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Cardiotoxic Effect of Adjuvant Subcutaneous versus Intravenous Trastuzumab in HER-2 Positive Breast Cancer

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ABSTRACT

Background: Another option to intravenous (IV) trastuzumab is subcutaneous (S.C.) trastuzumab, which has received approval. There is a lack of information regarding the causes and prevalence of cardiotoxicity in patients treated with subcutaneous versus intravenous trastuzumab for early-stage of HER2-positive breast cancer.

Objectives: To compare cardiotoxic effects of IV versus SC trastuzumab.

Patients and methods: This retrospective study included 187 patients with HER2+ breast cancer treated with adjuvant trastuzumab (either IV or SC) for at least 6 months, stage (I, II, III), with initial ejection fraction (EF) (≥ 55 %) and followed up at least 2 times with echocardiography during treatment. We compared patients who received IV (88 patients) versus SC (99 patients) trastuzumab as regard patients and disease characteristics, treatment received, cardiotoxicity development and its pattern, treatment discontinuation, progression status, and its pattern. Analysis of different variables to identify predictors of trastuzumab induced cardiotoxicity in both groups was done.

Results: The overall incidence of trastuzumab induced cardiotoxicity was 16.6%. By comparing both groups, there was no significant difference as regard patients, disease characteristics, cardiotoxicity and treatment received except for number of anthracycline cycles. There were no detected risk factors for cardiotoxicity in both groups except number of anthracycline cycles.

Conclusion: There was no significant variance in cardiotoxicity between both groups. Both the IV and SC formulas of trastuzumab had equivalent safety profiles in our study. When deciding between these formulations, other factors—such as patient preference, value to patients and the healthcare system, and cost—might also be taken into account.

Keywords: Cardiotoxicity, Early breast cancer, Subcutaneous, Trastuzumab, HER2-positive.

INTRODUCTION

Breast cancer is the most often diagnosed cancer globally, with over 2 million new cases were anticipated in 2020. Additionally, it is the primary cause of cancer-related mortality in women, resulting in over 680,000 fatalities [1]. Breast cancer is the most common malignancy in females in the United States and is second only to lung cancer as a cause of cancer death [2]. Although there are varying incidence rates of breast cancer between industrialised as well as developing countries, it still stands as the most prevalent form of female cancer in Egypt [1]. In Egypt breast cancer accounts for 16.4 % of all cancers (the leading cause of cancer incidence) and death rate about 10.3% of all reported cases [3].

There are various molecular subtypes of breast cancer, gene amplification or protein overexpression of human epidermal growth factor receptor 2 (HER2) is one of them. This subtype is linked to aggressive biological behaviour as well as poses a significant risk of distant recurrence. The danger has significantly decreased owing to the effective creation of the anti-HER2 monoclonal antibody trastuzumab [3].

Trastuzumab, when used alongside adjuvant chemotherapy in many well-designed, prospective randomised studies, has revealed to enhance disease-specific results for ladies with HER2-positive illness [4]. Trastuzumab can cause cardiotoxicity, leading to reduced left ventricular ejection fraction (LVEF) as well as, in rare cases, congestive heart failure [5].

A subcutaneous (SC) version of trastuzumab has been created to address the constraints of intravenous delivery. Subcutaneous formulation has a rapid mode of administration, eliminating the need for portacath insertion, therefore enhancing treatment convenience and patient compliance [6].

It is possible to obtain some information regarding the cardiotoxicity of fixed-dose SC trastuzumab, which has been the subject of controversy: HannaH trial: stated comparable efficacy and safety of SC trastuzumab versus IV trastuzumab with same cardiac adverse events [7]. Another study in 2021 reported significant difference of cardiotoxicity with lower cardiotoxicity rate of SC form versus intravenous form [8].In this work we aimed to compare the patients who received SC versus IV trastuzumab as regard all detailed patients, disease characteristics, outcome and cardiotoxicity.

PATIENTS AND METHODS

Patients: This retrospective study included patients of HER-2 positive breast cancer treated with adjuvant trastuzumab either IV or SC through the period from January 2018 to December 2021.

Inclusion criteria:

Cases with histologically confirmed HER2+ breast cancer (stage I, II, III). Staging was done according to AJCC cancer TNM staging manual, 2017 [9]. Patients with initial EF (≥ 55 %) who were followed up at least

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2 times with echocardiography during treatment, and who received at least 6 months of trastuzumab.

Exclusion criteria: Incomplete medical data, and patients who were irregular in receiving trastuzumab.

Methods:

Complete data were collected from patients archived files: Patients characteristics (Age, sex, weight, body mass index, menopausal status; premenopausal, perimenopausal, postmenopausal, comorbidities, and family history), disease characteristics (site of disease (right, left, or bilateral), pathological subtypes (invasive lobular carcinoma (ILC), invasive duct carcinoma (IDC), or others), stage, grade, hormonal status (Estrogen receptor (ER), progesterone receptor (PR), HER2NEU expression, KI-67), treatment data (as radiotherapy, chemotherapy received, type of chemotherapy regimen, received anthracycline or not, type of anthracycline (epirubicin or doxorubicin), number of anthracycline cycles, route of trastuzumab administration (IV or SC), number of trastuzumab cycles, initial EF and serial follow up EF, toxicity of treatment (cardiotoxicity developed or not and its type: a cardiac event was defined as a decrease in LVEF by ≥ 10% from baseline, and to a value < 50%, or as the development of congestive heart failure [10], treatment discontinuation due to trastuzumab induced cardiotoxicity or not, toxicity of chemotherapy (GIT, haematological, others), progression status during 2 years follow up after trastuzumab administration, and type of progression if present (local recurrence or distant metastasis or both).

We compared both groups (patients who received IV trastuzumab versus SC) as regard patients characteristics, disease characteristics, and all other parameters. Analysis of different variables to identify predictors of trastuzumab induced cardiotoxicity in both groups, and in patients who developed cardiotoxicity was done.

Disease free survival (DFS) was calculated in months from the date of diagnosis to the date of progression [11].

Ethical approval: Approval (IRB number 4/2022 ONCO 31) from Ethical Committee, Faculty of Medicine, Menoufia University was optained. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

The statistics collected were tabulated and analyzed by SPSS (Statistical Package for the Social Sciences) version 23.0 on IBM compatible computer (SPSS Inc. Armonk, NY: IBM Crop.) Two types of statistics were performed: descriptive statistics: e.g. percentage (%), mean, standard deviation (SD), median, and range in addition to analytic statistics. The Chi-square test (χ^2) was used for comparing categorical variables. Student's t-test was functioned for comparison of the means of continuous quantitative. P-value ≤ 0.05 was statistically significant.

RESULTS

This retrospective study included 187 patients with HER-2 positive early breast cancer treated by adjuvant trastuzumab. The studied patients were classified into two groups, group 1 included 88 patients (who received IV formula) and group 2 included 99 patients (who received SC formula). There was no significant difference between the two groups regarding patients and disease characteristics (Tables 1, 2). The mean age ± SD in group 1 was 45.02, while in group 2 was 44.75. IDC was the most common histological subtype in both groups. Stage II was the most prevalent.

Table (1): Patients characteristics.

Personal characters	Group I (IV ttt) (n=88)	Group II (SC ttt) (n=99)	Chi square test	P value
Sex Male Female	 1(1.1%) 87(98.9%)	 0(0.0%) 99(100.0%)	1.131	0.288
Age in years Mean± SD Median Range	 45.02±10.24 45.00 27-70	 44.75±9.69 44.00 25-70	*0.189	0.850
Age group ≤ 45 years >45 years	 43(48.9%) 45(51.1%)	 51(51.5%) 48(48.5%)	0.131	0.717
Weight in Kg Mean± SD Median Range	 82.93±19.14 82.00 50-144	 84.34±16.42 83.00 50-135	*0.543	0.588
Weight groups ≤ 83 Kg >83 Kg	 46(52.3%) 42(47.7%)	 47(47.5%) 52(52.5%)	0.429	0.512
BMI in Kg/m^2 Mean± SD Median Range	 31.32±6.22 33.00 17-43	 32.03±5.74 32.00 18-43	*1.125	0.262
BMI groups ≤ 32 Kg/m^2 >32 Kg/m^2	 43(48.9%) 45(51.1%)	 56(56.6%) 43(43.4%)	1.109	0.292
Menstrual status Premenopausal Postmenopausal	 62(71.3%) 25(28.7%)	 72(72.7%) 27(27.3%)	0.049	0.824
Family history Negative Positive	 78(88.6%) 10(11.4%)	 78(78.8%) 21(21.2%)	3.267	0.071
Comorbidities Absent Present	 70(79.5%) 18(20.5%)	 84(84.8%) 15(15.2%)	0.902	0.342
Comorbidity types Hypertension Diabetes Both Hepatic	 7(38.9%) 4(22.2%) 2(11.1) 5(27.8%)	 8(53.3%) 2(13.3%) 1(6.7%) 4(6.7%)	0.913	0.822

*: Student t-test

Table (2): Disease characteristics.

Parameter	Group I (IV ttt) (n=88)	Group II (SC ttt) (n=99)	Chi square test	P value
Tumour side				
Right	51(58.0%)	49(49.5%)	2.68	0.262
Left	36(40.9%)	50(50.5%)		
Bilateral	1(1.1%)	0(0.0%)		
Pathological subtypes				
IDC	85(96.6%)	99(100.0%)		
ILC	1(1.1%)	0(0.0%)	3.43	0.180
Mixed	2(2.3%)	0(0.0%)		
Grades				
Grade I, II	73(83%)	84(84.8%)	1.280	0.527
Grade III	15(17.0%)	15(15.2%)		
ER status				
Positive	51(58.0%)	66(66.7%)	1.510	0.219
Negative	37(42.0%)	33(33.3%)		
PR status				
Positive	44(50.0%)	62(62.6%)	3.025	0.082
Negative	44(50.0%)	37(37.4%)		
Ki 67				
Not done	4(4.5%)	5(5.1%)	0.150	0.928
Low	16(18.2%)	16(16.1%)		
High	68(77.3%)	78(78.8%)		
P T status				
T1	12(13.6%)	13(13.1%)	6.09	0.107
T2	61(69.3%)	57(57.6%)		
T3	10(11.4%)	25(25.3%)		
T4	5 (5.7%)	4(4.0%)		
P N status				
N0	24(27.3%)	36(36.4%)	6.88	0.076
N1	33(37.5%)	38(38.4%)		
N2	22(25.0%)	11(11.1%)		
N3	9 (10.2%)	14(14.1%)		
Stage				
Stage 1	4(4.5%)	9(9.1%)	2.146	0.342
Stage 2	49(55.7%)	47(47.5%)		
Stage 3	35(39.8%)	43(43.4%)		

There was significant difference between the two groups regarding initial EF, and number of anthracycline cycles being more in SC group. There was no significant difference between the two groups regarding receiving radiotherapy, chemo regimen, type of anthracycline and number of trastuzumab cycles. The majority of patients received radiotherapy in both groups. Most of patients received epirubicin (as anthracycline based chemotherapy) in both groups (Table 3, figure 1).

Table (3): Treatment data.

Parameter	Group I (IV ttt) (n=88)	Group II (SC ttt) (n=99)	Chi square test	P value
Radiotherapy Received Not received	 72(81.8%) 16(18.2%)	 84(84.8%) 15(15.2%)	0.309	0.578
Chemo regimen Anthracycline + cyclophosphamide± fluorouracil Anthracycline-taxanes Taxanes	 4(4.5%) 82(93.2%) 2(2.3%)	 3(3.0%) 91(91.9%) 5(5.1%)	1.254	0.534
Type of anthracycline Doxorubicin Epirubicin	 20(23.3%) 66(76.7%)	 21(22.3%) 73(77.7%)	0.021	0.884
Anthracycline cycles Mean± SD Median Range	 3.26±0.54 3.00 3.0-6.0	 3.71±0.52 4.00 3.0-6.0	*5.72	<0.001
Trastuzumab cycles Mean± SD Median Range	 15.94±2.23 17.00 6.00-17.00	 15.77±2.52 17.00 4.00-17.00	*0.478	0.633
Initial EF Mean± SD Median Range	 67.50±4.23 67.00 58.0- 81.0	 64.36±4.27 64.00 56.0- 77.0	*5.02	<0.001

*: Student t-test

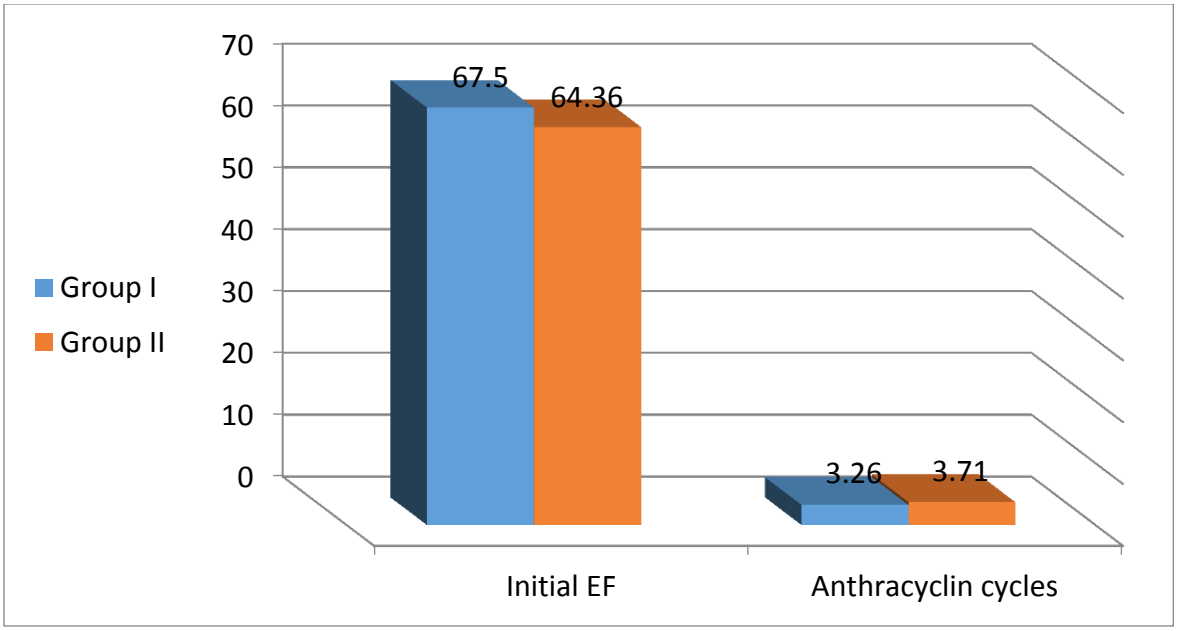

Figure (1): Number of Anthracycline cycles and initial EF in different groups

There was no significant difference between the two groups regarding toxicity of chemotherapy, cardiac toxicity during trastuzumab administration and its pattern, treatment discontinuation due to cardiotoxicity (table 4).

.**Table (4):** Toxicity of treatment in both groups

Parameter	Group I (IV ttt) (n=88)	Group II (SC ttt) (n=99)	Chi square test	P value
Toxicity of chemotherapy ± trastuzumab No toxicity GIT Haematological	 71(80.7%) 6(6.8%) 11(12.5%)	 86(86.8%) 5(5.1%) 8(8.1%)	1.355	0.508
Cardiac toxicity during trastuzumab administration Absent Present	 74(84.1%) 14(15.9%)	 82(82.8%) 17(17.2%)	0.054	0.817
Pattern of cardiac toxicity Decreased EF≥10% Decreased EF<50% No cardiotoxicity	 10(11.4%) 4(4.5%) 74(84.1%)	 10(10.1%) 7(7.1%) 82(82.8%)	0.583	0.747
Treatment discontinuation duo to cardiotoxicity Yes No	 4(4.7%) 82(95.3%)	 6(6.1%) 93(93.9%)	0.179	0.672

There was significant variance among the two groups regarding progression, being more in IV group, but no significant difference was found regarding the type of progression (table 5).

Table (5): Progression of disease in both groups

Parameter	Group I (IV ttt) (n=88)	Group II (SC ttt) (n=99)	Chi square test	P value
Progression Absent Present	 75(85.2%) 13(14.8%)	 95(95.9%) 4(4.1%)	6.49	0.011
Type of progression Local Metastatic Local+metastatic	 2(15.4%) 10(76.9%) 1(7.7%)	 1(25.0%) 2(50.0%) 1(25.0%)	1.253	0.534

The mean DFS in IV group was 15.067 months versus 17.263 in SC group, with no significant difference (p value =0.71) (Figure 2).

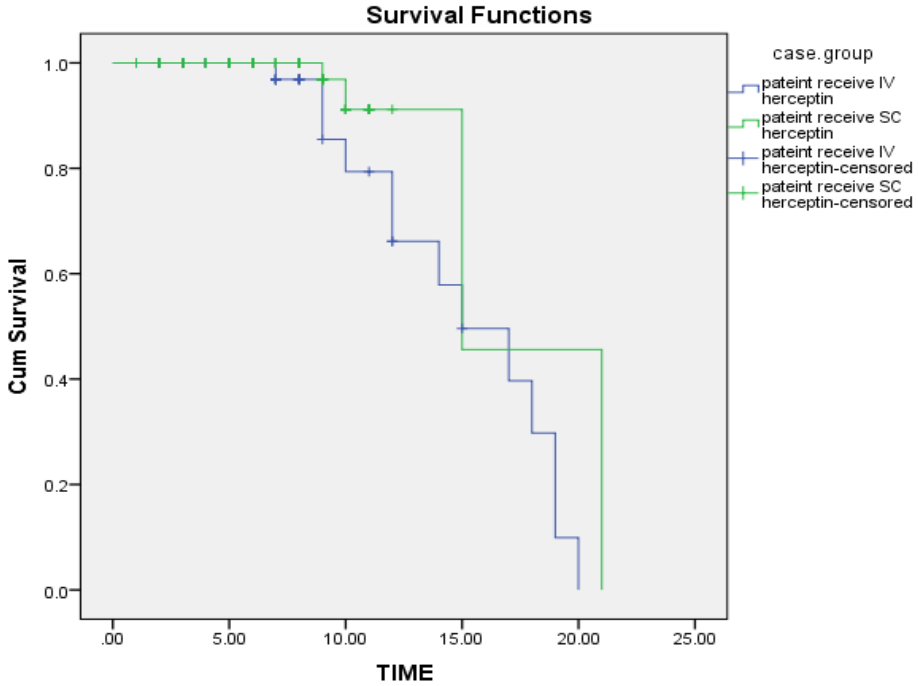

Figure (2): Disease Free Survival for both groups

There was no significant correlation between incidence of cardiotoxicity and patient characteristics, and treatment parameters except for number of trastuzumab cycles (Tables 6, 7).

Table (6): Correlation between cardiotoxicity and personal characteristics

Personal characters	Cardiotoxicity			Chi square test	P value
	Absent (n=156)	Present (n=31)	Total (n=187)		
Sex Male Female	 1(0.6%) 155(99.4%)	 0(0.0%) 31(100.0%)	 1(0.5%) 186(99.5%)	0.200	0.655
Age group ≤ 45 years >45 years	 81(51.9%) 75(48.1%)	 13(41.9%) 18(58.1%)	 94(50.3%) 93(49.7%)	1.032	0.310
Weight groups ≤ 83 Kg >83 Kg	 77(49.4%) 16(50.6%)	 16(51.6%) 15(48.4%)	 93(49.7%) 94(50.3%)	0.053	0.819
BMI groups ≤ 32 Kg/m^2 >32 Kg/m^2	 81(51.9%) 75(48.1%)	 18(58.1%) 13(41.9%)	 99(52.9%) 88(47.1%)	0.392	0.532
Menstrual status Premenopausal Postmenopausal	 112(72.3%) 43(27.7%)	 22(71.0%) 9(29.0%)	 134(72.0%) 52(28.0%)	0.021	0.884
Family history Negative Positive	 127(81.4%) 29(18.6%)	 29(93.5%) 2(6.5%)	 156(83.4%) 31(16.6%)	2.755	0.097
Comorbidities Absent Present	 130(83.3%) 26(16.7%)	 24(77.4%) 7(22.6%)	 154(82.4%) 33(17.6%)	0.622	0.430
Comorbidity types Hypertension Diabetes Both Hepatic	 12(46.2%) 4(15.4%) 3(11.5) 7(26.9%)	 3(42.8%) 2(28.6%) 0(0.0%) 2(28.6%)	 15(45.5%) 6(18.2%) 3(9.1%) 9(27.3%)	1.354	0.716

Table (7): Correlation between cardiotoxicity and treatment parameters

Cardiotoxicity	Cardiotoxicity			Chi square test	P value
	Absent (n=156)	Present (n=31)	Total (n=187)		
Treatment IV SC	 74(47.4%) 82(52.6%)	 14(45.2%) 17(54.8%)	 88(47.1%) 99(52.9%)	0.054	0.817
Chemo regimen Anthracycline + cyclophosphamide± fluorouracil Anthracycline- taxanes Taxanes	 7(4.5%) 144(92.3%) 5(3.2%)	 0(0.0%) 29(93.5%) 2(6.5%)	 7(3.7%) 173(92.6%) 7(3.7%)	2.123	0.346
Type of anthracycline Doxorubicin Epirubicin	 34(22.5%) 117(77.5%)	 7(24.1%) 22(75.9%)	 41(22.8%) 139(77.2%)	0.036	0.849
Anthracycline cycles	3.48±0.55	3.58±0.68	3.49±0.58	0.923	0.357
Trastuzumab cycles	16.21±1.59	14.00±4.29	15.85±2.38	4.940	<0.001
Radiotherapy Received Not received	 130(83.3%) 26(16.7%)	 26(83.9%) 5(16.1%)	 156(83.4%) 31(16.6%)	0.005	0.941
Initial EF	65.64±4.31	66.84±5.46	65.84±4.53	1.347	0.180

DISCUSSION

There is significant difference between this study and **De Sanctis *et al.* [8],** as regard median age; (it was smaller in our study (45 vs 55 years), and as regard median weight (82 vs 62 kilogram), and BMI (33 vs 23.7) they were higher in our population. This may be explained by differences in life style, and food habits in our population.

In this study most of the patients received radiotherapy and anthracyclines, which is compatible with **De Sanctis *et al.* [8],** (83.4% vs 78.2 %), and (96.3% vs 90.4 %) respectively, while there was difference as regard the type of anthracycline received. 77 % of patients in our study received epirubicin vs 93.3 % in **De Sanctis *et al.* [8]** received doxorubicin

The mean initial ejection fraction in both groups > 55% in IV groups (67.5%), and SC group (64.4%), which is also consistent with **De Sanctis *et al.* [8],** who revealed that most patients had initial ejection fraction > 55%; 98.4% of patients in IV group, and 98.9% in SC group.

The incidence of trastuzumab-induced cardiotoxicity in patients with breast cancer varies in the published data, yet it was reported in 2%–7% when trastuzumab was used as monotherapy and up to 28% when combined with other chemotherapies, especially anthracyclines and taxanes [12], which is compatible with this study, where the overall incidence of trastuzumab induced cardiotoxicity was 16.6% (within the usual range).

In the present study there was no significant difference in the incidence of cardiac adverse events between IV and SC formula of trastuzumab (15.9% vs 17.2%) respectively, which is similar to that reported in the **Jackisch *et al.* [7]** trial (14.1% vs 14.8% in IV and SC formula respectively). In contrary to our results, the results reported by **De Sanctis *et al.* [8]** showed that IV administration was associated with a higher cardiac toxicity than the SC one (15.2% *vs* 8.4% respectively), both at univariate and multivariate analysis. This may be explained by underlying cardiac condition as more cardiac events were found in patients in the IV group using cardiological treatment (26.7% in IV. *vs* 14.3% in SC).

In this study, there was no significant difference between the two groups regarding treatment discontinuation due to cardiotoxicity (10 patients), 4 patients (4.7 %) in IV group vs 6 patients (6.1%) in SC group, which is explained by no difference in cardiac adverse events in both groups, and this is in line with **De Sanctis *et al.* [8]** as 20 patients (5.5%) discotinue treatment when LVEF decline for >8 weeks (8 patients in SC group vs 12 patients in IV group). This difference in number of patients may be related to the difference of recruited patients in both studies (188 patients in this study versus 363 patients in the other study).

In this study, there was a significant difference between the two groups regarding progression during 2 years follow up, being more in IV group than SC one (14.8%, and 4.1% respectively), which is in contrast to final analysis of **Jackisch *et al.* [7]** that confirmed the comparable efficacy of subcutaneous and intravenous trastuzumab. The prescription of either SC or IV trastuzumab in our study was based on availability and refundability and this may affect the progression.

Several studies have attempted to investigate the risk factors associated with trastuzumab-induced cardiotoxicity (TIC) in patients with HER2-positive breast cancer [13-16].

In the current study, there was no significant correlation between cardiotoxicity in HER 2 positive breast cancer patients and the following parameters; presence of comorbidities, age, weight, receiving radiotherapy, chemo regimen, and type of anthracycline. While other studies reported a diverse number of risk factors that include elderly age [13], African ethnicity [14] overweight, mastectomy surgery, concurrent anthracyclines [15], baseline LVEF value [16] and underlying cardiac conditions[8].

Considering the correlation between cardiotoxicity in HER 2 positive breast cancer patients and trastuzumab cycles, there was an inverse significant correlation. This may be due to discontinuity of treatment as a result of cardiotoxicity.

Study Limitations: A retrospective study, in addition to the limited number of patients included. On the other hand, mono-centric research, has the advantage of homogeneity in particular in treatment regimens and the number of follow-up visits, which were extremely consistent and adherent to guidelines and homogeneity of cardiological assessment by cardiologists.

CONCLUSIONS

This study suggests that SC and IV trastuzumab could have comparable safety profile, so the choice between them may be dependent on availability, patient's condition and preference.

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REFERENCES

1. **Sung H, Ferlay J, Siegel R *et al.* (2021):** Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin., 71(3):209-49.
2. **Siegel R, Miller K, Fuchs H *et al.* (2022):** Cancer statistics, 2022. CA Cancer J Clin., 72: 7-33.
3. **Moja L, Tagliabue L, Balduzzi S *et al.* (2012):** Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev., 12(4):CD006243. doi: 10.1002/14651858.CD006243
4. **Slamon D, Eiermann W, Robert N *et al.* (2011):** Adjuvant trastuzumab in HER2-positive breast cancer. New England Journal of Medicine, 365(14):1273-83.
5. **Nemeth B, Varga Z, Wu W *et al.* (2017):** Trastuzumab cardiotoxicity: from clinical trials to

experimental studies. British Journal of Pharmacology, 174(21):3727-48.

6. **Pivot X, Gligorov J, Müller V (2013):** Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol., 14(10):962–970.
7. **Jackisch C, Stroyakovisky D, Pivot X *et al.* (2019):** Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: final analysis of the HannaH phase III randomized clinical trial. JAMA Oncology, 5(5):e 190339. doi: 10.1001/jamaoncol.2019.0339.
8. **De Sanctis R, Giordano L, D'Antonio F *et al.* (2021):** Clinical predictors of cardiac toxicity in HER2-positive early breast cancer patients treated with adjuvant sc versus iv trastuzumab. The Breast, 57:80-85.
9. **Amin M, Edge S, Greene F *et al.* (2017):** The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin., 67 (2): 93-99
10. **Curigliano G, Cardinale D, Suter T (2012):** ESMO Guidelines Working Group. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Onco., 23(7)155-166.
11. **Kilickap S, Demirci U, Karadurmus N *et al.* (2018):** Endpoints in oncology clinical trials. J Buon., 23(7):1-6.
12. **Bria E, Cuppone F, Fornier M *et al.* (2008):** Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Research and Treatment, 109:231-39.
13. **Serrano C, Cortés J, De Mattos-Arruda L *et al.* (2012):** Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. Annals of Oncology, 23(4):897-902.
14. **Baron K, Brown J, Heiss B *et al.* (2014):** Trastuzumab-induced cardiomyopathy: incidence and associated risk factors in an inner-city population. Journal of Cardiac Failure, 20(8):555-59.
15. **Seidman A, Hudis C, Pierri M *et al.* (2002):** Cardiac dysfunction in the trastuzumab clinical trials experience. Journal of Clinical Oncology, 20(5):1215-21.
16. **Cochet A, Quilichini G, Dygai-Cochet I *et al.* (2011):** Baseline diastolic dysfunction as a predictive factor of trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer. Breast Cancer Research and Treatment, 130:845-54.