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 HER2-overexpressed localised breast cancer. It is generally well tolerated, with a low incidence of adverse effects.

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 trastuzumab • Breast cancer

© De Gruyter Open
Cardiotoxicity of the adjuvant trastuzumab in a Saudi population: clinical experience of a single institution

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

[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 Abdullah 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 trastuzumab.

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/m²), 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
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 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 cardiotoxicity 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/m² 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
Cardiotoxicity of the adjuvant trastuzumab in a Saudi population: clinical experience of a single institution

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].

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

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Group with no cardiac complications %</th>
<th>Group with cardiac complications %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>32.4</td>
<td>70</td>
<td>0.042</td>
</tr>
<tr>
<td>&lt;40</td>
<td>67.6</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>43.6</td>
<td>25</td>
<td>0.322</td>
</tr>
<tr>
<td>≥25</td>
<td>56.4</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24.3</td>
<td>45</td>
<td>0.323</td>
</tr>
<tr>
<td>No</td>
<td>75.7</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.5</td>
<td>45</td>
<td>0.127</td>
</tr>
<tr>
<td>No</td>
<td>86.5</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With anthracycline</td>
<td>91.8</td>
<td>95</td>
<td>1.000</td>
</tr>
<tr>
<td>Without anthracycline</td>
<td>8.2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Concomitant radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>75</td>
<td>0.323</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
When cardiotoxicity cannot be prevented by means of risk stratification, early detection becomes paramount to prevent irreversible cardiac damage. Several ongoing 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


