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Research Article

Cardiotoxic adverse effects of trastuzumab in breast cancer outpatients in Sunpasitthiprasong Hospital, Ubonratchathani: A retrospective cohort study

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ABSTRACT

Trastuzumab, a monoclonal antibody, is recommened for agjuvant of non-metastatic and recurrent or stage IV HER2-positive breast cancer. Although the main adverse effect is that greatly reduces the cardiac function, the incidence of cardiac adverse effect has never been systematically evaluated in Sunpasitthiprasong Hospital. To determine the adverse effects and risk factors with trastuzumab-induced cardiotoxicity. A retrospective cohort study with the percentages changes of left ventricular ejection fraction (%LVEF) in the breast cancer patients. The inclusion criterias were the patient who had been followed-up at outpatient oncology clinic, patients who did not have the %LVEF were excluded from the study. The primary endpoint was the incidence of cardiotoxicity. The mean age of 66 patients treated with trastuzumab was 51.98±10.19 years. Of these, 26 patients (39.39%) had the cardiotoxicity. There were mean of %LVEF baseline was 69.64±7.14% and the mean of %LVEF after receiving trastuzumab was 63.09±9.20%. Mean reduction of %LVEF before and after receiving trastuzumab was 6.55±10.80, there was a statistically significant difference (P<0.001). The mean of %LVEF after receiving trastuzumab was 56.96±7.75% and 38.50±0.50% in patients had a cardiotoxicity and the patients who had a discontinued treatment, respectively. However, the duration of trastuzumab exposure was directly correlated with statistically significant reduction of %LVEF in breast cancer patients (P=0.021, β=0.215, R^2=0.046). Among breast cancer patients treated with trastuzumab, 39.39% of the patients had cardiac adverse events, most of which were found to have %LVEF reduced greater than 10%. The duration of trastuzumab exposure resulted in an increased of %LVEF reduction.

Keywords:
Trastuzumab, Cardiotoxicity, Breast cancer

1. INTRODUCTION

Breast cancer is the most common cancer in women. In 2014, there were an approximately 232,670 new cases of breast and approximately 40,000 deaths in the United States[1]. Breast cancer also be the most common cancer in Thailand. Women have been diagnosed with new cases of breast cancer as high as 24.66%[2]. Multimodality of treatments including surgery, radiation, chemotherapy, hormonal therapy and targeted therapy have been integrated for breast cancer treatment. The combination therapy shown to increase the response and survival rate. However, adverse events were the most important issue which diminished efficacy of treatment.

Trastuzumab is a monoclonal antibody group that has received approval from both the US Food and Drug Administration (FDA) and Thai FDA. In Thailand, Trastuzumab can be used in both early stage and metastasis breast cancer patients with human epidermal growth factor receptor 2 posotive (HER2+). It was found that 25-30% of breast cancer patients had an overexpression of HER2 protein[3]. Trastuzumab can be given in combination with chemotherapy. The typical period of adjuvant trastuzumab for HER2+ breast cancer (BC), in both the

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adjuvant and the metastatic setting. Five-year OS in the adjuvant setting was 86.4% (95% CI, 84.0% to 88.7%). The median survival of patients with advanced BC was 25.1 months (95% CI, 10.1 to 42.5 months)[4].

Regarding to specific targeted site of action of trastuzumab, it has less side effects than chemotherapy. These include rash, low white blood cell count, infection. Trastuzumab has also been found to be associated with a significant serious cardiotoxicity effects, particularly heart failure, both symptomatic and asymptomatic heart failure. Therefore, all patients prior to initiation of trastuzumab must have their cardiac function assessed by an Echocardiogram assay or multigated acquisition (MUGA scan). Left ventricular ejection fraction (%LVEF) should be greater than 50% and cardiac function should be monitored during treatment by an Echocardiogram or MUGA scan every 3 months. According to the study, 5-7% of cardiotoxicity related to trastuzumab treatment, cardiotoxicity increased by 13% when trastuzumab was administered in combination with paclitaxel, and by 27% when anthracyclines were added[5]. Mechanism of trastuzumab induced cardiotoxicity was different from anthracyclines and it can be reversible when the drug is discontinuationed[6]. A subsequent meta-analysis of adjuvant treatment trials confirmed that adjuvant trastuzumab is associated with statistically significant an increased risk of severity grade 3 and 4 congestive heart failure and the relative risk (RR) was 3.14 (95%CI, 2.03-5.02; $P<0.00001$)[7]. The rate of discontinuation of treatment due to trastuzumab induced cardiotoxicity was 5.2% during the 1-year period[8].

A study of the literature database was performed to identify the patient risk factors associated with trastuzumab-induced cardiotoxicity. The study found that, hypertension (OR 1.61, 95% CI 1.14-2.26; $P<0.01$), diabetes (OR 1.62; 95% CI 1.10-2.38; $P<0.02$), previous anthracycline use (OR 2.14; 95% CI 1.17-3.92; $P<0.02$), and older age ($P=0.013$) were all shown to be associated with trastuzumab-induced cardiotoxicity[9]. Other studies have indicated that age, hypertension, preexisting cardiac dysfunction, baseline LVEF<50%, and previous anthracycline treatment or radiotherapy to left chest wall and concomitant chemotherapy are associated with higher incidence of cardiotoxicity[10-12].

Sunpasitthiprasong Hospital is a 1,000 beds tertiary level hospital. The hospital has numerous new cases of breast cancer. Trastuzumab has been prescribed for HER-2 positve breast cancer patient according to Thailand national formulary. Cardiac monitoring has been required at baseline and every 3 months during trastuzumab treatment. However, data on the incidence of trastuzumab-induced cardiotoxicity has never been systematically evaluated in Sunpasitthiprasong Hospital. Therefore, the aim of this study was to determine the adverse effects and factors that may be associated with trastuzumab-induced cardiotoxicity in breast cancer outpatients in Sunpasitthiprasong Hospital, Ubonratchathani.

2. MATERIALS AND METHODS

2.1. Study design and patient population

A retrospective cohort study was performed among breast cancer patients. Patients were identified from hospital electronic medical database using medication code of trastuzumab. Data collection in our study was based on electronic medical chart review. The study inclusion criterias were the patient who had been followed-up at outpatient oncology Clinic, Sunpasitthiprasong Hospital, Ubonratchathani during January 1, 2016 to December 31, 2018 and the patients who had been data recorded in the hospital medical chart with %LVEF data. Patients who did not have the %LVEF data or patients who had only baseline %LVEF data were excluded from the study. The primary endpoint was the incidence of cardiotoxicity and secondary endpoint was the risk factors that may be associated with trastuzumab-induced cardiotoxicity.

2.2. Data collection

The demographic data on each visit were collected including, age, underlying disease, date of diagnosis, history of chemotherapy regimen, TNM staging, hormonal status and HER-2 status. Data were monitored for history of trastuzumab treatment, %LVEF, date of followed-up at each visit. The cardiac function assessed by an Echocardiogram and MUGA scan. %LVEF of each patient was determined at the baseline before received and every 3 months until the completion trastuzuamb treatment. The cardiotoxicity was defined as a decline in %LVEF greater than 10% from baseline or had decreased %LVEF to less than 50%[13-14]. The lowest %LVEF level of patients after trastuzuamb treatment was selected for analysis.

2.3. Statistical analysis

The sample size calculations in this study were calculated based on a 5% incidence of trastuzumab-induced cardiotoxicity in breast cancer patients recieving trastuzumab[5]. Therefore, the sample size should be at least 95 people. All demographic data were presented by descriptive statistics. Categorical data (underlying disease, history of chemotherapy regimen, history of trastuzumab treatment, TNM staging, hormonal status, HER-2 status with FISH test) were described as frequency and percentage. For the continuous variables following the normal distribution, data were presented in mean with standard deviation (SD), otherwise, the median with interquartile range (IQR) was used.

Descriptive statistics were applied to perform cardiotoxicity outcome. Cardiotoxicity incidence was

reported as frequency and percentage. LVEF percentages after trastuzumab treatment was reported as mean±SD (for normal distribution) or median±IQR (for non-normal distribution). Chi-Square test was used to compare the percentage of the cardiotoxicity between the age groups and the underlying disease groups. Independent-Samples T-tests or Mann-Whitney U test were used to compare the means or the median of continuous variables between groups. Univariate analysis using Chi-Square test was applied to compared between cardiotoxicity incidence outcome and risk factors including age groups and the cardiovascular disease comorbidity groups. Simple linear regression was used to analyze the relationship between duration of trastuzumab treatment and %LVEF reduction. All tests with a *P* value of less than 0.05 considered to indicate statistical significance.

3. RESULTS

3.1. Patients and treatments

One hundred breast cancer patients who received trastuzumab were followed-up at Oncology Clinic, Sunpasitthiprasong Hospital, Ubonratchathani during January 1, 2016 to December 31, 2018. Of these, 66 patients met the study criterias. Thirty-four patients were excluded according to the study exclusion criteria, 19 patients did not have baseline of %LVEF data and 15 patients had less than one %LVEF data (Figure 1). The mean age was 51 years old and majority of patients were diagnosed as stage II and stage III breast cancer were 31.82% and 63.64%, respectively. 30.3% of patients had underlying disease. The most common underlying diseases were hypertension followed by hypertension with dyslipidemia. The mean %LVEF at baseline was 69.64±7.14% and the most patients (43.94%) had the %LVEF baseline range of 70-79%. All patients received doxorubicin-based chemotherapy before trastuzumab treatment. The number of treatment cycles with trastuzumab from 4 to 18 cycles and the median number of treatment cycles with trastuzumab were 18 (IQR 1). 55 patients (83.33%) had completed for one-year trastuzumab treatment. 11 patients (16.67%) discontinued therapy before the complete treatment including, 9 patients (13.64%) were diagnosed with disease progression and 2 patients (3.03%) had decreased %LVEF to less than 50% (Table 1). Mean %LVEF after received trastuzumab was 63.09±9.20%. Majority of the %LVEF after trastuzumab treatment was in the range of 60-69%. Mean reduction of %LVEF after trastuzumab treatment was 6.55±10.80 which was significantly lower before trastuzumab treatment (69.64± 7.14% vs 63.09±9.20%; *P*<0.001) (Table 2).

3.2. Cardiotoxicity

Cardiac monitoring is performed in all 66 patients who recieved trastuzumab at baseline and at least once after treatment. Thirty six patients (54.55%) and 10 patients (15.15%) were monitored for cardiac function 2 times and 3 times after treatment, respectively. Cardiotoxicity was observed in 26 patients (39.39%). All of cardiotoxicity had the %LVEF reduction greater than 10% from baseline and 3 (4.55%) of this patients had the %LVEF value less than 50% (Table 3). Two patients

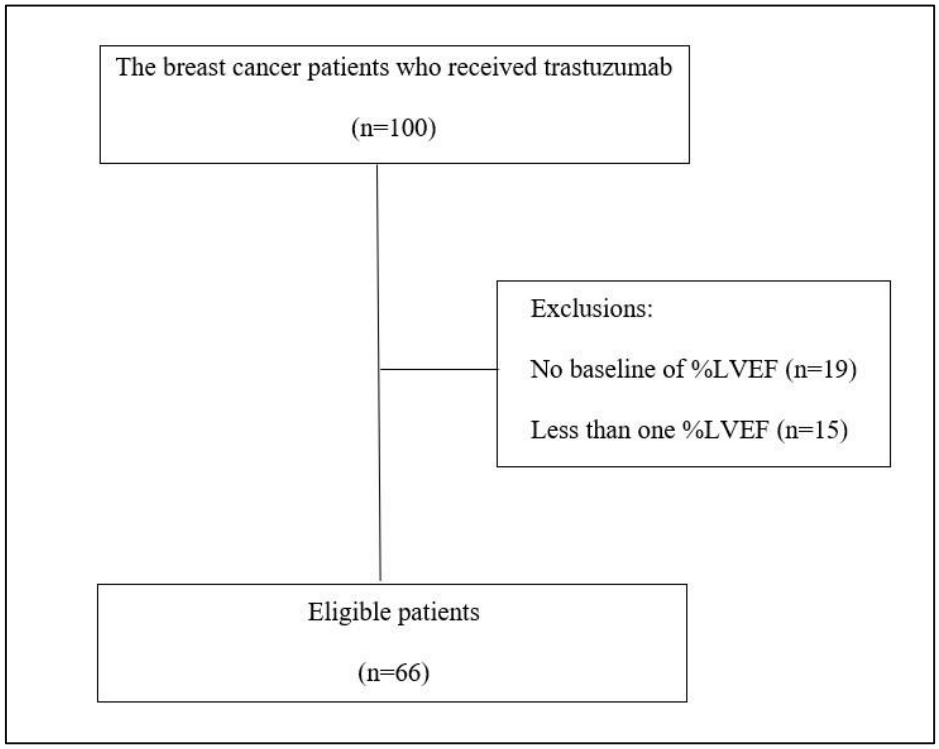

Figure 1. The patient inclusion flow.

Table 1 Demographic data of breast cancer outpatients in the study.

Characteristics	Total (N=66)
Age (years old)	
20-30	1 (1.52%)
31-40	9 (13.64%)
41-50	20 (30.30%)
51-60	22 (33.33%)
61-70	12 (18.18%)
71-80	2 (3.03%)
mean±SD (years old)	51.98±10.19
Stage of disease	
Stage II	21 (31.82%)
Stage III	42 (63.64%)
Stage IV	3 (4.55%)
Hormone status	
ER positive	25 (37.88%)
PR positive	29 (43.94%)
HER2 status	
HER2 2+	15 (22.73%)
HER2 3+	51 (77.27%)
FISH positive	54 (81.82%)
Co-morbidity	
Hypertension	7 (10.61%)
Diabetes melitus	2 (3.03%)
Dyslipidemia	1 (1.52%)
Cardiovascular disease	2 (3.03%)
Hypertension with Diabetes melitus	2 (3.03%)
Hypertension with Dyslipidemia	4 (6.06%)
Hypertension with Diabetes mellitus and Dyslipidemia	2 (3.03%)
No co-morbidity	46 (69.70%)
%LVEF baseline range	
50-59	4 (6.06%)
60-69	28 (42.42%)
70-79	29 (43.94%)
80-89	5 (7.58%)
Mean LVEF before trastuzumab treatment±SD (%)	69.64±7.14
Previous chemotherapy treatment	
AC regimen folllowed TH	36 (54.55%)
AC regimen folllowed TH weekly	2 (3.03%)
AC regimen folllowed T and H	24 (36.36%)
FAC regimen folllowed TH	1 (1.52%)
FAC regimen folllowed H	1 (1.52%)
AC regimen folllowed DOC and H	1 (1.52%)
AC regimen folllowed H	1 (1.52%)
Time to complete treatment	
Complete treatment 1 year	55 (83.33%)
Incomplete treatment, progression of disease	9 (13.64%)
Discontinuation treatment, %LVEF less than 50%	2 (3.03%)

SD; Standard deviation, HER2; Human growth factor receptor type II, ER; Estrogen receptor, PR; Progesterone receptor, FISH; Fluorescence in situ hybridization); AC regimen; Doxorubicin 60 mg/m2 IV q 3 weeklyand Cyclophosphamide 600 mg/m2 IV q 3 weekly, FAC regimen; Fluorouracil 500 mg/m2 IV q 3 weekly, Doxorubicin 50 mg/m2 IV q 3 weeklyand Cyclophosphamide 500 mg/m2 IV q 3 weekly, TH; Paclitaxel 175 mg/m2 IV q 3 weekly and Trastuzumab 8 mg/kg loading dose follow by 6 mg/kg q 3 weekly, TH weekly; Paclitaxel 80 mg/m2 IV q weekly and Trastuzumab 4 mg/kg loading dose follow by 2 mg/kg q weekly x12 weeks, T; Paclitaxel 175 mg/m2 IV q 3 weekly, H; Trastuzumab 8 mg/kg loading dose follow by 6 mg/kg q 3 weekly, DOC; Docetaxel 60-100 mg/m2 IV q 3 weekly

Table 2. Range of %LVEF after received trastuzumab.

	Total (N=66)	*P*-value[a]
Range of %LVEFafter received trastuzumab, n (%)		
30-39	2 (3.03%)	
40-49	1 (1.52%)	
50-59	15 (22.73%)	
60-69	31 (46.97%)	
70-79	14 (21.21%)	
80-89	3 (4.55%)	
Mean LVEF±SD (%)		
Before trastuzumab treatment±SD (%)	69.64 ± 7.14	*P*<0.001
After trastuzumab treatment±SD (%)	63.09 ± 9.20	
Mean reduction of %LVEF after trastuzumab treatment	6.55 ±10.80	

a. Paired Sample T-Test

Table 3. Incidence of cardiotoxicity.

Cardiotoxicity, n (%)	Total (N=66)
All cardiotoxicity	26 (39.39%)
%LVEF reduction was greater than 10%	26 (39.39%)
%LVEF reduction was greater than 10% value less than 50%	3 (4.55%)

Table 4. Incident of cardiotoxicity among group.

	Total, N (%)	Cardiotoxicity (N=26)	*P*-value[a]
Age group (N=66)			
Less than 60 years	53 (80.30%)	22 (84.62%)	0.358
Above 60 years	13 (19.70%)	4 (15.38%)	
CVD Comorbidity group (N=66)			
CVD Comorbidity	20 (30.30%)	7 (26.92%)	0.517
No CVD Comorbidity	46 (69.70%)	19 (73.08%)	

CVD; Cardiovascular disease
a. Chi-Square test

had to discontinue trastuzumab treatment because the %LVEF value was less than 50% from baseline. First patient, age 63 years old, without underlying disease had stage III breast cancer which previously received an doxorubicin/cyclophosphamide (AC regimen). There were three times followed-up for %LVEF monitoring and receiving a total of 17 cycles of trastuzumab prior to discontinuation. %LVEF at third followed up was 38%. The second patient, aged 58 years old with hypertension for underlying disease, had stage III breast cancer which had previously received an AC regimen, there were two times followed-up for %LVEF monitoring and receiving a total of 4 cycles of trastuzumab prior discontinuation. LVEF at second followed up was 39%. However, one patient who still continued trastuzumab treatment even though the %LVEF value was less than 50% from baseline, 48% of %LVEF.

There was no difference between patients with less than 60 years old group, 22 (84.62%) of patients with cardiotoxicity event and above 60 years old group that was found 4 (15.38%) of patients (*P*=0.358). Concordant to CVD co-morbidity group, 7 (26.92%) of patients with cardiotoxicity event in no CVD Co-morbidity group not difference compare to CVD co-morbidity group that was found 19 (73.08%) of patients (*P*=0.517) (Table 4). However, longer duration of trastuzumab treatment significant but week associated with declined %LVEF significantly (*P*=0.021, β=0.215, R^2=0.046) (Figure 2).

4. DISCUSSION

In our study, the majority of breast cancer patients were aged between 51-60 years with mean age of 51.98± 10.19 years. Comparing to the statistics of National Cancer Institute (Thailand) in year 2020[15]. most of the new cases of breast cancer patients by age-group were 50-59 years, 198 (30.23%) patients. In addition, the most of patients in our study had stage III breast cancer, 42 (63.64%) patients. Barron et al, which evaluate cardiotoxicity from trastuzumab treatment, in breast cancer patient reported mean age of included patients was 57.4±10.5 years old[16].

Trastuzumab cardiac toxicity in breast cancer outpatients in this study, there were 26 (39.39%) of patients who had the trastuzumab cardiac toxicity which was considered a relatively high incidence. It was consistent with the study by Tarantini et al. (2012) which a greater incidence of cardiac dysfunction event and heart failure with early breast cancer patients who were treated with trastuzumab-based therapy. 27% of women with trastuzumab-related cardiotoxicity was detected, 20% of this patient showed asymptomatic reduction in %LVEF of

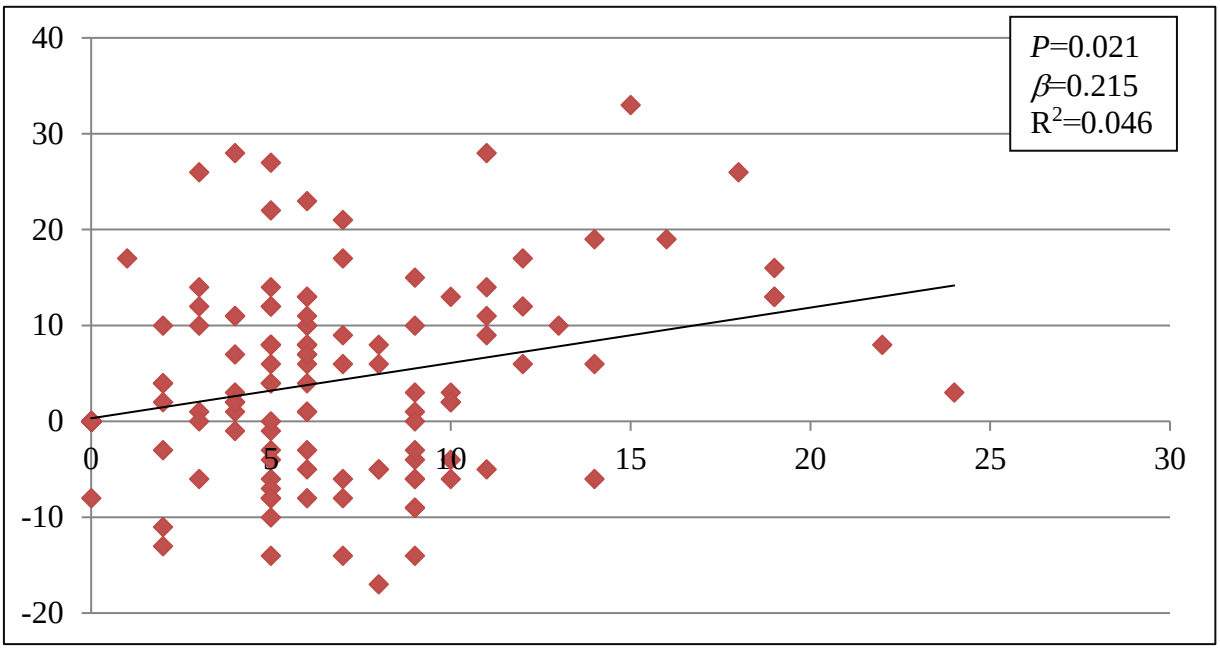

Figure 2. Duration of trastuzumab treatment and percentage LVEF decline.

more than 10% but less than 20%. Our results, incidence of cardiotoxicity showed higher than Tarantini et al. (2012), because previous study had only 87% of patient receiving anthracycline based adjuvant chemotherapy compare to all patient in our study[17].

Mean %LVEF after trastuzumab treatment in this study was 63.09±9.20%. Majority of the %LVEF after trastuzumab treatment was in the range of 60-69%. Cardiotoxicity was observed in 26 patients (39.39%) with the %LVEF reduction was greater than 10% from baseline and 3 (4.55%) of this patients had the %LVEF value less than 50%. Mean reduction of %LVEF after trastuzumab treatment was 6.55±10.80%, significant lower before trastuzumab treatment (69.64±7.14% vs 63.09±9.20%; P<0.001). The declinded mean %LVEF after trastuzumab treatment in our study was similar with the other study. In the Barron et al. (2019) study showed the mean LVEF at baseline significant delcined during trastuzumab treatment (59.3±4.84% vs 50.4±5.22%; P<0.0001). This is because the patient characteristics in the study were similar, ie, the mean aged was not over 60 years old, most of them also were stage II breast cancer, previous anthracycline treatment[16].

There was no difference in the risk factor of trastuzumab related cardiac toxicity in both groups of patients over aged 60 years old or less than 60 years old group and the groups with or without a history of cardiovascular disease which resulted was different from the study of Serrano et al[18]., the resulted in elderly (age≥70 years) breast cancer patients receiving trastuzumab found that, the patients with a history of cardiac disease (P=0.017) and diabetes (P=0.010) were statistically significant risk factor for the cardiotoxicity risk factor. This may be due to CVD risk factor in elderly patient may provided great effect increase cardiotoxicity after trastuzumab treatment compare to our study which majority patient was 51-60 years and only 3.03% of patients over aged 70 years.

Our study still had some limitation including 1) This study collected %LVEF only from hospital medical record. This may not cover outside hospital %LVEF evaluation. 2) Number of participants in this study was lower than calculated sample size. This caused from %LVEF evaluation is an optional to followed up after trastuzumab treatment during the study period. Some patients who lack of follow up %LVEF data were excluded from the study. Lastly, 3) The nature of retrospective studies, some collected information may incomplete such as comorbidity and concomitant medication. In addition, for the reason that the methodology of this study with the data collected in 2016-2018 including 1) This study had been submitted and approved for the hospital ethics committee since 2020, therefore the study data must be collected before 2020. According to the retrospective study design make our study can included the patient data from 2016-2018. 2) Trastuzumab, the duration of trastuzumab standard treatment is 12 months included the duration of %LVEF followed-up in our study both baseline and complete treatment, this make this study was not include the patients between 2019-2020, because this group of patients did not complete trastuzumab treatment. And, 3) The standard of trastuzumab dosing and treatment regimen have not been changed since 1998 (Herceptin was the first targeted therapy by the US Food and Drug Administration; FDA in 1998 to treat HER2+ metastatic breast cancer and in 2006 to treat HER2+ early breast) (Herceptin, Roche). Regardless of the trastuzumab standard treatment regimen between 2016-2018 vs. 2019-2022, the cardio-toxicity outcomes are unlikely to be changed.

5. CONCLUSION

The incidence of trastuzumab induced cardiotoxicity in breast cancer patients were 39.39%. Majority of trastuzumab cardiotoxicty was %LVEF reduced greater than 10%. The %LVEF is significant declined after trastuzumab treatment. The duration of trastuzumab treatment is only risk factor associated with declined of %LVEF in this study.

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Conflict of interest
None to declare.

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Ethic approval
This study was conducted in accordance with the ethics of human research and was accredited by the Human Research Ethics Committee, Sunpasitthiprasong Hospital, Ubonratchathani, project code 068/62R

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Author contribution
WT, WW and MS designed and organized research. WT acquired, analysed and interpreted the data. WW and MS supervised the study. WT and MS performed the statistical analysis. WT wrote the manuscript. WW and MS revised the review. All authors contributed toward data analysis, drafting and critically revising the review; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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