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Comparing trastuzumab-related cardiotoxicity between elderly and younger patients with breast cancer: a prospective cohort study

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Abstract. – OBJECTIVE: Trastuzumab is an HER-2 targeted humanized monoclonal antibody that significantly improves metastatic and non-metastatic breast cancer therapeutic outcomes. This study compares trastuzumab outcomes between two age cohorts in the Kuwait Cancer Control Centre (KCCC).

PATIENTS AND METHODS: In a prospective comparative observational study, 93 HER-2 positive breast cancer patients undergoing different chemotherapy protocols + trastuzumab between April 2016 and April 2019 were included and divided into two cohorts based on their age (<60 and ≥60 years old). The individual decline in the LVEF from the baseline was calculated and compared between the two age cohorts. Logistic regression analysis was applied to investigate the association between age, comorbidities, BMI, anthracycline treatment, and baseline LVEF value, and trastuzumab-induced cardiotoxicity after adjustments made for the disease stage.

RESULTS: The median baseline LVEF was 65% in both age cohorts (IQR 8% and 9% for older and younger patients, respectively). Whereas the median LVEF post-trastuzumab treatment was 51% and 55% in older and younger patients, respectively (IQR 8%; *p*-value = 0.22), even though older patients had significantly lower exposure to anthracyclines compared to younger patients (60% and 84.1%, respectively; *p*-value <0.001). 86.7% and 55.6% of older and younger patients, respectively, developed ≥10% decline in their LVEF from the baseline. Statistically, age was the only factor that significantly correlated with developing ≥10% decline in the LVEF (OR 4; *p*-value <0.012).

CONCLUSIONS: Breast cancer patients aged 60 years and above in Kuwait were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline value compared to younger patients during trastuzumab treatment. Previous exposure to anthracyclines and comorbidities were not associated with a significantly increased cardiotoxicity risk in this study.

Key Words:
Trastuzumab, Cardiotoxicity, Breast cancer, Chemotherapy.

Introduction

Trastuzumab is a humanized monoclonal antibody that targets the human epidermal growth factor receptor-2 (HER-2)[1]. Around 15-30% of breast cancer patients exhibit overexpression of HER-2[2]. This molecular feature is associated with more aggressive breast tumors and is considered an independent prognostic factor of the disease[2]. Previous studies[3,4] reported a 24-58% improvement in the 4-year disease-free survival and 23-35% in the 5-year overall survival among eligible non-metastatic breast cancer patients after introducing trastuzumab treatment. Also, trastuzumab improved the therapeutic outcomes and disease progression in metastatic patients. As a result, trastuzumab became the standard of care in HER-2 positive breast cancer management[5]. Even though trastuzumab is considered well-tolerated, it is associated with an increased risk of cardiotoxicity[6]. A recently published population-based study of cardiovascular disease (CVD) mortality risk among 3,234,256 patients with 28 cancer types in the USA who were registered in the Surveillance, Epidemiology and End Results (SEER) program between 1973-2012 showed that 38% and 11% mortality cases occurred during this period due to cancer and cardiovascular dis-

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eases respectively[7]. This study raised concerns about the increased prevalence of CVD-related mortality among cancer patients. According to the HERA, BCIRG-006, NSABP B-31, Intergroup N9831, and Finnish FinHer trials, patients who received trastuzumab had a 2.45-fold higher risk of cardiotoxicity when compared to patients who did not receive trastuzumab[8].

The clinical presentation of the cardiotoxicity can range from an asymptomatic decline in myocardial function to a full clinical picture of congestive heart failure (CHF)[9]. Previous studies[10,11] suggested that cardiotoxicity can be precipitated during chemotherapy (early-onset), leading to discontinuation of the treatment or many years after completing the treatment (late-onset). The exact mechanism of trastuzumab cardiotoxicity is not well understood; however, different pathways have been described in the literature. The main role of trastuzumab is binding to the tumour sites that overexpress HER-2 receptors and attracting the immune cells to the binding sites, which triggers antibody-dependent cellular toxicity (ADCC)[12]. Also, it has been suggested that interference with HER-2 function leads to an accumulation of reactive oxygen species within the cardiomyocytes and triggers a subsequent oxidative stress reaction that is likely to play a major role in the development of cardiac dysfunction[13]. Also, trastuzumab has been shown to inhibit MAPK and PI3K/Akt pathways, which has an important role in the suppression of breast tumours growth, proliferation, and survival signaling pathways[9].

The risk of cardiotoxicity increases if trastuzumab is co-administered with other potential cardiotoxic chemotherapeutic drugs such as anthracyclines[14]. Unlike anthracyclines, trastuzumab-induced cardiotoxicity is usually reversible, not dose-related, and re-challenge is usually well tolerated[15]. Other risk factors correlated with increased risk of cardiotoxicity include low baseline Left Ventricular Ejection Fraction (LVEF) and chronic comorbidities such as hypertension, ischemic heart disease, and renal dysfunction[16,17]. A single study[18] suggests that diabetes increases the risk of trastuzumab-induced cardiotoxicity through the chronic oxidative stress reaction pathways. Besides, age is considered a potential risk factor of cancer treatment-related toxicities because some older adults have different pharmacokinetic and pharmacodynamic responses to medication compared to younger adults due to physiological changes in body organs function and regulatory systems[19]. This includes cardiovascular, renal, hepatic, and gastrointestinal systems. Also, advanced age is associated with changes in body composition manifested by decreased body water, increased body fat, and decreased body mass[20]. These changes can significantly impact the volume distribution and bioavailability of many drugs, consequently changing their efficacy and/or safety profiles[21]. Unfortunately, there is currently a lack of evidence-based information about trastuzumab treatment outcomes in older patients with cancer.

The USA National Cancer Institute (NCI) defines cardiotoxicity as the 'toxicity that affects the heart', which can occur directly as a consequence of drugs side effects or indirectly due to physiological alteration in the haemodynamic flow or thrombosis[22]. The most commonly occurring treatment induced cardiotoxicity is myocardial-dysfunction. In clinical practice, the LVEF is an accepted measure of systolic cardiac function and an indicator of prognosis[23]. The most commonly used method to assess the LVEF is 2D echocardiography, although newer techniques such as 3D echocardiography, cardiac magnetic resonance (CMR) imaging, and speckle tracking to assess myocardial dysfunction are gaining popularity in the field of cardiac imaging[24-26]. There is no solid evidence supporting routine monitoring of cardiac biomarkers such as troponins and brain natriuretic peptides (BNP) to predict cardiotoxicity in asymptomatic patients; however, these markers should be considered in cases of high-risk patients, a significant decline in LVEF, or the presence of new CHF symptoms[27].

Consensus on the definition of cancer treatment induced cardiotoxicity has not been reached. However, major societies agree on >10% decline in LVEF from baseline study as a definition of cardiotoxicity, while the lower limit value of LVEF used to define cardiotoxicity is still controversial[28-30]. According to the European Society for Medical Oncology (ESMO) recent recommendations, any patient with baseline LVEF <50% will be commenced on cardioprotective therapy[29]. A decrease in LVEF >10% with LVEF <50%, an absolute decrease >20%, or presence of symptoms of heart failure, would require clinical interventions. This includes temporary withholding of cardiotoxic treatment, referral to cardio-oncology, commencing cardioprotective medications, and/or switching alternative non-cardiotoxic treatment[29].

There is a lack of prospective papers evaluating and comparing trastuzumab tolerance between older and younger patients with breast

cancer. Therefore, we conducted a prospective clinical study to monitor patients receiving potential cardiotoxic treatment and identify the factors significantly associated with trastuzumab-induced cardiotoxicity.

Patients and Methods

In a comparative prospective observational study, a total of 93 breast cancer patients were included and divided into two cohorts according to their age (<60 years or ≥60 years). The principal characteristics of patients included were newly diagnosed HER-2 positive breast cancer patients who were aged 21 years and above, and candidates for trastuzumab ± chemotherapy who could communicate in either Arabic or English. All patients provided informed consent to allow retrieving their medical notes during our study period. On the other hand, patients excluded were those not eligible for trastuzumab, those who received trastuzumab before or preferred to be treated outside Kuwait. In addition, we excluded patients with a previous history of tumours, incomplete follow-up, and pregnant patients. Research approval was obtained from the research committee in the Ministry of Health (MOH) of Kuwait on the 26th of October, 2015 (number 303/2015). Data were collected between April 2016 and April 2019 from the medical oncology department at the Kuwait Cancer Control Centre (KCCC) in Kuwait.

Data was collected and documented manually in individualized data collection forms using individual patients; case notes. Baseline comorbidities were scored as absent or present using Charlson Comorbidity Index (CCI)[31]. Based on clinical recommendations by major oncology societies, the baseline LVEF was documented before starting potential cardiotoxic chemotherapeutic drugs (anthracyclines and/or trastuzumab) and monitored every three months during trastuzumab therapy. Occasionally, LVEF assessment was urgently requested for patients with symptoms of CHF. A significant decline in the LVEF was confirmed by repeated echocardiography within two to three weeks in the cardiology clinic.

In accordance with the ESMO guidelines, we defined cardiotoxicity in our study as ≥10% decline in the LVEF from the baseline to investigate the factors that were statistically correlated with a clinically significant decline in the LVEF during cancer treatment. Patients were further stratified based on individual LVEF value (<50% or ≥50%) during trastuzumab treatment for clinical significance (Figure 1). The subgroup of patients with ≥10% decline in their LVEF from the baseline and reached LVEF values <50% were analyzed separately. Besides, the impact of baseline LVEF on treatment-induced cardiotoxicity was investigated. The results were compared between the two age cohorts.

The primary outcome of this research was to investigate whether advanced age was an independent risk factor of trastuzumab-induced cardiotoxicity or not. The secondary outcome was identifying the factors statistically correlated with trastuzumab-induced cardiotoxicity manifested by a significant decline (≥10%) in the LVEF from the baseline. Besides, investigating the impact of the baseline LVEF value on reaching a post-treatment LVEF value below the lower limit of acceptable LVEF function (50%) in older and younger patients with breast cancer. In addition, we documented the consequent intervention of either withholding treatment (temporary discontinuation and re-challenge) or discontinuing treatment permanently to compare treatment tolerance between the two age cohorts.

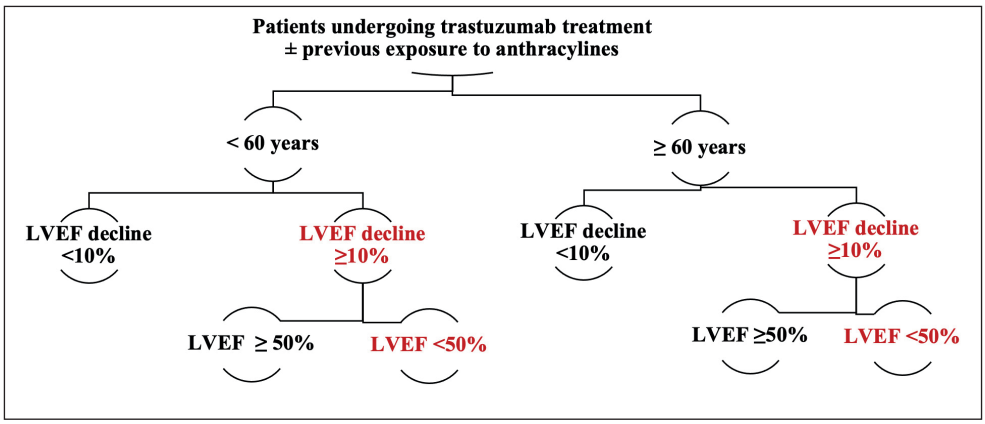

Figure 1. Patients' stratification based on their LVEF decline from the baseline and LVEF value during trastuzumab treatment in the two age cohorts.

Statistical Analysis

Descriptive analysis was performed using Microsoft Excel™ in 2016 and Stata version 16. Binary and categorical descriptive variables were expressed using percentage, while continuous variables were expressed using the median. In addition, the range and interquartile range (mid-spread) were calculated to show statistical dispersion. Regression analyses were performed to investigate the association between the baseline predisposing factors and treatment-related cardiotoxicity. The impact of patients' age on treatment-related cardiotoxicity was calculated using multivariate logistic regression analysis with adjustments made for performance status, comorbidities, and disease stage as these variables were expected to impact the therapeutic outcomes from a clinical point of view considering a *p*-value <0.05 as statistically significant.

Results

A total of 93 patients matched our criteria (63 younger and 30 older patients). The baseline characteristics showed that older patients had a higher comorbidity burden compared to younger patients. On the other hand, younger patients had higher previous exposure to anthracycline treatment (Table I). The median duration of patients' follow-up from diagnosis was 23 months (IQR= 8.2).

On diagnosis, no statistical differences were detected in the tumor metastases status between the two age cohorts. The majority of cases were non-metastatic and accounted for 93.3% and 81% of older and younger patients, respectively (*p*-value 0.11). However, based on the TNM scoring system, a higher rate of early-stage breast cancer (stage II) was detected in the older age cohort when compared to the younger age cohort [40% and 22.2% respectively; *p*-value = 0.046].

The baseline LVEF values did not differ by age cohort (median= 65%, IQR= 9% and 8% for older and younger patients respectively; *p*-value = 0.59). Whilst post-treatment LVEF levels were slightly lower in the older patients, this was statistically insignificant among older patients compared to younger patients (median= 55% and 51% respectively, IQR= 8%; *p*-value = 0.22), even though younger patients had higher overall exposure to potentially cardiotoxic treatment (anthracycline) prior to trastuzumab therapy (84.1% and 60% of younger and older patients, respectively; *p*-value <0.001).

During trastuzumab treatment, the individual decline in LVEF from the baseline value was calculated, and the outcome values were categorized as either <10% or ≥10% decline (Table I). The consequent intervention of either with-holding treatment (temporary discontinuation and re-challenge) or permanent discontinuing treatment was documented to compare treatment tolerance between the two age cohorts. Overall, 34.4% of patients from both age cohorts had a clinically insignificant (<10%) decline in their LVEF from the baseline value indicating good tolerance to treatment. Younger patients showed better tolerance to trastuzumab than older patients (44.4% and 13.3%, respectively; *p*-value <0.001), even though they had higher overall exposure to anthracycline prior to trastuzumab therapy (81% and 60% of younger and older patients, respectively; *p*-value <0.001). On the other hand, a clinically significant decline (≥10%) in the LVEF was documented in 65.6% of patients receiving trastuzumab combining both age cohorts. Older patients had a significantly higher rate of LVEF decline compared to younger patients (86.7% and 55.6%, respectively; *p*-value <0.001). As a result, the subsequent requirement for treatment intervention of with-holding or discontinuing trastuzumab treatment was relatively higher among the older age cohort.

The intervention was dependent on individual LVEF values and/or the existence of clinical symptoms of congestive heart failure rather than the percentage decline in the LVEF from the baseline value. Among patients who had ≥10% decline, 73.1% (n=19) and 71.4% (n=25) of older and younger patients, respectively, maintained acceptable LVEF (≥50%) and completed their treatment (Figure 2). Among those patients, 11.8% (n=11: six older and five younger patients) had LVEF values equal to 50% during the first six months of treatment. Therefore, they discontinued trastuzumab for 1-2 months and received a cardio-protective drug such as an Angiotensin-Converting Enzyme Inhibitor (ACE-I) or Beta Blocker (BB). Trastuzumab treatment was re-started (re-challenged) after restoring clinically accepted LVEF levels (≥55%). Among those, none of the patients developed clinical symptoms of CHF.

Only 18.3% (n=17) of patients developed ≥10% decline and reached LVEF values <50% combining both age cohorts. Statistical analyses of this subgroup of patients showed that the distribution was not significantly different by age cohort (23.3% and 15.9% in older and younger patients, respectively; *p*-value= 0.2;

Table I. Descriptive statistics of patients' cohorts.

	Patient	Group 1 <60 yrs n= 63	Group 2 ≥60 yrs n= 30
	Age (years)		
	Median	45	65
	*IQR	14	8
	Range	(22-59)	(70-83)
	****BMI (kg/m^2)***		
	Median	28	28.5
	IQR	7	11
	Range	(20-45)	(22-42)
	BMI category n (%)		
	<18.5	0	0
	18.5- 24.9	18/63 (28.6%)	6/30 (20%)
	25- 29.9	18/63 (28.6%)	10/30 (33.3%)
	≥30	27/63 (42.86%)	14/30 (46.67%)
	Baseline hemoglobin level (g/dL)		
	Median	12	11.85
	IQR	1.1 (11.5-12.6)	1.5 (11-12.5)
	Range	(9.4-14)	(10-13.8)
	Comorbidities		
	Patients with ≥1 comorbidity n (%)	32/63 (50.79%)	26/30 (86.8%)
	Patients with ≥3 comorbidities n (%)	2/60 (3.17%)	10/30 (33.3%)
Patient Characteristics	***Medical history***		
	Hypertension n (%)	13/63 (20.6%)	18/30 (60%)
	Diabetes mellitus n (%)	9/63 (14.3%)	15/30 (50%)
	Dyslipidaemia n (%)	3/63 (4.8%)	7/30 (23.3%)
	Ischemic heart disease n (%)	–	1/30 (3.3%)
	Renal dysfunction n (%)	1/63 (1.6%)	3/30 (10%)
	Hepatic dysfunction n (%)	–	1/30 (3.3%)
Tumor Characteristics	***Status of metastases***		
	Non-metastatic cases n (%)	51/63 (81%)	28/30 (93.3%)
	Metastatic cases n (%)	12/63 (19%)	2/30 (6.7%)
	****TNM stage n (%)***		
	II	14/63 (22.2%)	12/30 (40%)
	III	37/63 (58.7%)	16/30 (53.3%)
	IV	12/63 (19%)	2/30 (6.7%)
	Exposure to anthracycline	53/63 (84.1%)	18/30 (60%)
****LVEF Monitoring During Trastuzumab Treatment**	***Decline in the LVEF n (%)***		
	<10%	28/63 (44.4%)	4/30 (13.3%)
	≥10%	35/63 (55.6%)	26/30 (86.7%)
	No intervention n (%)	48/63 (76.2%)	17/30 (56.7%)
	Intervention n (%)		
	With-hold Trastuzumab	9/63 (14.3%)	8/30 (26.7%)
	Discontinue Trastuzumab	6/63 (9.5%)	5/30 (16.7%)

Figure 3). Permanent trastuzumab treatment discontinuation occurred in 11.8% (n=11) of patients combining both age cohorts, representing 16.7% (n=5) of older and 9.5% (n=6) of younger patients who were not considered eligible for a re-challenge following cardioprotective therapy. Otherwise, treatment was re-initiated and completed. Only one patient from the younger age cohort had clinical symptoms of CHF, while all other patients were asymptomatic.

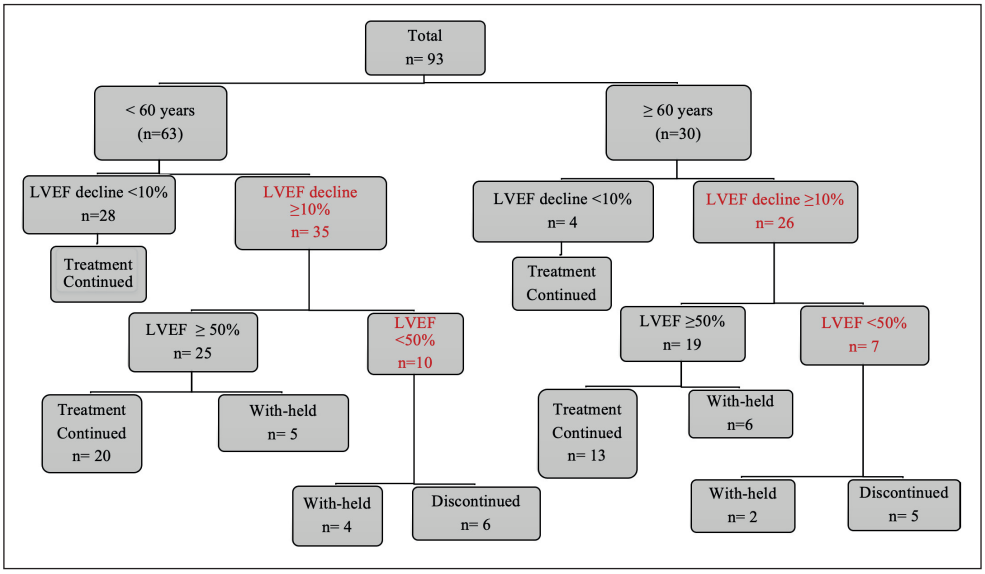

Figure 2. Comparing the incidence of LVEF decline (<10% or ≥10%) from the baseline value between younger and older breast cancer patients undergoing trastuzumab treatment and the clinical intervention of withholding or discontinuing treatment

In subgroup analyses of patients who maintained clinically accepted LVEF values (≥50%), despite the percentage decline from baseline LVEF, no statistical differences were detected in the patients' distribution between the two age cohorts (82.5% and 76.7% in younger and older patients, respectively, *p*-value= 0.4; Figure 4).

In subgroup analyses of patients who had ≥10% decline in their LVEF, the proportions of patients who reached values below normal ranges (<50%) and who maintained acceptable LVEF values (≥50%) were approximately equally distributed between the two age cohorts, representing 73% and 71% of older and younger patients respectively. Similarly, among patients who developed ≥10% decline in their LVEF from the baseline value, the proportion of patients who reached an LVEF value below normal ranges (<50%) was comparable between the two age cohorts (27% and 29% in older and younger patients, respectively, *p*-value= 0.88). Overall, age was not correlated with developing LVEF below normal ranges among patients who developed ≥10% decline during trastuzumab treatment.

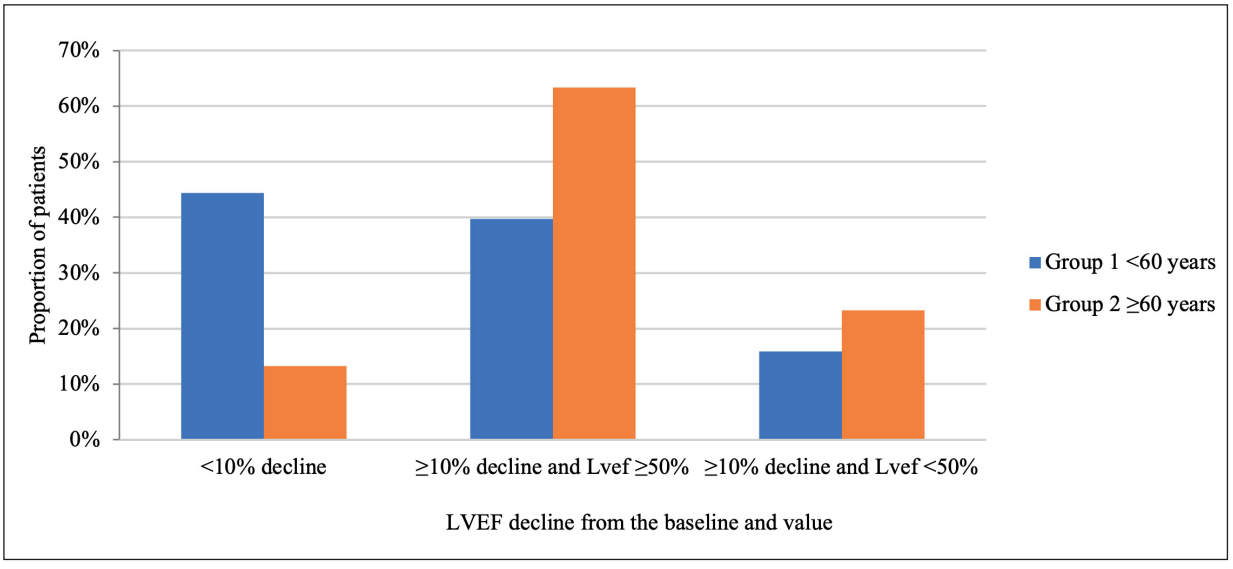

Figure 3. Comparing the decline in the LVEF from the baseline value (<10% or ≥10%) and the LVEF value (<50% or ≥50%) during trastuzumab therapy between the two age cohorts.

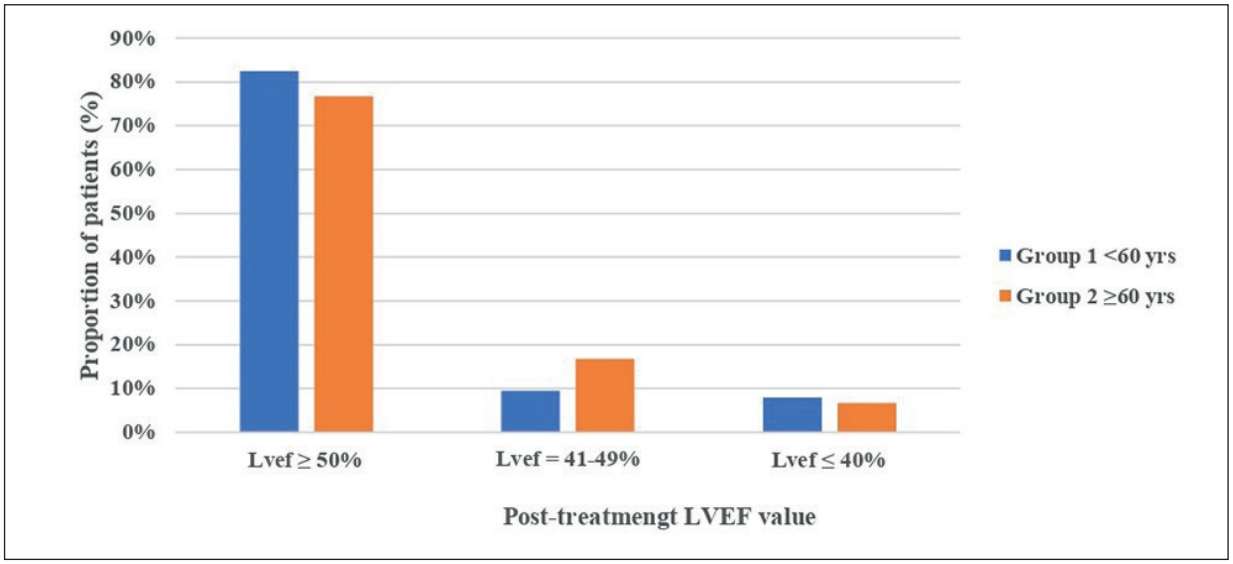

Figure 4. Comparing post-treatment LVEF value documented for patients undergoing trastuzumab treatment between the two age cohorts.

Investigating the Risk Factors Correlated with Treatment-Induced Cardiotoxicity

In a simple descriptive comparison of the baseline characteristics of older and younger patients who developed ≥10% decline in their LVEF from the baseline value, the median baseline LVEF was 65% in both age cohorts with comparable interquartile ranges (IQR=9% and 8% in older and younger patients, respectively). The median Body Mass Index (BMI) difference was statistically insignificant between the two age cohorts. The prevalence of baseline comorbidities was significantly higher among older patients compared to younger patients (84.6% and 51%, respectively; *p*-value <0.001). Hypertension was reported in 65.4% and 20% of older and younger patients, respectively (*p*-value <0.001). Similarly, diabetes was reported in 48% and 17.1% of older and younger, respectively (*p*-value <0.001). None of the patients from the two age cohorts had a history of ischemic heart disease. Only two patients from the older age cohort had a history of pulmonary embolism.

Potential cardiotoxic drugs documented in our study were previous exposure to anthracycline treatment and/or concomitant administration of taxanes. Our data showed that all patients from both age cohorts received paclitaxel concomitantly with trastuzumab except for two patients from the older age cohort who received targeted monotherapy. Younger patients had significantly higher exposure to anthracycline treatment prior to trastuzumab treatment (81% and 60% of younger and older patients, respectively; *p*-value <0.001). Among those patients, 77% and 54.9% of older and younger patients developed a ≥10% decline in their LVEF from the baseline.

The only difference detected in the baseline characteristics between older and younger patients who developed a significant decline in their LVEF during trastuzumab treatment was a higher prevalence of comorbidities among older patients. On the other hand, a higher exposure to anthracycline treatment prior to trastuzumab was detected among younger patients. A logistic regression analysis was conducted to determine the baseline factors associated with increased risk of trastuzumab-induced cardiotoxicity, defined as developing a clinically significant decline (≥10%) in the LVEF from the baseline value. The analysis included age, BMI, comorbidities, and previous exposure to anthracycline treatment (Table II).

Our data analysis showed that age was the only factor significantly associated with treatment-induced cardiotoxicity. Older patients were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline than younger patients. In contrast to what was expected, previous exposure to anthracycline treatment, having multiple comorbidities at baseline, and history of hypertension or diabetes were not associated with increased risk of cardiotoxicity based on our model selection.

Impact of Baseline LVEF

The impact of baseline LVEF values was investigated separately to be correlated with treatment-induced cardiotoxicity. The continuous

Table II. Investigating the factors that are correlated with ≥10% decline from the baseline LVEF among breast cancer patients undergoing trastuzumab treatment.

Factors	Odds Ratio	CI (95%)	*p*-value
Age	4	1.35-1.86	0.012
BMI	0.98	0.91-1.05	0.57
Comorbidities score ≥3	3.1	0.63-15.22	0.16
History of hypertension	1.54	0.61-3.93	0.36
History of diabetes	1.93	0.68-5.5	0.22
Anthracycline treatment	0.44	0.16-1.26	0.13

LVEF values were categorized into two groups (≥60% or <60%) for clinical significance, as 60% is considered the midpoint of the normal LVEF range (50-70%). A logistic regression analysis was conducted to investigate the correlation between baseline LVEF category and developing ≥10% decline from the baseline value or reaching a value below normal ranges (<50%).

The LVEF baseline category was not correlated with developing ≥10% decline during trastuzumab treatment (*p*-value=0.15). However, patients with baseline LVEF values less than 60% were less likely to maintain LVEF within normal ranges (*p*-value=0.002). For demonstration, a subgroup analysis was conducted among younger patients who reached LVEF value <50% during trastuzumab treatment, and data showed that those patients had a median baseline LVEF of 58% (IQR 7, range 50%-65%). In comparison, patients who maintained LVEF value ≥50% had a median baseline of 65% (IQR 7, range 56%-75%). Therefore, the baseline LVEF may not contribute to developing ≥10% decline during cardiotoxic treatment but still may result in a value below normal ranges <50% that is considered treatment-induced cardiotoxicity.

Discussion

The present study showed that ≥10% decline in the LVEF from the baseline value occurred in 65.6% of patients combining the two age cohorts, representing 55.6% and 86.7% of younger and older patients, respectively. However, only 18.3% of patients reached a value below accepted LVEF limits (<50%), with no statistical difference in patients' distribution by age cohorts. Baseline characteristics, including age, BMI, comorbidity score of ≥3, history of hypertension or diabetes, baseline LVEF value, and previous exposure to anthracycline treatment, were investigated as potential predisposing factors of cardiotoxicity. Age was associated with a 4-fold higher risk of developing ≥10% decline in the LVEF from the baseline during trastuzumab treatment. Also, a baseline LVEF value <60% was significantly associated with reaching LVEF value below normal ranges (<50%). Statistically, patients who started chemotherapy with a baseline LVEF value below 60% were 81% less likely to maintain LVEF within normal ranges. Other factors failed to be correlated with treatment-induced cardiotoxicity.

Alghafar et al[30] reported relatively comparable results in a retrospective population-based study conducted in Oman, which also lies in the same gulf region. Their data showed that 24% of patients developed ≥10% decline in the LVEF from the baseline and reached a value below <50%. Also, a relatively comparable incidence was reported in a prospective descriptive observational study among 1065 Uruguayan breast cancer patients[31]. Among those, 75% experienced ≥10% decline in the LVEF from the baseline; however, only 9.7% reached a value below <50%. These findings were within the range of reported international data but higher than what was initially reported in controlled clinical trials[32]. Unlike clinical practice, patients recruited in clinical trials were highly selected, excluding patients with advanced age, multiple comorbidities, or receiving cardioprotective drugs. As a result, the potential cardiotoxicity risk decreases among selected patients.

Although advanced age was associated with a higher proportion of patients developing ≥10% decline in their LVEF from the baseline value, this did not contribute to high proportions of patients reaching LVEF values below normal ranges (LVEF <50%) compared to younger patients. Older patients had a relatively higher rate of temporary trastuzumab discontinuation; however, a cardio-protective drug such as an Angiotensin-Converting Enzyme Inhibitor (ACE-I) or

Beta Blocker (BB) was prescribed, and trastuzumab treatment re-initiated (re-challenged) after restoring clinically accepted LVEF levels (≥55%). Consequently, the proportion of patients who had permanent trastuzumab treatment discontinuation was not statistically different between the two age cohorts.

Besides advanced age, chronic comorbidities were considered as predisposing factors for cancer treatment-related cardiotoxicity in the literature. Onitilo et al[33] suggested that diabetes-related chronic oxidative stress reaction pathways contribute to the trastuzumab-induced cardiotoxicity. Also, hypertension and renal dysfunction were considered risk factors for cardiovascular diseases and treatment-induced cardiotoxicity. In addition to the previously discussed risk factors, a few studies correlated obesity with increased cardiotoxicity risks[34,35]. In contrast to what has been published, data from the present study showed that the event of cardiotoxicity was not correlated with multiple baseline comorbidities, history of hypertension or diabetes, or BMI[30]. Besides, none of the patients who developed cardiotoxicity had a history of ischemic heart disease (IHD). Surprisingly, the only two patients who had a history of IHD maintained acceptable LVEF value during trastuzumab treatment indicating good tolerance. These findings were consistent with the Omani population-based study.

In contrast to what has been reported in all previous studies, exposure to anthracycline treatment was not correlated with cardiotoxicity in the present study. Some articles suggested that genetic predisposition increases the sensitivity of anthracycline-related cardiotoxicity in some patients[36,37]. Lack of genetic predisposition could be the case in the present study population, but this could not be confirmed. More studies are required to validate applying genetic testing in clinical practice as it will dramatically enhance the prescribing pattern in managing breast cancer patients despite age. Also, probably the number of patients receiving anthracycline treatment was insufficient to detect the impact of anthracycline exposure on treatment-related cardiotoxicity. It is anticipated that including a larger number may alter the results.

Treatment-induced cardiotoxicity contributed to an 11.8% rate of trastuzumab treatment permanent discontinuation in Kuwait, which was relatively higher than rates reported in the literature. According to the Swiss Cardiovascular Centre experience, trastuzumab discontinuation occurred in only 4.3% of patients[38]. The international multicentre HERA trial reported a 3.6% rate of trastuzumab treatment discontinuation[39]. Besides, the Uruguayan population-based study reported a 7.4% rate of trastuzumab treatment discontinuation. The relatively higher rate of trastuzumab discontinuation reported in the present study was not always attributed to a failure in achieving accepted LVEF level during cardioprotective treatment, but because 4.3% of patients had rapidly progressive disease and very poor quality of life. As a result, patients were considered ineligible for treatment re-challenge and being exposed to additional cardiac complications. Among those, 2.2% had their active cancer treatment discontinued without re-challenge and transferred to receive palliative treatment in the Palliative Care Center (PCC).

Conclusions

Overall, breast cancer patients aged 60 years and above in Kuwait were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline value than younger patients during trastuzumab treatment. Previous exposure to cardiotoxic treatment and comorbidities may be potential but were not significant risk factors of treatment-induced cardiotoxicity in the present study. Trastuzumab treatment was not associated with a significantly higher risk of treatment discontinuation among older breast cancer patients when compared to younger patients as they showed acceptable tolerance under regular LVEF monitoring and appropriate cardioprotective interventions when indicated.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

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