 receptor and inhibits carcinoma cellular proliferation [5]. Trastuzumab therapy is important in the treatment of early and advanced disease as shown in multiple randomised trials. Significant clinical benefits of trastuzumab in the treatment of early-stage breast cancer have been observed. Four large trials (and several smaller trials) evaluating adjuvant trastuzumab demonstrated significant improvements in disease-free survival (DFS; 36-52% reduction in DFS events) and overall survival (OS; 33-37% reduction in deaths), irrespective of tumour size, nodal status hormone receptor status, or age [6-10]. On the basis of data from these trials, adjuvant trastuzumab has become the foundation of care for HER2- positive early breast cancer.

Its use as an adjuvant treatment for a period of 1 year is currently an international standard of care in HER 2 - overexpressed localised breast cancer. It is generally well tolerated, with a low incidence of adverse effects

* *E-mail: rashahamdy532@yahoo.com*

[11] of which the most relevant is cardiotoxicity. It is typically manifested by an asymptomatic decrease in left ventricular ejection fraction (LVEF) and less often by clinical heart failure (HF) [12].

The mechanisms of trastuzumab-induced cardiotoxicity is not fully understood, but is distinct from that of anthracyclines. Anthracyclines cause type I cardiotoxicity, which is dose dependent, irreversible and normally associated with biopsy changes, whereas trastuzumab causes type II cardiotoxicity, which is dose independent, largely reversible and does not produce ultrastructural changes on histological examination. Trastuzumab-induced cardiomyopathy may be the result of a 'dual-hit' mechanism. First, trastuzumab directly inhibits antiapoptotic pathways. Second, trastuzumab upregulates angiotensin II (ANG II), which leads to an increase in reactive oxygen species (ROS) production and inhibition of neuregulin-1 (NRG-1) signalling [13].

It requires careful monitoring of the LVEF before and during treatment. Trastuzumab cardiotoxicity was originally described in women with metastatic breast cancer and in several subsequent trials of adjuvant trastuzumab, about 80% of trials show cardiotoxicity [14]. However, the incidence of cardiotoxicity amongst populations of women treated outside of this clinical trial, in real life, is not well known.

The purpose of this study is to evaluate the incidence of cardiotoxicity in patients with histologically confirmed localised HER2-positive breast cancer treated with adjuvant trastuzumab in clinical practice in a single institution in Saudi Arabia by describing its characteristics and potential associated risk factors.

Methods

This is a retrospective observational single institutional study conducted at the Department of Medical Oncology, in the Oncology Center of King Abdulla Medical City (KAMC), Makkah, Kingdom of Saudi Arabia from June 2011 to January 2014. Eligible patients had localised breast cancer verified histologically and HER2-positive status assessed by immunohistochemistry (3+) or fluorescent in situ hybridisation positivity, had adequate cardiac function with normal LVEF ≥ 55% measured on echocardiography and received adjuvant tarstuzumab.

Ineligibility criteria included a history of documented congestive HF, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease and unstable arrhythmias. This study was approved by the institute review board of KAMC. The study respected the ethical rules for medical research involving human subjects as stipulated by the World Medical Association in the Declaration of Helsinki. Cardiac monitoring included physical examination and an assessment of LVEF by echocardiography: it was evaluated before trastuzumab administration and every 12 weeks thereafter for the duration of therapy.

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 symptoms or signs of HF.

The following cardiovascular risk factors were analysed: age, overweight body mass index (BMI ≥ 25 kg/m^2), hypertension, diabetes, anthracycline containing regimen and concomitant radiotherapy with trastuzumab.

Follow up

We tracked followed up data till January 2015. Any patients who were not reviewed in the last consultation were contacted again by telephone.

Statistical analysis

Data was recorded in case report form (CRF) for each patient. Data was analysed at KAMC Research Unit using SPSS software, version 20. A logistical regression analysis was performed to examine the variables associated with the development of cardiotoxicity. A p-value less than 0.05 was considered significant for all two-tailed comparisons.

Results

In this study, 57 patients with localised HER2-positive breast cancer were included. Seventy-five percent of patients were >40 years at diagnosis, 56% were premenopausal and 51.9% had stage II disease. About 58.8% of our patients were hormone receptor positive. All patients underwent surgery, 76.9% had radical mastectomy and 23.1% had conservative surgery with axillary lymph nodes dissection. The majority of patients received both anthracycline- and taxane-based chemotherapy (73.1%) and adjuvant radiotherapy (76.9%) (Table1). Before starting the trastuzumab treatment, 21% of the patients exhibited arterial hypertension and 15.7% of patients had diabetes.

Amongst the study cohort, 35% of the patients (20 patients) presented with cardiotoxicity according to the predefined criteria, 14% of patients had drop of ejection

Table 1. Characteristics of patients and treatment.

Characteristics	Numbers	%
Age		
<40 years	13	25.2
>40 years	44	74.8
Menopausal Status		
premenopausal	32	56.4
postmenopausal	22	38.2
perimenopausal	3	5.4
Breast		
Right	22	38.2
Left	33	57.4
Bilateral	2	3.4
Tumour size		
T1	20	34.6
T2	30	51.9
T3	6	11.7
T4	1	1.8
Lymph nodes		
N0	22	8.2
N1	18	30.8
N2	6	11.7
N3	11	19.3
Stage		
I	10	17.3
II	30	51.9
III	17	30.8
Hormone receptor status		
Positive	34	58.8
Negative	23	41.2
Surgery		
MRM	44	76.9
Conservative	13	23.1
Chemotherapy		
Anthracycline+taxane	42	73.1
Anthracycline only	10	17.3
Taxane only	5	9.6
Radiotherapy		
Yes	44	76.9
No	13	23.1

fraction (EF) below 50%, whilst 10 % and 15% drop of LVEF below their baseline levels were found in 30% and 5% of patients, respectively (Table 2).

Amongst these 20 patients who experienced cardiotoxicity, 11 patients had drop of LVEF early (within the first 6 months) of trastuzumab therapy and 9 patients had drop of LVEF late (within the last 6 months) of trastuzumab therapy.

In this study, 98.3% of our patients have completed treatment, of whom 21% (12 patients) had a provisional discontinuation of trastuzumab because of fall in LVEF. In 11 patients, treatment was resumed after the recovery of LVEF, the median recovery time of LVEF was 21 days in both anthracycline containing regimen or not, five of these cases received pharmacological treatment with

Table 2. Characteristics of the LVEF decrease in patients with cardiotoxicity (n = 20).

Cardiotoxicity criteria	No. patients	Percentage of patients with cardiotoxicity (%)	Percentage of patient total (%)
LVEF decrease <50%	8	40	14
LVEF decrease >10 points below baseline	17	85	30
LVEF decrease > 15 points below baseline	3	15	5%

angiotensin-converting-enzyme inhibitors/angiotensin receptor antagonists. Definitive trastuzumab interruption was necessary in one patient (1.75%) because of the non-recovery of the ventricular function. This case had grade 2 HF according to the New York Heart Association (NYHA). A good clinical improvement was reached under medical treatment but her LVEF was 35% in her last follow up.

We explored different potential risk factors that may be associated with trastuzumab-related cardiotoxicity. Patients older than 40 years were more likely to develop cardio-toxicity compared to those younger than 40 years. This difference was statistically significant (70% vs. 32.4%, respectively, p = 0.042). However, other factors were not significantly associated with the development of cardiotoxicity including hypertension, diabetes, BMI (<25 vs. >25) and receiving radiotherapy or not. Noteworthy, there is no significant difference in the risk of cardiotoxicity according to the type of chemotherapy (anthracycline containing vs non-anthracycline based) (Table 2).

Discussion

Trastuzumab is the standard drug for treating patients with breast cancer that overexpress HER2 with the most adverse effect being cardiotoxicity. In the initial trials of trastuzumab in metastatic breast cancer, the incidence of cardio toxicity was variable, with rates for patients who received trastuzumab alone, trastuzumab and paclitaxel and trastuzumab plus an anthracycline and cyclophosphamide of 3–7%, 13%, and 27%, respectively [15,16]. Of note is that the rate of 27% cardio toxicity with concurrent anthracyclines was noted in patients who had received more than 300 mg/m^2 of doxorubicin concurrent with trastuzumab. On the basis of this data, the concomitant use of anthracyclines and trastuzumab was discouraged because of the greater risk of causing cardiotoxicity. Subsequently, several adjuvant clinical trials observed cardiotoxicity, which

Table 3. Risk factors in group with and without cardiac complications.

Risk factor	Group with no cardiac complications		Group with cardiac complications		P value
	%	Number	%	Number	
Age					
≥40	32.4	12	70	14	0.042
<40	67.6	25	30	6	
BMI					0.322
<25	43.6	16	25	5	
≥25	56.4	21	75	15	
Hypertension					0.323
Yes	24.3	9	45	9	
No	75.7	28	55	11	
Diabetes					0.127
Yes	13.5	5	45	9	
No	86.5	32	55	11	
Chemotherapy					
With anthracycline	91.8	33	95	19	1.000
Without anthracycline	8.2	4	5	1	
Concomitant radiotherapy					
Yes	54	20	75	15	0.323
No	46	13	25	5	

was considered acceptable [14,17-19]. Cardiac function was carefully monitored, but difference exists amongst the trials and how cardiotoxicity was defined. In general, these trials demonstrated that the risk of symptomatic congestive HF was low (0–3.9%); but reveal a much greater asymptomatic decreases (3–34%) in LVEF [20]. However, the cardiotoxicity incidence rate in the population of women receiving treatment outside of clinical trials is unknown. The current study provides insight into the common experience of trastuzumab use in real life situations common in oncology clinics. In this retrospective study, 57 patients with localised HER2-positive breast cancer treated with trastuzumab in the adjuvant setting were evaluated; 35% of the patients exhibited cardiotoxicity and nearly 21% required discontinuation of the medication because of cardiac complications. The incidence of left ventricular (LV) dysfunction in our study (35%) is consistent with that reported in the combined analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 (34%) [7], less than that reported by the Meryem Aitelhaj et al. (38%) [21] and higher than that reported in the Breast Cancer International Research Group (BCIRG) 006 trial (18%) [22] and the HERceptin Adjuvant (HERA) trial (7.1%) [9].

In our study, 21% of patients had to suspend trastuzumab treatment, whether temporarily or definitively, because of cardiotoxicity. In the McArthur and Chia study [23], the rate of treatment suspension because of cardiac dysfunction was 21.6%, which is higher than the number reported in the HERA clinical trial [24], less than that reported in the Meryem Aitelhaj, et al. (23%) [21] and closer to the rate shown by our patient's series. However, the same study shows that most of the patients who discontinued treatment were able to restart it after recovering their cardiac function; in our study, 11(98.3%) of the patients who interrupted treatment were able to restart it after recovering their cardiac function.

The cardiotoxicity of trastuzumab is always reversible such as that reported in other retrospective studies in adjuvant and metastatic setting [21,25,26]. Symptomatic HF events have been observed much less frequently than asymptomatic LV dysfunction. About 1.9% of trastuzumab-treated patients in BCIRG 006, 4% in NSABP B- 31 and 0.6% in the HERA trial reported severe symptoms of HF (NYHA III/IV) [7,9,21]. Tarantini et al. reported 3% symptomatic HF incidence in a cohort of 499 women with HER2-positive early breast cancer from 10 Italian institutions treated with trastuzumab observed retrospectively [27]. In our study, 1.75% of patients complained of symptomatic HF.

We found no differences in the prevalence of cardiovascular risk factors between the group of patients with and without cardiac complications; excepted age > 40 years, it was paradoxically higher in the group of patients who developed cardiotoxicity. As most women with breast cancer are above 40 years, it should be clear that age is one of many risk factors and should not be regarded as a criterion for clinicians, but in this group of patients, cardiac monitoring must be more optimised and regular.

The risk factors with trastuzumab-related cardiotoxicity are not fully explained. The most well-known independent risk factors are advanced age and previous exposure to anthracyclines [27]. In contrast, concurrent treatment with trastuzumab and adjuvant radiation therapy does not increase the risk [29].

In the NSABP B-31 and NCTTG N9831 trials, age of ≥ 50 years, requirement for hypertension medications, previous exposure to anthracyclines and LVEF at baseline < 55% were risk factors for HF in the course of trastuzumab treatment in univariate analysis [25,30]. Other risk factors identified by multivariate analysis are preexisting cardiac dysfunction (i.e. decreased LVEF), older age, high BMI, and antihypertensive therapy, whilst diabetes, valvular heart disease and coronary artery disease did not significantly increase the risk [18,30,31]. In the HERA trial, overweight and obesity were risk factors for cardio toxicity but age, hypertension, dyslipidaemia and previous heart disease did not increase the risk of trastuzumab-related cardiotoxicity [9]. In a large retrospective cohort study, the authors observed that anthracycline and trastuzumab were associated with increased HF [32].

When cardiotoxicity cannot be prevented by means of risk stratification, early detection becomes paramount to prevent irreversible cardiac damage. Several on going studies are focused on the investigation of advanced imaging techniques, such as multigated acquisition scans, echocardiogram with tissue velocity imaging, strain imaging and cardiac magnetic resonance imaging to better detect subclinical LV dysfunction [33]. In addition, several serum biomarkers of cardiotoxicity, including C-reactive protein, B-type natriuretic peptide, cardiac troponin I, interleukin 1 receptor-like 1 and neuregulin 1 [34], are also under investigation.

The limitations of our study are its small sample size and short follow-up. Despite these limitations, our results revealed that trastuzumab-related cardiotoxicity in a patient receiving treatment outside of clinical trials setting is slightly higher than that shown by clinical trial estimates but most instances are transient, asymptomatic and reversible.

References

[1] Hortobagyi GN, de la Garza SJ, Pritchard K, et al: The global breast cancer burden: variations in epidemiology and survival. Clin Breast Cancer 2005, 6:391–401.

[2] Albain KS, de la Garza SJ, Pienkowski T, et al: Reducing the global breast cancer burden: the importance of patterns of care research. Clin Breast Cancer 2005, 6:412–420.

[3] Slamon DJ, Clark GM, Wong SG, et al: Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177-182, 1987

[4] Slamon DJ, Godolphin W, Jones LA, et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707-712,1999

[5] Force T, Krause DS, Van Etten RA: Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007, 7:332–344.

[6] Perez EA, Romond EH, Suman VJ, et al: Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/ without trastuzumab in patients with HER2- positive breast cancer. J Clin Oncol 25:6s, 2007 (suppl 18S; abstr 512)

[7] Romond EH, Perez EA, Bryant J, et al: Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353: 1673-1684, 2005

[8] Slamon DJ, Eiermann W, Robert NJ, et al: Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel(ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2neu positive early breast cancer patients: BCIRG006 study. Cancer Res 69:500s, 2009 (abstr 62)

[9] Piccart-Gebhart MJ, Procter M, Leyland- Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672, 2005

[10] Smith I, Procter M, Gelber RD, et al: 2-Year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomized controlled trial. Lancet 369:29-36, 2007

[11] Hudis CA: Trastuzumab—mechanism of action and use in clinical practice. N Engl J Med 2007, 357:39–51.

[12] Yavas O, Yazici M, Eren O, Oyan B: The acute effect of trastuzumab infusion on ECG parameters in metastatic breast cancer patients. Swiss Med Wkly 2007, 137:556–558.

[13] Tsang W, Moe G. Trastuzumab and heart failure. Cardiol Rounds. 2007;8:1–6.

[14] Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV: Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a metaanalysis of published randomized trials. BMC Cancer 2007, 7:153.

[15] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344:783.

[16] Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002; 20:1215.

[17] Wysocki PJ, Hutka M: Cardiotoxicity of 5-fluorouracil in a young colorectal cancer patient – case report and review of literature. Arch Med Sci 2009, 5:277–280.

[18] McKeage K, Perry CM: Trastuzumab: a review of its use in the treatment of metastatic breast cancer overexpressing HER2. Drugs 2002, 62:209–243.

[19] Suter TM, Procter M, Van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, et al: Trastuzumab-associated cardiac adverse effects in the Herceptin Adjuvant Trial. J Clin Oncol 2007, 25:3859–3865.

[20] Telli M, et al: Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. JCO 2007, 25(23):3525–3533.

[21] Meryem Aitelhaj, Siham LKhouyaali, Ghizlane Rais, Amina Mohtaram,et al: Cardiac safety of the adjuvant Trastuzumab in a Moroccan population: observational monocentric study of about 100 patients. BMC Research Notes 2013, 6:339

[22] Slamon D, Eiermann W, Robert N: 006 oboB BCIRG 006:2nd interim analysis chase III randomised trial comparing doxorubicine and cyclophosphamide followed by docetaxel (AC/T) with doxorubicine and cyclo phosphamid followed by docetaxel and trastuzumab (AC/ETH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. In Proceedings of San Antonio breast cancer symposium (SABCS). San Antonio: Breast Cancer Research and Treatment; 2006.

[23] McArthur HL, Chia S: Cardiotoxicity of trastuzumab in clinical practice. N Engl J Med 2007, 357:94–95.

[24] Montemurro F, Redana S, Valabrega G, Martinello R, Aglietta M, Almiero R: Trastuzumab-related cardiotoxicity in the herceptin dyuvant trial.J Clin Oncol 2008, 26:2052–2053.

[25] Tan-Chiu E, Yothers G, Romond E, et al: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in nodepositive, human epidermal growth factor receptor 2-over - expressing breast cancer: NSABP B-31. J Clin Oncol 2005, 23:7811–7819.

[26] Ewer MS, Vooletich MT, Durand JB, et al: Reversibility of trastuzumab related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005, 23:7820–7826.

[27] Wadhwa D, Fallah-Rad N, Grenier D, et al: Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. Breast Cancer Res Treat 2009, 117:357–364.

[28] Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK: Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. Mayo Clin Proc 2008, 83:197–203.

[29] Gluba A, Pietrucha T, Banach M, Piotrowski G, Rysz J: The role of polymorphisms within paraoxonases (192 Gln/Arg in PON1 and 311Ser/Cys in PON2) in the modulation of cardiovascular risk: a pilot study. Angiology 2010, 61:157–165.

[30] Perez EA, Suman VJ, Davidson NE, et al: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the NorthCentral Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008, 26:1231–1238.

[31] Pentassuglia L, Graf M, Lane H, et al: Inhibition of ErbB2 by receptor tyrosine kinase inhibitors causes myofibrillar structural damage without cell death in adult rat cardiomyocytes. Exp Cell Res 2009, 315:1302–1312.

[32] Bowles A: Risk of heart failure in breast cancer patients after anthracyclines and Trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012, 104:1293–1305.

[33] Tocchetti C., Ragone G., Coppola C, et al: Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. Eur J Heart Fail 2012,14: 130–137 .

[34] Braden A., Stankowski R., Engel J., et al: Breast cancer biomarkers: risk assessment, diagnosis, prognosis, prediction of treatment efficacy and toxicity, and recurrence. Curr Pharm Des 25 November 2013 (Epub ahead of print).