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Cardiotoxicity among Patients Using Pertuzumab, Trastuzumab and Taxane with HER2-Positive Early-Stage Breast Cancer: A Single-Centre Experience

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Authors' contributions

This work was carried out in collaboration among all authors. Study conception, design, supervision, methodology, data curation, Formal analysis, Writing – original draft done by author ASA. Authors AAA, ATT, LEM, NFA and SSA did the data collection, analysis, interpretation of results, draft manuscript preparation. Author MR did the investigation, data curation, formalanalysis. Author MAF Study conception, design, supervision, data curation done by Author MAF. All authors read and approved the final manuscript.

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ABSTRACT

Aim: In this study, we aimed to investigate the incidence rate, risk factors, and mortality rates in patients with early-stage breast cancer using anti-HER2 (Human epidermal growth factor receptor-2) treatment.
Patients and Methods: A total of 106 patients diagnosed with human epidermal growth factor 2 (HER2)-positive early-stage breast cancer and receiving anti-HER2 treatment at King Abdulaziz Medical City (KAMC) from 2015 to 2019 were included in the analysis to assess the incidence of

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cardiotoxicity was collected as a retrospective study. Univariate and multivariate analyses as well as multiple exact logistic regression analysis were conducted to understand the relationships between the left ventricular ejection fraction (LVEF) and treatment combinations and comorbidities
Results: The LVEF measurements using an echocardiography method at the baseline (before any treatment) and during the anti-HER2 therapy were assessed. The results suggest that the higher the drug combination, the higher the odds ratio for the declined ejection fraction (EF) patient group. Further, patients treated with the pertuzumab and trastuzumab combination were four times more likely to have a decline in their EF than those who did not use the pertuzumab and trastuzumab drug combination (OR 4.28, 95% CI [1.68–10.91]).
Conclusion: This study demonstrated that the drug combination considered here is associated with reduced LVEF and, similarly, comorbidities were also related to EF. However, a larger study in a global patient population will confirm the present observations.

Keywords: HER2; cardiotoxicity; breast cancer; chemotherapy; left ventricular ejection fraction.

1. INTRODUCTION

Cancer is the most prevalent cause of death globally among non-communicable diseases. Breast cancer is the second most common form of cancer [1,2] and is categorised based on its aetiology, molecular features, clinical conditions and other factors. For clinical diagnosis and treatment, breast cancer is largely classified according to the receptors, such as estrogen receptor, progesterone receptor and human epidermal growth factor 2 (HER2) receptors. The prevalence of specific hormone receptor–based breast cancer varies globally. Reports suggest that such variation of the receptor (estrogen/progesterone), positive or negative, varies depending on the geographical region and ethnic group [3,4]. Breast cancer is the most diagnosed cancer in women in Saudi Arabia, with a prevalence of 21.8% [2]. The mortality rate due to breast cancer is high and is experiencing an increasing trend [5]. In 2020, diagnosed breast cancer patients were an estimated 2.3 million, with a global death toll of 6,85,000. The scenario is not different in Saudi Arabia. The most recent study of cancer-related mortality among Saudi women has found that breast cancer is the ninth leading cause of death [6–8]. According to the Saudi Cancer Registry of the King Faisal Specialist Hospital and Research Centre, around 930 new cases of breast cancer are diagnosed each year in Saudi Arabia. In 2010, of 5,378 cancer diagnoses in Saudi Arabia, 1,473 (27.4%) were for breast cancer, making it the most common newly diagnosed cancer among women [9].

Clinical trials demonstrated that combining taxanes with trastuzumab and pertuzumab as targeted therapy for HER2 significantly improves the overall response rates and survival as a first-line therapy, followed by pertuzumab and trastuzumab as maintenance therapy. Although many clinical studies have reported that cardiac adverse events, such as decreased ejection fraction (EF) and heart failure (HF), are associated with using this combination, the huge benefit of this targeted therapy warrants its use in most breast cancer cases, with close monitoring of cardiac functions.

Trastuzumab as monotherapy is associated with cardiotoxicity, but the exact mechanism of toxicity remains unknown. In patients with normal left ventricular function before starting trastuzumab therapy, the risk of HF is low.

Cardiac adverse events, such as decreased EF and HF, have been of specific concern in patients with HER2-positive breast cancer. Further studies that focus on evaluating and monitoring the incidence of cardiotoxicity are required to guide early management and/or improve outcomes.

Studies of patients treated for the active disease with reduced cardiac function at baseline have reported serious adverse events attributable to HER2-directed therapy. Thus, we have estimated the incidence and associated risk factors of cardiotoxicity effects from anti-HER2 treatment among all patients treated for HER2-positive early-stage breast cancer at a single centre.

2. METHODS

2.1 Study Design

This single-site retrospective study was designed to understand and evaluate the incidence of cardiotoxicity in early-stage breast cancer patients who were receiving anti-HER2 medications, such as pertuzumab, trastuzumab

and taxane. An extensive assessment was done for possible risk factors associated with early-stage breast cancer patients who underwent anti-HER2 treatment (Fig. 1).

2.2 Study Location and Duration

The study was conducted at King Abdulaziz Medical City (KAMC), Jeddah, Saudi Arabia. The data was considered for patients with breast cancer for five years in this treatment centre, and information related to the patients was collected from January 2015 to December 2019. Patient selection was done strictly following the approved eligibility criteria according to the study design and protocol.

2.3 Patient Inclusion Criteria

The study design contains precise inclusion and exclusion criteria for patient selection. During patient selection, each prospective patient's report was carefully reviewed by the study investigator. Every patient in this study underwent a left ventricular ejection fraction (LVEF) measurement using an echocardiography method at the baseline (before any treatment) and during anti-HER2 therapy. According to the instruction of the International Agency for Research on Cancer (IARC), Saudi Arabia, the estimated age-standardised incidence rate (ASIR) for breast cancer was 22.4 per 100,000 women in 2008 [10]. In this study, the patients' ages were considered following the IARC recommendations.

Only adult female patients, aged ≥ 22.4 years, were considered eligible for this study. Furthermore, histologically confirmed diagnosis of HER2-positive early-stage breast cancer for the study population was obtained from medical reports.

Only patients who were undergoing anti-HER2 treatment between 2015 and 2019 and had the required medical records were eligible for this study. It was carefully observed during the medical record assessment that patients were being treated with specific therapeutic agents, including pertuzumab, trastuzumab and taxane.

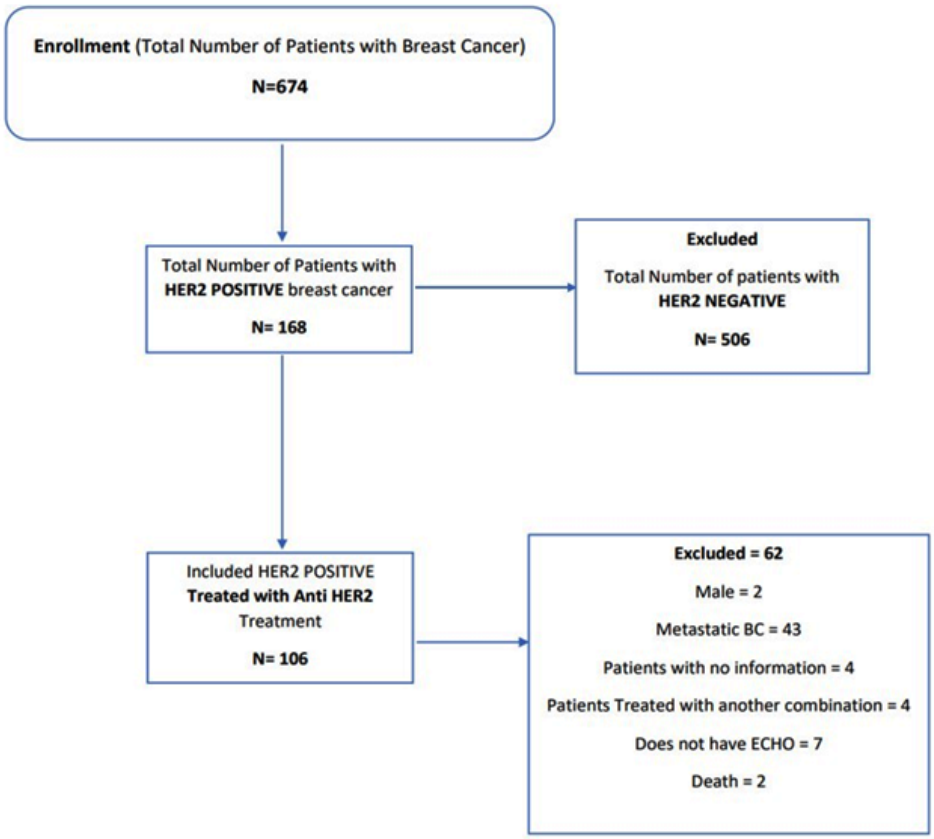

Fig. 1. Patient enrolment, screening, inclusion and exclusion in the study

During the screening, patients with HER2-negative reports were excluded from the study. Additionally, patients who did not meet the inclusion criteria mentioned in (Fig. 1), such as patients having metastatic breast cancer, male cancer patients and patients undergoing other radiation and chemotherapeutic treatments, were excluded from the study.

2.4 Cardiotoxicity Consideration and Evaluation

Besides the mentioned criteria, each report was keenly investigated for cardiotoxicity during patient selection. Cardiotoxicity was considered as (1) a reduction of LVEF, either globally or specifically in the interventricular septum; (2) symptoms or signs associated with HF; and (3) a reduction in LVEF baseline values from 5%–< 55% in the presence of signs or symptoms of HF and a reduction in LVEF ≥ 10%–< 55% without signs or symptoms of HF. Specifically, a 1% decline in the EF basal reading was considered an indicator of cardiotoxicity incidence.

2.5 Other Parameters

The parameters considered for this study included the LVEF percentage at pre-and post-treatment stages, menopausal state, BMI, hormone receptor status and stage of the disease. Additionally, associated comorbidities were also considered, such as cardiovascular risk factors, hypertension, coronary artery disease, congestive HF, kidney disease, diabetes mellitus and any other comorbidities.

2.6 Statistical Analysis

A detailed descriptive analysis was conducted for the obtained patient data. All categorical data were expressed as percentages and numerical data were presented as mean (±SD). We conducted chi-square ($\chi 2$) tests and Fisher exact tests for less frequent (< 5) samples to compare between the patients with and without declined EF. Multiple exact logistic regression with a standard maximum-likelihood-based estimator was applied to examine the association between the declined EF and applied medications. All statistical tests were conducted two-tailed, and findings were considered statistically significant at $P < 0.05$. All analyses were conducted using SAS statistical software (version 9.4, SAS Institute Inc. Cary, NC).

3. RESULTS

3.1 Patient Screening and Demographic Analysis

The initial patient enrolment comprised 674 patients. However, due to the strict inclusion and exclusion criteria, the final dataset contained 106 patients (Fig. 1). The median age of the patients was 50 years. The age range of the patients was between 27 and 89 years (Table 1).

3.2 Menopausal Stage

It was observed that almost half of the selected study participants (42.45%, n = 45) were at the postmenopausal stage. Conversely, 33.96% (n = 36) and 23.58% (n = 25) of the patients were at the premenopausal and perimenopausal stages, respectively (Table 1).

3.3 Obesity and Comorbidity

It was noted that 50.94% (n = 54) of the patients were either overweight or obese (Table 1). Evaluation of the comorbidities suggested that 30.19% of the patients (n = 32) had comorbidities. Assessment of the comorbidities revealed that the patients had hypertension (19.81%, n = 21), dyslipidemia (9.43%, n = 10), osteoporosis (8.9%, n = 9), diabetes mellitus (16.98%, n = 18) and cardiovascular complications (5.66%, n = 6) (Table 1). Among the comorbidities, hypertension and diabetes mellitus were observed to be prevalent among the study population.

Our observation suggested a significant ($P < 0.0001$) presence of comorbidities among the declined EF (35.42%) patient group compared to the non-declined EF patient population (25.86%).

3.4 Hormonal status

All the patients were examined for the presence of specific hormonal receptors. Progesterone and estrogen receptor presence was investigated. Most of the patients (66.05%, n = 70) had estrogen-positive reports, followed by progesterone-positive (50%, n = 53), progesterone-negative (49.06%, n = 52) and estrogen-negative (33.02%, n = 35) results. Only two patients did not show any positive or negative results for progesterone or estrogen receptor presence.

Table 1. Baseline demographic and clinical characteristics for female early-stage breast cancer patients at NGHA, Jeddah

Parameter	Patients' characteristics	P-value
	n (%)[1]	
Total		
Median age (range)	50 (27–89)	< .0001 [2]
BMI		0.84 [3]
Non-obese	52 (49.06)	
Overweight/obese	54 (50.94)	
Comorbidity		< .0001
Yes	32 (30.19)	
No	74 (69.81)	
Hypertension		< .0001
Yes	21 (19.81)	
No	85 (80.19)	
Dyslipidemia		< .0001
Yes	10 (9.43)	
No	96 (90.57)	
Osteoporosis		< .0001
Yes	9 (8.49)	
No	97 (91.51)	
Diabetes Mellitus		< .0001
Yes	18 (16.98)	
No	88 (83.02)	
Cardiovascular Disease		< .0001
Yes	6 (5.66)	
No	100 (94.34)	
Medication after diagnosis		
Pertuzumab		0.43
Yes	57 (53.77)	
No	49 (46.23)	
Taxol		< .0001
Yes	98 (92.45)	
No	8 (7.55)	
Trastuzumab Taxol		< .0001
Yes	103 (97.17)	
No	3 (2.83)	
Menopausal status		0.05
Perimenopause	25 (23.58)	
Postmenopausal	45 (42.45)	
Premenopausal	36 (33.96)	
Estrogen receptors (ER)		< .0001
Positive	70 (66.05)	
Negative	35 (33.02)	
NA	1 (0.94)	
Progesterone receptors (PR)		< .0001
Positive	53 (50)	
Negative	52 (49.06)	
NA	1 (0.94)	

[1] *n = sample size in percentage (%); t-test was used for continuous variable*
[2] *T-test was applied for continuous variables*
[3] *Fisher's exact test was applied for < 5 sample frequency and chi-square (X^2) test for > 5 sample frequency*

3.5 Medication after Diagnosis

Most of the patients (97.17%, n = 103) were receiving a combination of trastuzumab and taxol as treatment for HER-positive early-stage breast cancer, followed by taxol (92.45%, n = 98) and pertuzumab (53.77%, n = 57) (Table 1). In univariate analysis, a statistically significant difference was observed in the declined and non-

declined EF patient groups between the patients treated with pertuzumab (P = 0.001), the patients treated with a combination of pertuzumab and trastuzumab (P = 0.001) and the patients treated with a combination of pertuzumab, trastuzumab and taxol (P = 0.0008) (Table 1, Fig. 2).

In multivariate analysis, there were statistically significant associations between pertuzumab (OR 3.52, 95% CI [1.5–8.22]) and patients treated with a combination of, pertuzumab and trastuzumab (OR 4.28, 95% CI [1.68, 10.91]) and patients treated with a combination of pertuzumab, trastuzumab and taxol (OR 4.56, 95% CI [1.8, 11.54]). Patients treated with pertuzumab had thrice the odds ratio for the declined EF patient group (OR 3.52, 95% CI [1.5–8.22]). It was further observed that the higher the drug combination, the higher the odds ratio for the declined EF patient group (Table 2). Moreover, we noted that the patients treated with the pertuzumab and trastuzumab combination were four times more likely to have a decline in their EF than those who did not use the pertuzumab and trastuzumab combination (OR 4.28, 95% CI [1.68–10.91]). A similar trend was observed for the patients treated with an additional combination of pertuzumab, trastuzumab and taxol (Table 2).

The pre-and post-comorbidity (risk factors and association with a decline in ejection fraction (EF) comparisons of number of the patients (Fig. 3) suggested that there was a significant difference in the EFs for hypertension, dyslipidemia, diabetes mellitus and cardiovascular disease.

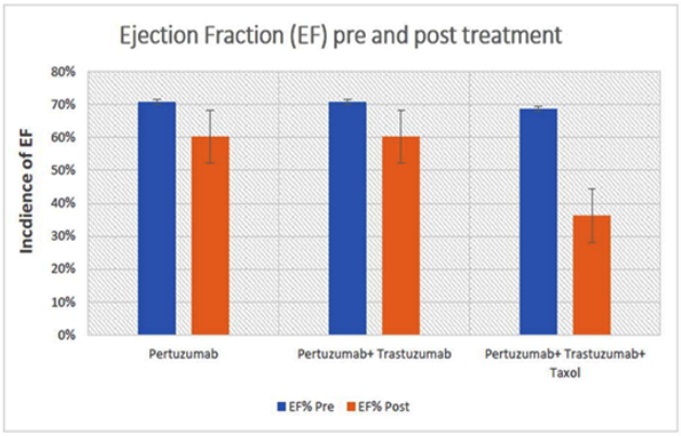

Fig. 2. A comparative presentation of EF at pre-and post-treatment using pertuzumab, a combination of pertuzumab and trastuzumab and a combination of pertuzumab, trastuzumab and taxol

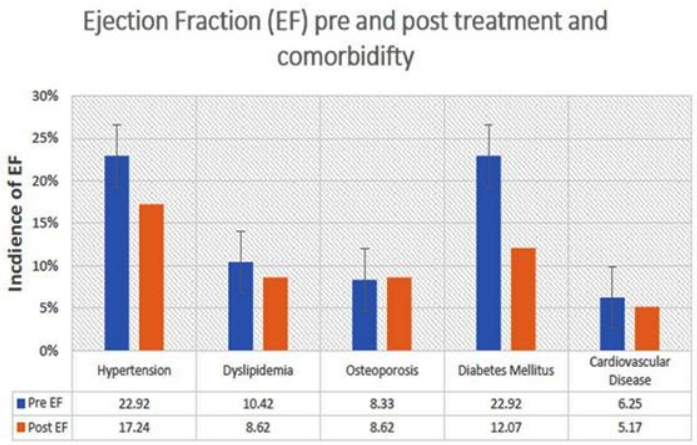

Fig. 3. A comparative presentation of the EF regarding different comorbidities

Table 2. Risk factors associated with a decline in EF for female early-stage breast cancer patients at NGHA, Jeddah

	Baseline Declined EF	Declined EF Pre vs Post	P-value[2]
	n (%)	OR (95%CI)[1]	
Age groups			0.13
27–50	50 (47.17)	Ref	
51–80	56 (52.83)	2.03 (0.79, 5.21)	
Comorbidity			0.08
Yes	32 (30.19)	2.38 (0.88, 6.41)	
No	74 (69.81)	Ref	
Pertuzumab			0.003
0.003			
Yes	57 (53.77)	3.52 (1.5, 8.22)	
No	49 (46.23)	Ref	
Pertuzumab + Trastuzumab			0.002
Yes	57 (53.77)	4.28 (1.68, 10.91)	
No	49 (46.23)	Ref	
Pertuzumab+Trastuzumab+Taxol0.00			0.001
1			
Taxol			
Yes	54 (50.94)	4.56 (1.8, 11.54)	
No	52 (49.06)	Ref	
Progesterone receptors (PR)			0.48
Positive	53 (50)	0.59 (0.25, 1.38)	
Negative	52 (49.06)	Ref	
NA[3]	1 (0.94)	0.01 (0.02, 1.88)	

1 Odds ratio and confidence interval were calculated using exact multiple logistic regression

2 Reference = Ref

3 'NA' = Not available

4. DISCUSSION

Cancer has emerged as a curse to human society in this century, taking a toll on millions of lives irrespective of geographical region, gender and age. Breast cancer's global prevalence is rising and, presently, breast cancer is the second most common cancer in the world [1]. Several factors are found to be responsible for inducing or promoting breast cancer, categorised as hereditary, demographic, reproductive, hormonal, breast-associated and lifestyle-associated factors [1]. However, there has been no established linear association or relationship of these factors in inducing or aiding the progression of breast cancer. Although the relationship or influence of individual factors is known in many cases, their collective impact has not been discovered.

The advancement of medical science saved millions of lives this century by applying some wonder life-saving drugs. For HER2-positive breast cancer, trastuzumab, pertuzumab and taxol have been used for decades worldwide [11]. As a first-line treatment, these drugs were successful in improving the time required for disease progression, response time, specific targeting to solid tumours, and the time required for treatment failure [12].

These drugs are used in different combinations as part of chemotherapy, depending on the diagnosis [13]. Such combination therapy has also demonstrated improvement in the overall survival of the patient [12]. Over the decades, the usage of pertuzumab, trastuzumab and taxol as potentially reliable therapeutic agents for breast cancer treatment has increased, and they are being used differently on a case-by-case basis [14,15]. Using pertuzumab, trastuzumab and taxol as part of the first-line chemotherapeutic treatment for HER2-positive early-stage breast cancer has helped many patients to survive longer and combat the disease. Trastuzumab, a monoclonal antibody used for HER2-positive breast cancer, remains the gold standard of treatment so far [16].

However, side effect prevention has been a concern in the application of these chemotherapeutic agents [17]. Most of the reported side effects are infusion-related, such as fever and chills. Apart from these, there is a range of recorded mild-to-moderate adverse responses that include myalgia, diarrhoea, haematotoxicity, infections, rash, arthralgia and others [18–20].

Cardiotoxicity has been a serious concern in using these drugs. A serious adverse event, symptomatic HF, is reported in 1–4% of patients and LVEF association was also noted. In most cases, the cardiological events were reversible and temporary and discontinuation of the therapeutic agent improved the condition [21]. Ewer and Ewer [22] argued that the cardiotoxicity-related alteration due to trastuzumab use may have microscopic ultrastructural changes in the heart muscles, which are partially reversible after the discontinuation of the medication. However, in most of the reports related to cardiotoxicity-related issues due to using trastuzumab, it has been suggested that it was mainly anthracycline-induced, and the trastuzumab-induced cardiac changes are reversible [23]. Several recent reports have suggested multiple ways of tackling such cardiotoxicity [24,25].

In this study, we have witnessed the induction of cardiotoxicity in early-stage breast cancer patients who are being treated with various combinations of pertuzumab, trastuzumab and taxol. Our results are statistically significant and are, as per the reports, related to cardiotoxicity associated with these drugs. Another report had also earlier suggested cardiotoxicity association due to treatment with the trastuzumab and pertuzumab combination [26]. Recently, Abdel-Razaq et al. [27] reported that 90% of HER2-positive breast cancer patients showed trastuzumab-induced cardiotoxicity in Saudi Arabia. Similar to our observations, Abulkhair et al. [28] reported trastuzumab-associated cardiotoxicity in HER2-positive breast cancer patients in a single institution-based retrospective study. Another single-centre study in the Saudi Arabia region reported persistently low LVEF during follow-up in most of the patients due to drug-induced cardiomyopathy [29]. It was observed in this study that LVEF reduction is associated with the increasing combination of pertuzumab, trastuzumab and taxol. Moreover, associations with comorbidities were also observed in the present study population.

Caron and Nohria [30] recommended categorising high-risk HER2-positive breast cancer patients who may show association with cardiotoxicity due to therapeutic effects and considering modified treatment regimens, such as using anthracycline-free treatment regimen, dose reduction and other possibilities to avoid cardiotoxicity.

5. CONCLUSION

In this study, we observed a statistically significant association between reduced LVEF and various combinations of pertuzumab, trastuzumab and taxol. An association between comorbidities and LVEF reduction was also found in the present HER2-positive early-stage breast cancer patient population.

6. RECOMMENDATIONS

Additional larger multicentre-based studies are essential to understand and establish the cardiotoxicity effects of trastuzumab, pertuzumab and taxol. A diverse patient population, increased number of drug combinations, longer study durations and attention to individual comorbidities may help in understanding the relation of cardiotoxicity during the use of these chemotherapeutic agents.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our country and area of research. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Furthermore, the research was not funded by the producing company but by the authors' personal efforts.

CONSENT

It is not applicable

ETHICAL APPROVAL

Appropriate ethical approval was obtained from the Institutional Review Board (No: SP21J/048/03).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Canc: Target Ther. 2019;11:151.
2. Alghamdi IG, Hussain II, Alghamdi MS, El-Sheemy MA. The incidence rate of female breast cancer in Saudi Arabia: An observational descriptive epidemiological analysis of data from Saudi Cancer Registry 2001–2008. Breast Canc: Target Ther. 2013;5:103.
3. Milne RL, Kuchenbaecker KB, Michailidou K, Beesley J, Kar S, Lindström S, et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Nature genetics. 2017;49 (12):1767-78.
4. Malone KH, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol Biomarkers Prev. 2002;11 (7):601-7.
5. Azamjah N, Soltan-Zadeh Y, Zayeri F. Global trend of breast cancer mortality rate: a 25-year study. Asian Pacific journal of cancer prevention: APJCP. 2019 ;20(7):2015.
6. Registry N. Cancer Incidence Report Saudi Arabia 2002. Riyadh; 2007.
7. Mokdad AH, Jaber S, Aziz MI, Al Buhairan F, Al Ghaithi A, Al Hamad NM. The stateof health in the Arabworld, 1990010: an analysisof the burden of diseases, injuries, and risk factors. Lancet. 2014;383:309–320.
   DOI:10.1016/S0140-6736(13)62189-3
8. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans K. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2095–2128.
   DOI:10.1016/S0140-6736(12)61728-0
9. Alotaibi RM, Rezk HR, Juliana CI, Guure C. Breast cancer mortality in Saudi Arabia: Modelling observed and unobserved factors. PloS one. 2018;13(10):e0206148.
10. International Agency for Research on Cancer. Cancer Fact Sheet. International Agency for Research on Cancer; 2008. [Accessed May 10, 2013]. GLOBOCAN. Available: http://globocan.iarc.fr/factsheets/ cancers/all.asp
11. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. N Engl J Med. 2005 Oct 20;353(16):1734-6.
    DOI: 10.1056/NEJMe058196.
12. Leyland-Jones B. Trastuzumab: hopes and realities. Lancet Oncol. 2002;3(3):137-44.
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
14. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomized, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21(4):519-30.
15. Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018;29(3):646-53.
16. Maximiano S, Magalhaes P, Guerreiro MP, Morgado M. Trastuzumab in the treatment of breast cancer. Bio Drugs. 2016;30 (2):75-86.
17. Gao J, Swain SM. Pertuzumab for the treatment of breast cancer: a safety review. Expert Opin Drug Saf. 2016; 15(6):853-63.
18. Lambert L. Biological drugs in breast cancer: increasing understanding for the pharmacist. SA Pharmac J. 2014;81(8):24-7.
19. Mehta A, Tripathy D. Co-targeting estrogen receptor and HER2 pathways in breast cancer. The breast. 2014;23(1):2-9.
20. Ishizuna K, Ninomiya J, Ogawa T, Tsuji E. Hepatotoxicity induced by trastuzumab used for breast cancer adjuvant therapy: a case report. J Med Case Rep. 2014;8(1):1-4.
21. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK.

Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. In Mayo Clinic Proceedings. Elsevier. 2008;83(2):197-203.
22. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf. 2008;31(6):459-67.
23. Keefe DL. Trastuzumab- associated cardiotoxicity. Cancer. 2002;95(7):1592-600.
24. Mohan N, Jiang J, Dokmanovic M, Wu WJ. Trastuzumab-mediated cardiotoxicity: current understanding, challenges, and frontiers. AntibTher. 2018;1(1):13-7.
25. Guglin M, Krischer J, Tamura R, Fink A, Bello-Matricaria L, McCaskill-Stevens W, et al. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. J Am Coll Cardiol. 2019;73(22): 2859-68.
26. Portera CC, Walshe JM, Rosing DR, Denduluri N, Berman AW, Vatas U, et al. Cardiac toxicity and efficacy of trastuzumab combined with pertuzumab in patients with [corrected] human epidermal growth factor receptor 2-positive metastatic breast cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2008;14(9):2710-6.
27. Abdel-Razaq W, Alzahrani M, Al Yami M, Almugibl F, Almotham M, Alregaibah R. Risk factors associated with trastuzumab-induced cardiotoxicity in patients with human epidermal growth factor receptor 2-positive breast cancer. J Pharm Bioallied Sci. 2019;11(4):348.
28. Abulkhair OA, Saadeddin A, Sedky L, Otaibi SA, Gasmelseed A. Trastuzumab associated cardiac toxicity: who is at risk in Saudi Arabia? A single institution study. Pan Arab Journal of Oncol. 2014;7(2).
29. Jamiel A, Abualkhair O, Ahmed A, Al-Mallah M. 5. Incidence of herceptin induced cardiomyopathy in treated breast cancer patients: A prospective single center study in Saudi Arabia. J Saudi Heart Assoc. 2017;29(4):326.
30. Caron J, Nohria A. Cardiac toxicity from breast cancer treatment: can we avoid this? Current Oncol Rep. 2018;20(8):1-8.

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