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# The effect of anthracycline chemotherapy on reducing left ventricular ejection fraction in breast cancer patients at Putri Bidadari Hospital Stabat

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## ABSTRACT

**Introduction:** Breast cancer is the most common cancer and also the leading cause of death from cancer in women. Anthracycline chemotherapy is one of the most effective chemotherapy agents and is often used in the treatment of breast cancer. However, its use can cause cardiotoxicity which is characterized by a decrease in LVEF. Regulation of the Minister of Health of the Republic of Indonesia states that breast cancer patients who receive anthracycline chemotherapy must have an echocardiography examination after 2 cycles. This study aimed to assess the effect of anthracycline chemotherapy on reducing LVEF in breast cancer patients.

**Methods:** This study was an observational study with a cross-sectional design. The data used was secondary data in the form of LVEF values of breast cancer patients before being given anthracycline dose chemotherapy with 60 mg/m$^2$ of body surface area (BSA), after being given 2 cycles and after 4 cycles with a total of 22 respondents. Data were analyzed using the Paired T-test. The limitations of this study were small sample size (22 patients) and study was limited to only one hospital.

**Results:** The results of this study obtained p values for LVEF 1-LVEF 2 of 0.748 and LVEF 2-LVEF 3 of 0.215 with an average decrease in LVEF of 0.318% for LVEF 1-LVEF 2 and 1.409% for LVEF 2 and LVEF 3 with p value 0.000 and 0.001.

**Conclusion:** Based on the results of this study it is known that there are differences in LVEF values before and after administration of chemotherapy but there are no significant differences and cannot be classified as cardiotoxicity so that echocardiographic examinations in patients in close proximity are not effective enough to detect anthracycline-induced cardiotoxicity.

**Keywords:** Chemotherapy, anthracyclines, LVEF, cardiotoxicity.
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## INTRODUCTION

Breast cancer is one of the most common cancers, in 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths globally. As of the end of 2020, there were 7.8 million living women diagnosed with breast cancer in the last 5 years.[1] The prevalence of breast cancer in Indonesia in 2020 found a total of 68,858 new cases (16.6%) of a total of 396,914 new cases of cancer with a total death of more than 22 thousand cases.[2]

Breast cancer treatment often consists of a combination of surgical removal, radiation therapy and drugs such as hormonal therapy and chemotherapy.[1] Anthracyclines are chemotherapeutic agents used in the treatment of all stages of breast cancer. One of the most effective anthracycline chemotherapy agents used to treat breast cancer is doxorubicin, however the use of this agent is associated with cardiotoxicity, cardiorespiratory disorders, fatigue, poor quality of life, fat gain, and muscle loss. Anthracycline-related cardiotoxicity is of particular concern because it can lead to myocardial damage and cardiovascular disease many years later in women treated with anthracyclines both in the early and long term.[3,4]

Echocardiography is one of the examinations used for initial screening of cancer patients when they will be given cardiotoxic chemotherapy (one of which is an anthracycline agent, namely doxorubicin. In addition, echocardiography is also used to evaluate the side effects of cardiotoxic chemotherapy, which is confirmed by the decision of the Minister of Health of the Republic of Indonesia number HK.01.07/MENKES/6485/2021 concerning the national formulary which states that an echocardiographic examination should be carried out every 2 cycles of therapy in breast cancer patients.[5] However, using echocardiography to assess left ventricular ejection fraction shows high diagnostic sensitivity and predictive ability low in detecting subclinical myocardial damage besides that heart damage can only be assessed as early as a year by echocardiography in chemotherapy

patients without previous CVD, that's why the development of a diagnostic tool for detecting heart damage in anthracycline-induced chemotherapy patients is highly desirable. Based on this background, this study aimed to evaluate the effect of anthracycline chemotherapy on reducing LVEF in breast cancer patients.

## METHODS

This research was an observational study with a cross-sectional design to assess the effect of anthracycline chemotherapy on the reduction of left ventricular ejection fraction in breast cancer patients at Putri Bidadari Hospital. The sampling technique in this study was carried out using the total sampling method, which is a sampling technique that the number of samples is the same as the population of 22 breast cancer patients treated at Putri Bidadari Stabat Hospital.

Data collection begins with submitted a permit application to the institution, then the researcher sets a date and time and then carried out data collection. The data used in this study were secondary data obtained from the Oncology department of Putri Bidadari Stabat Hospital in the form of patient data who were to carry out first-line chemotherapy with a regimen that included anthracyclines. LVEF measurements were carried out by echocardiography 3 times, namely before being given chemotherapy, after chemotherapy cycles 1 to 2 and after chemotherapy cycles 3 to 4.

Data were analyzed using the SPSS program with univariate and bivariate using a parametric paired t-test to see differences in LVEF before receiving anthracycline chemotherapy, after the 2nd and 4th cycles. The difference was said to be significant if the p value <0.05.

## RESULTS

This study involved 22 people who had been adjusted according to the inclusion and exclusion criteria. Table 1 showed that the average age of the respondents is 47 years with the youngest being 32 years and the oldest being 64 years. It is also known that the average LVEF value of patients before being given anthracycline chemotherapy (LVEF) was 64.27% with a minimum LVEF of 50% and a maximum LVEF of 80%. In LVEF after being given 2 cycles of anthracycline chemotherapy (LVEF 2) the average LVEF was 63.95% with a minimum LVEF of 51% and a maximum LVEF of 72%. On echocardiographic examination after 4 cycles (LVEF 3) an average LVEF of 62.55% was obtained with a minimum LVEF of 48% and a maximum LVEF of 70%. Table 2 showed the results of the data normality test using the Kolmogorov Smirnov test with a p>0.05 value for all LVEF, which means the data is normally distributed. Table 3 showed the data homogeneity test using the Levene test and the results obtained are a p value of 0.784 (p> 0.05). This means that the research data is homogeneous so that the research can be continued using the selected parametric test, that is the paired t test.

**Table 1. Frequency distribution**

| Variable | Mean | Min | Max |
|---|---|---|---|
| Age | 47 years old | 32 years old | 64 years old |
| LVEF 1 | 64.27% | 50 % | 80 % |
| LVEF 2 | 63.95% | 51% | 72 % |
| LVEF 3 | 62.55% | 48% | 70 % |

**Table 2. The result for normality test**

| Echocardiography | P value |
|---|---|
| LVEF 1 (Before) | 0.072 |
| LVEF 2 (after 2 cycles) | 0.065 |
| LVEF 3 (after 4 cycles) | 0.179 |

**Table 3. Homogeneity test**

| Echocardiography | P value |
|---|---|
| LVEF | 0.784 |

**Table 4. The effect of using anthracycline chemotherapy on reducing LVEF in breast cancer patients**

| | Mean | P value | Sig |
|---|---|---|---|
| LVEF 1-LVEF 2 | 0.318 | 0.000 | 0.748 |
| LVEF 2-LVEF 3 | 1.409 | 0.001 | 0.215 |

The results of the paired T-test to obtain a comparison of the LVEF value before being given chemotherapy with the LVEF value after 2 cycles of chemotherapy, a p value of 0.000 was obtained which indicated that there was a difference between the LVEF value before and after 2 cycles of chemotherapy (Table 4). However, the paired t test for LVEF 1-LVEF 2 showed a significance value of 0.748 (p> 0.05). of 0.318%. Furthermore, a test was performed on the LVEF value after administration of 2 cycles of chemotherapy and the next 2 cycles. A p value of 0.001 was obtained which indicated that there was a difference between the LVEF values after 2 cycles of chemotherapy and the following 2 cycles. However, in the paired t-test, a significance value of 0.218 (p> 0.05) was obtained which showed no significant difference with the average difference in LVEF after 2 cycles of chemotherapy (cycles 1 and 2) and 2 cycles thereafter (cycle 3 and 4) only 1.409%.

## DISCUSSION

This study found that there is no significant difference in LVEF in patients. This is because LVEF measurements with echocardiography are carried out in close time intervals, namely after every 2 cycles of anthracycline chemotherapy so that the difference in LVEF shown is not too significant. In addition, it was also found that several respondents had the same LVEF values between before and after chemotherapy.

The result of the study found that the average age of patients is 47 years, which according to the WHO age category belongs to the adult group. This is also one of the reasons for the absence of a significant relationship in this study. Age is a risk factor for cardiovascular disease in addition to several other

aggravating factors such as administration of anthracycline chemotherapy. The American Heart Association) reports that the incidence of cardiovascular disease in US men and women is 40% in the age group 40–59 years, 75% in the age group 60–79 years, and 86% in the age group over 80 years.[6] Age can also be a factor in assessing cardiotoxicity in patients receiving anthracycline chemotherapy where the risk of cardiotoxicity with anthracyclines increases with older age regardless of comorbidity and performance status. In addition, older patients have greater cardiovascular risk factors.[7]

The mechanism of anthracycline-induced cardiotoxicity occurs due to the formation of excess reactive oxygen species and the formation of iron complexes. Some other literature states that anthracyclines can inhibit topoisomerase 2β which can damage double strands in DNA and cause cardiomyocyte death.[8] Risk factors for anthracycline-associated cardiotoxicity include cumulative lifetime dose, infusion regimen, pre-existing cardiac disease, and cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, obesity, and older age (>65 years.[9]

Anthracyclines are one of the most widely used chemotherapeutic agents and have been shown to be effective in various tumors, especially breast cancer. Even so, the cardiotoxic effect is still one of the things that is detrimental to patients. A retrospective study conducted in the 1980s in a pediatric population divided anthracycline-induced cardiotoxicity by time and onset, i.e., acute, following a single dose or a single course of anthracyclines characterized by onset of clinical manifestations within 2 weeks of the end of the cycle. treatment, intermediate onset that develops within 1 year of onset is the most common and clinically relevant type and usually presents as a hypokinetic, dilated cardiomyopathy leading to heart failure. The third type is chronic onset that develops years or even decades after the end of chemotherapy. The clinical relevance of this classification is unclear and cannot be applied to adults.[10]

The timing of anthracycline-induced cardiotoxicity is not well defined because to date there are no prospective studies that have monitored cardiac function regularly in adults for >3 years. This has resulted in unclear recommendations for monitoring cancer patients treated with chemotherapy containing anthracyclines, and often limited to symptomatic or symptomatic patients. Although several guidelines are available, there is no consensus on the optimal monitoring strategy scheme for anthracycline-induced cardiotoxicity. Although there are recommendations for monitoring the possibility of cardiotoxicity in the literature, it is still so general that it cannot determine how often or for how long cardiac function should be monitored after anthracycline administration.

In Indonesia, a regulation has been wrote in the Decree of the Minister of Health of the Republic of Indonesia number HK.01.07/MENKES/6485/2021 which states that an echocardiographic examination must be carried out every 2 cycles of therapy for breast cancer patients receiving anthracycline chemotherapy such as epirubicin and doxorubicin.[5] However, several major limitations of this approach in clinical practice have been emphasized in that not all patients treated with chemotherapy require repeated LVEF monitoring as the guidelines suggest. In this study, LVEF was examined every 2 cycles after administration of chemotherapy and it can be seen that administration of anthracycline chemotherapy can have an effect on reducing LVEF which can be determined through echocardiography. However, the LVEF reduction value obtained was not too much different between before administration, after 2 cycles and the next 2 cycles with an average decrease of <10 so that it does not meet the cardiotoxicity criteria as defined by international oncology guidelines which state that cardiotoxicity is characterized by LVEF absolute decrease of more than 10% with a decrease below the normal limit of 50%.[11]

The results obtained in this study are in line with research conducted by Hasnah (2019) which showed that there was no significant difference in the decrease in LVEF before and after giving 2 cycles of chemotherapy.[12] It is necessary to reassess because there are many other risk factors that can be related to disorders of the heart besides the effects of the anthracycline itself. Echocardiographic examinations carried out in adjacent cycles are also ineffective and can have a negative impact on patient management and the cost-effectiveness ratio for the health system. In addition, much doubt has been raised about the usefulness of cardiac function monitoring as the majority of cardiotoxicity after anthracycline-containing therapy occurs within the first year and is related to anthracycline dose and LVEF at the end of treatment.

The limitations of this study were small sample size (22 patients) and study was limited to only one hospital. Therefore, further research to carefully observe the effect of anthracycline chemotherapy on reducing left ventricular ejection fraction still needed.

## CONCLUSION

The results of the study concluded that there were differences in LVEF values before and after administration of anthracycline chemotherapy in breast cancer patients. The difference obtained in the LVEF value before administration, after 2 cycles and the next 2 cycles was not clinically significant.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest related to the material presented in this article.

## ETHICAL STATEMENT

Ethical approval (No. 1041/KEPK/FKUMSU/2023) was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Muhammadiyah University, North Sumatra.

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## AUTHOR CONTRIBUTION

All of the authors equally contribute to the study from the conceptual framework, data gathering, and data analysis until reporting the study results through publication.

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