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CORRELATION BETWEEN CHANGES OF NT-PRO BNP AND HS-TROPONIN I LEVELS WITH CARDIOTOXICITY IN BREAST CANCER AFTER THREE CYCLES OF CAF CHEMOTHERAPY

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ABSTRACT

Chemotherapy by Cyclophosphamide, Adriamycin, and Fluorouracil (CAF) regimen in patients with locally advanced breast cancer has a risk of cardiotoxicity. Cardiotoxicity examination standards using left ventricular ejection fraction (LVEF) by echocardiography are considered insensitive for the detection of subclinical ventricular dysfunction. NT-pro BNP and Hs-Troponin I (hs-TnI) as cardiac biomarkers are expected to help in detection of early cardiotoxicity. This study was intended to analyze the correlation between changes of NT-pro BNP and hs-TnI levels with cardiotoxicity in breast cancer after three cycles of chemotherapy. This was a cross-sectional observational study performed at the Dr. Soetomo General Hospital Surabaya. The subjects consisted of 23 breast cancer patients who underwent chemotherapy with CAF regimen. NT-proBNP and hs-TnI examination were carried out using CLIA methods (Immulite 1000, ADVIA Centaur TnI-Ultra). Cardiotoxicity was determined based on >10% decrease of LVEF using echocardiography. There were significant increases of NT pro-BNP and hs-TnI levels before and after treatment (p=0.000, p=0.002). A significant decrease of LVEF was obtained before and after treatment (p=0.000), but only 2 patients (8.7%) showed cardiotoxicity. There was no correlation between changes of NT-pro BNP and hs-TnI levels with changes of LVEF before and after chemotherapy (p=0.666 and r=0.095; p=0.254 and r=-0.28). There was no correlation between changes of NT-pro BNP and hs-TnI levels with cardiotoxicity, which was assessed based on LVEF reduction, in locally advanced breast cancer after three-cycles of chemotherapy with CAF regimen.

Key words: Breast cancer, fluorouracil, adriamycin, and cyclophosphamide regimen, NT-pro BNP, hs-TnI, cardiotoxicity

INTRODUCTION

Breast cancer is the most frequent cancer in the world and with approximately 25% incidence among all cancers in female.[1] In Indonesia, the incidence of breast cancer is 40 cases in 100,000 females. This number has been increasing since 2002, showing 26 cases in 100,000 females.[2] Most locally advanced breast cancer patients will undergo chemotherapy with Cyclofosfamid, Adriamycin, and Fluorouracil (CAF) regimen as the first line therapy. These three agents could cause complication such as cardiotoxicity. Adriamycin belongs to the anthracycline group which has the most cardiotoxicity effect. Breast cancer patients who receive CAF regimen are 5-times higher at increased risk of developing cardiotoxicity compared to patients with other regimens. Incidence of cardiotoxicity varies between 5.1-48%.[3-5] The incidence in one center in Jakarta, Indonesia is quite high, at rate of 36.6%.[6]

Breast cancer patients who receive CAF regimen should be carefully monitored, especially cardiac monitoring. Modalities to monitor heart condition should be ideal, highly sensitive, highly specific, non invasive, and easily accessible. Echocardiography can be used to easily assess diastolic dysfunction but it has a low sensitivity and specificity.[7] This limitation leads to studies on other modalities that can help to detect cardiotoxicity in breast cancer patients who received chemotherapy. Cardiac biomarkers, such as NT-pro BNP and hs-Troponin I (hs-TnI), are expected to play a role in early detection of cardiotoxicity and as an alternative when echocardiography is not available. This study aimed to analyze the correlation between changes of NT-pro BNP and hs-TnI levels with cardiotoxicity in locally advanced breast cancer patients after three cycles of chemotherapy with CAF

regimen.

METHODS

This was a cross-sectional observational study performed at the Dr. Soetomo General Hospital Airlangga University, Surabaya, from September 2017 to July 2018. The subjects consisted of 23 breast cancer patients who underwent chemotherapy with CAF regimen.

The NT-proBNP level was measured with Immulite 1,000 (SIEMENS). The principle of NT-proBNP measurement with Immulite 1,000 was a solid-two-phase site chemiluminescent immunoassay using specific antibodies (sheep polyclonal anti-NT-proBNP) attached to the solid phase of plastic beads, alkaline phosphatase enzymes conjugate with sheep polyclonal anti-NT-proBNP and chemiluminescent substrates. Antibody-coated beads were used in the test unit. This unit test functioned as a site for antigen-antibody reaction, incubation, washing and the formation of signal.[8]

Hs-TnI level was measured with ADVIA Centaur TnI-Ultra assay (SIEMENS) Based on the principle of three-site sandwich immunoassay. Additional reagents, non-magnetic latex particles, were used to reduce nonspecific bonds. Binary Lite reagent which consisted of acridinium ester-labeled polyclonal anti-troponin I antibodies and biotin-labeled anti-troponin I monoclonal antibodies. Solid phase reagents were magnetic latex particles conjugated with streptavidin. All reagents were contained in ReadyPack®. Antibodies in Binary Lite reagents bound to troponin I in the sample while Biotin contained in the immune complex bound to streptavidin-labeled magnetic particles.[9]

Cardiotoxicity was determined after echocardiography showed >10% decrease of the Left Ventricular Ejection Fraction (LVEF) from the initial LVEF value. NT-proBNP and hs-Tn I were measured and echocardiography was carried out before and after three cycles of chemotherapy.

Data were analyzed using Pearson correlation test if the data were normally distributed and Spearman correlation test if the distribution was not normal. The p-value <0.05 was considered as statistically significant. The study was approved by the Medical Ethics Committee of the Dr. Soetomo Hospital Surabaya Indonesia (0352/KEPK/VI/2018).

RESULTS AND DISCUSSION

The majority of subjects were in range of 40-50 years (39.13%) and Infiltrating Ductal Carcinoma (IDC) was the most frequent type (95.65%) of the

Table 1. Baseline characteristics

Characteristics	Total n = 23
Age	
30-39 years	3 (13.0)
40-49 years	9 (39.1)
50-59 years	8 (34.8)
>60 years	3 (13.0)
Location	
Right	12 (52.2)
Left	11 (47.8)
Histopathology	
Infiltrating Ductal Carcinoma (IDC)	22 (95.7)
Infiltrating Lobular Carcinoma (ILC)	1 (4.3)
Echocardiography before chemotherapy	
Diastolic dysfunction	4 (17.4)
Concentric LVH	4 (17.4)
Normal echo	15 (65.2)
Echocardiography after chemotherapy	
Diastolic dysfunction	14 (60.9)
Concentric LVH	2 (8.7)
Normal echo	7 (30.4)
Surface area, mean ± SD	1.51 ± 0.12
Weight (kg), mean ± SD	56.60 ± 7.19
Height (cm), mean ± SD	152.04 ± 8.66
Body mass index, mean ± SD	24.62 ± 3.50

breast cancer. The coefficient of variation on the statistics of the body surface area was less than 10%, illustrating that subjects had almost the same anthropometric tendency. Baseline characteristics of this study could be seen in Table 1.

Level of NT-pro BNP after three cycles of chemotherapy was increased (245.91±176.45 pg/mL). The Kolmogorov Smirnov test showed that all data were normally distributed. There were significant differences between the level of NT-pro BNP and hs-TnI before and after chemotherapy with p=0.000 and p=0.002, respectively. There was increase of hs-TnI levels after three cycles of chemotherapy were also increased (0.0437 0.0511 ng/mL).

There was a significant difference of LVEF levels before and after chemotherapy (p=0.000). The LVEF before and after chemotherapy was 67.98±4.06%, and 64.07±3.53%, respectively. However, this decrease was <ten percent and the after chemotherapy LVEF was >50%. Only two subjects (8.7%) had > 10% decrease of LVEF.

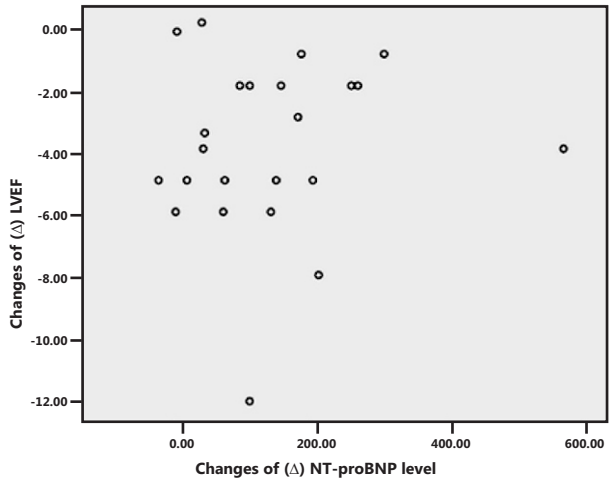

Figure 1. Correlation between changes of NT-pro BNP level and LVEF

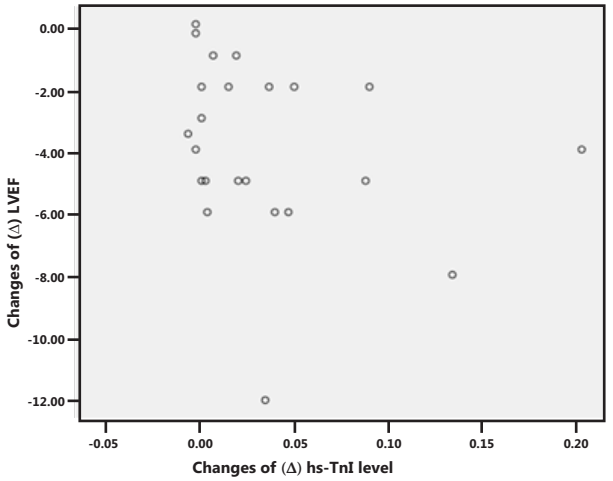

Figure 2. Correlation between changes of hs-TnI level and LVEF

Analysis with Pearson correlation test showed no significant correlation between changes of NT-pro BNP level and LVEF (p=0.666; r = 0.095; p=0.254; r = -0.248) (Figure 1 and 2).

From 23 subjects in this study, the majority of subjects (39.13%) was in age range of 40-50 years and IDC was the most frequent breast cancer type (95.65%). These findings were similar with a study from Pasaribu *et al*. which showed that the mean age of locally advanced breast cancer patients was 48.64±7.787 years old and 75% patients had a histopathology of IDC.[10] Mean height, weight, and body surface area were 152,04 cm, 56.61 kg, and 1.51 cm^2, respectively. Coefficient of the variation of body surface area < than 10% showed that most of the subjects had a similar anthropometric profile, thus chemotherapy dose given to the subjects tended to be similar and did not vary between subjects.

NT-pro BNP level was significantly increased after three cycles of chemotherapy. Some prior studies also demonstrated the increase of NT-pro BNP level in six up to twelve months after chemotherapy with anthracycline regimen, even though those studies did not serially measure NT-pro BNP level during follow up. All those studies showed that NT-pro BNP could be used as a marker to detect subclinical cardiotoxicity.[11-13]

This study also showed a significant increase of hs-TnI level after three cycles of chemotherapy. A previous study by Sawaya *et al*. in early detection and prediction of cardiotoxicity in chemotherapy-treated patients showed that 12 of 43 breast cancer patients who received either Doxorubicin 240 mg/m^2 or Epirubicin 300 mg/m^2 showed increased hs-TnI levels.[14] Ky *et al*. also demonstrated a significant correlation of troponin I level in breast cancer patients three months after chemotherapy.[15]

The Echocardiography after three cycles of chemotherapy with CAF regimen showed that only 7 (30.4%) subjects had normal findings, compared to 15 (65.2%) subjects with normal findings before chemotherapy. In the assessment of LVEF by echocardiography, there was a significant reduction of LVEF after chemotherapy. This finding was also observed in the study by Ismail which explained that cardiotoxic effect of Doxorubicin marked with reduction of LVEF occurred in a cumulative dose > 300 mg/m^2.[16]

This study showed that there was no significant correlation between changes of NT-pro BNP level and cardiotoxicity (p=0.666) in breast cancer patients after three cycles of chemotherapy. This result was different from the previous study by Ky *et al*. which showed a correlation between an increased level of

BNP > 100 pg/mL and cardiotoxicity during or after chemotherapy (p=0.007). Other small studies also demonstrated the relationship between increased BNP or NT-pro BNP levels and left ventricular dysfunction.[17,18] None the less, not all studies showed the capability of NT-pro BNP in detection of cardiotoxicity during chemotherapy with anthracycline regimen.[14,19] No significant correlation between changes of NT-pro BNP level with cardiotoxicity in this study could be associated by different timing of examination. Measurement of NT-pro BNP level and echocardiography after chemotherapy were not carried out at the same time.

This study also showed no significant correlation between changes of hs-TnI level and cardiotoxicity (p=0.254) in breast cancer patients after three cycles of chemotherapy. This finding contradicted with previous studies that showed a correlation between increased troponin I levels and LVEF reduction. The previous study showed that the increased troponin level in post-chemotherapy setting had a different pattern compared within acute myocardial infarction setting. After chemotherapy, troponin I reached its peak level in 24 hours in 55% of patients, while in 33% of patients troponin I reached its peak level in less than 12 hours.[20]

No significant correlation between changes of hs-TnI level and cardiotoxicity in this study could be caused by inappropriate timing of blood sample collection after chemotherapy. In addition, the reduction of LVEF observed in this study was not simultaneously associated with cardiotoxicity. Mean LVEF after chemotherapy was still within the normal limit > 50% (64.07 ± 3.525%). Only 2 patients (8.7%) showed >10% reduction of LVEF compared to the baseline value. Measurement of LVEF depends on image quality, is unable to detect a small regional change in myocard, and varies in different condition.[21] In general, myocardial dysfunction after chemotherapy merely affects regional segments of myocard, not all entire segments. Healthy segments of myocardium could compensate the diseased segments, leading to tendency of normal LVEF in the early stage of disease.[14]

CONCLUSION AND SUGGESTION

There was no correlation between changes of NT-pro BNP level and changes of hs-TnI level with cardiotoxicity, based on the reduction of LVEF, in locally advanced breast cancer patients after three cycles of chemotherapy with CAF regimen. Serial measurement of NT-pro BNP and hs-TnI level was needed to evaluate the increasing pattern. Blood collection and echocardiography should be performed at the same time to more accurately determine the correlation. Subclinical left ventricular systolic dysfunction during and after chemotherapy could be assessed early using NT-pro BNP and hs-TnI.

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