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BMI and TLC Influences Doxorubicin/Epirubicin Neoadjuvant Chemotherapy Response in Patients with Locally Advanced Breast Cancer

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Abstract

Anthracycline-based neoadjuvant chemotherapy is the recommended therapy for locally advanced breast cancer (LABC) patients. Unfortunately, no study has reported the relationship between body mass index (BMI), total lymphocyte count (TLC), and responses to this type of chemotherapy. This study aimed to determine the relationship between BMI, TLC, and response to doxorubicin/epirubicin neoadjuvant chemotherapy in LABC patients. A retrospective cohort design was applied to medical records of LABC patients undergoing neoadjuvant chemotherapy at Ulin General Hospital Banjarmasin, Indonesia, from July to December 2021. BMI and TLC data were assessed based on the values before chemotherapy, while the chemotherapy response was measured using the RECIST 1.1 criteria after 3 cycles. Multinomial logistic regression test with 95% confidence level was used to analyze these data. The results showed that as many as 71% of patients experienced a Partial Response (PR), while 5% and 23% of the patien demonstrated stable disease (SD) and progressive disease (PD), respectively. Each increase in BMI of 1 kg/m^2 was significantly associated with an increase in the occurrence of PR and PD by 1.26 times and 1.29 times, respectively, when compared to the occurrence of PD. Meanwhile, an increase in TLC of 100 cells/mm^3 was associated with an increase in the occurrence of PR by 6.83 times and an increase in the occurrence of SD. of 6.94 when compared to the occurrence of PD. Therefore, there is a significant relationship between BMI, TLC, and response to anthracycline-based neoadjuvant chemotherapy in LABC patients.

Keywords: Anthracyclines, body mass index, locally advanced breast cancer, neoadjuvant chemotherapy, total lymphocyte count

Introduction

Breast cancer is the most common malignancy in the world (10.4% of all cancers) and is the leading cause of death for women aged between 20–50 years.[1] Locally advanced breast cancer (LABC) is a subset of breast cancer characterized by the most advanced breast tumor without distant metastasis. LABC is a breast cancer with a high rate of locoregional and systemic failure.[1,2,3] Multimodality treatment of LABC includes surgery, chemotherapy, and radiotherapy in combination with hormonal therapy and targeted therapy if needed.[4] Neoadjuvant chemotherapy is the treatment of choice for LABC. There are 2 classes of neoadjuvant chemotherapy commonly used: taxane-based and anthracyclines.[5,6]

Assessment of changes in tumor mass is particularly important in the clinical evaluation of cancer therapy. Assessment of response to neoadjuvant chemotherapy can be classified according to the Response Evaluation Criteria

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in Solid Tumors (RECIST) criteria.[7] Several factors influence the response to chemotherapy, including disease stage, receptor subtype, patient's age, patient's body mass index, and tumor size before chemotherapy.[8] Other studies have also stated that there is a relationship between peripheral blood lymphocyte (PBL), neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), with chemotherapy response.[9,10]

Nutrition is an important factor in the treatment and development of cancer.[11] The observational study of Rao et al.[12] showed that nutritional status before chemotherapy affected quality of life, strength, and response to chemotherapy in patients with breast malignancy. Decreased anthropometric parameters of breast cancer patients during chemotherapy lowered the prognosis of the disease.[13] However, a prospective cohort study in the United States showed conflicting results: weight gain after breast cancer increased recurrence and mortality from breast cancer compared to women with a body mass index (BMI) <25.[14,15] BMI as a parameter of nutritional condition is potentially the influential factor in the response of neoadjuvant chemotherapy in LABC patients.

Total Lymphocyte Count (TLC) can be used as a nutritional parameter and predict disease prognosis.[16] Previous studies have established that lymphocytes will go down in a state of acute hunger and increase after being given food back, but this study is still being carried out in experimental animals.[17] In addition, peripheral blood lymphocytes are an indicator of immune system function in cancer patients, and their number is associated with tumor prognosis. Lymphocytes have an antineoplastic effect role through apoptosis-induced T cell immune response. Chemotherapy can alter the balance of lymphocyte subpopulation and cause lymphocyte depletion, and potentially interfere with the effectiveness of the antitumor immune response. Conesa et al. reported that a low baseline peripheral blood lymphocyte count and a large decrease in peripheral blood lymphocyte count after chemotherapy confer a poor prognosis for breast cancer recurrence. Further, baseline absolute lymphopenia is a strong independent prognostic factor for disease-free and overall survival.[10,18] TLC is potentially an influencing factor in the response to neoadjuvant chemotherapy in LABC.

The purpose of this study is to determine the relationship between BMI and TLC with the anthracycline-based neoadjuvant chemotherapy response in patients with LABC.

Methods

This study was an observational research design with a cohort-retrospective approach. The subjects of this study were patients at Ulin Hospital who were diagnosed with LABC by an oncology surgeon. The samples were LABC patients who underwent a neoadjuvant chemotherapy regimen of Doxorubicin/ Epirubicin at Ulin Hospital Banjarmasin from July 2021 to December 2021. The sampling technique used was purposive sampling. Subject inclusion criteria were those of locally advanced breast cancer patients. Research subjects were excluded if the breast cancer was in early, advanced, and metastatic stages.

The independent variables in this study were BMI and TLC assessed before chemotherapy administration. The examination of BMI and TLC was carried out before the first cycle. If there are anemia and leukopenia conditions, the examination would be carried out after the condition had been corrected. BMI and TLC were analyzed as continuous data. The dependent variable in this study was the response to doxorubicin/epirubicin which was assessed after 3 cycles of chemotherapy administration and was categorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). These variables were obtained from the patient's medical record.

Analysis of the relationship between variables was carried out by multinomial logistic regression test, both bivariate and multivariate, with a 95% confidence level.

This research has obtained a letter of ethics from the Health Research Ethics Committee, Faculty of Medicine, University of Lambung Mangkurat Banjarmasin-Indonesia with No. 07/ KEPK-FK ULM/EC/1/2022

Results

This study was conducted on 94 subjects who met the inclusion and exclusion criteria; the characteristics of the patients are shown in Table 1.

Based on Table 1, the mean age of the 94 LABC patients who received anthracycline-based neoadjuvant chemotherapy was 49.68 years. Most of the patients experienced Partial

Table 1 Patient Characteristics

Characteristics	(n=94)	Mean±SD	Min	Max
Age		49.68±8.99	28.00	72.00
Response to anthracycline-based chemotherapy		-	-	-
Complete Response (CR)	0 (0%)			
Partial Response (PR)	67 (71%)			
Stable Disease (SD)	5 (5%)			
Progressive Disease (PD)	22 (23%)			
BMI (kg/m^2)*		23.12±5.16	15.98	35.18
Underweight (BMI<18.5)	18 (29%)			
Normal (18.5 <BMI<25.0)	49 (52%)			
Overweight (BMI >25.0)	27 (29%)			
Total Lymphocyte Count (TLC)** cell/mm^3		164.94±74.45	15.27	519.2
Normal (800-4000)	0 (0%)			
Abnormal (TLC < 800)	94 (100%)			

*BMI: body mass index; **TLC: total lymphocyte count

Response (PR) with a total 67 (71%) patients, 5 (5%) patients showed Stable Disease (SD), 22 (23%) patients experienced Progressive Disease (PD), and there were no patients who experienced Complete Response (CR).

In measuring the patient's BMI, the average BMI of the patient was 23.12±5.16 kg/m^2, which means it was in normal condition. Forty-nine patients (52%) had normal BMI conditions. The number of patients with the obese condition was 27 people with the highest score of 35.18 kg/m^2 while the number of patients with the thin condition was 18 people with the lowest score 15.98 kg/m^2.

Based on the measurement of the patient's TLC, it was found that the TLC values of all patients were beyond the Normal Reference Value (800–4000 cells/mm^3) with an average TLC of 164.94±74.4 cells/mm^3. The highest TLC value recorded was TLC value of 519.2 cells/mm^3.

The bivariate analysis of the relationship between the BMI variable and TLC with response to anthracycline-based neoadjuvant chemotherapy in LABC patients is presented in Table 2.

The results of the bivariate analysis in Table 2 show that each increase in BMI of 1 kg/m^2 was significantly associated with an increase in the occurrence of PR by 1.22 times compared to the occurrence of PD (RR 1.22, 95%CI 1.076–1.382, p=0.002), and each increase in BMI of 1 kg/m^2 was significantly associated with an increase in the occurrence of SD by 1.25 times compared to the occurrence of PD (RR 1.25, 95%CI 1.018–1.544, p=0.034).

Table 2 Bivariate Analysis of the Relationship between BMI and TLC with Response to Neoadjuvant Chemotherapy Based on Anthracyclines

Independent Variable	RR	95%CI*	*p* value
Partial response vs progressive disease			
Body mass index	1.22	1.076–1382	0.002
Total lymphocyte count	5.46	2,009–14,849	0.001
Stable disease vs progressive disease			
Body mass index	1.25	1.018–1.544	0.034
Total lymphocyte count	5.66	1.253–25.557	0.024

*95%CI = 95% *confidence interval*

Table 3 Multivariate Analysis of the Relationship between BMI and TLC with Response to Neoadjuvant Chemotherapy Based on Anthracyclines

Independent Variable	aRR	95%CI*	p-value
Partial response vs progressive disease			
Body mass index	1.26	1.085–1.458	0.002
Total lymphocyte count	6.83	2.213–21.063	0.001
Stable disease vs progressive disease			
Body mass index	1.29	1.034 –1.615	0.024
Total lymphocyte count	6.94	1.419–33.929	0.017

*95%CI = 95% *confidence interval*

Meanwhile, an increase in TLC of 100 cells/m3 was significantly associated with an increase in the occurrence of PR by 5.46 times compared to the occurrence of PD (RR 5.46, 95%CI 2.009–14,849, p=0.001), and an increase in TLC of 100 cellsm3/ was significantly associated with an increase in the occurrence of SD by 5.66 compared to the occurrence of PD (RR 5.66, 95%CI 1.253–25.557, p=0.024).

The effect of the BMI variable and TLC on the response to anthracycline-based neoadjuvant chemotherapy for LABC patients, with adjustment to each other's variables, is shown in Table 3.

Table 3 shows the multivariate analysis after adjusting the variables. It can be seen that every increase in BMI of 1 kg/m^2 was significantly associated with an increase in the occurrence of PR by 1.26 times compared to the occurrence of PD (aRR 1.26, 95%CI 1.085–1.451, p=0.002), and each increase in BMI of 1 kg/m2 was significantly associated with an increase in the occurrence of SD by 1.29 times compared to the occurrence of PD (aRR 1.29, 95%CI 1.034–1.615, p=0.024).

Meanwhile, after adjusting to each other, an increase in TLC of 100 cells/m3 was significantly associated with an increase in the occurrence of PR by 6.83 times compared to the occurrence of PD (aRR 6.83, 95%CI 2.213-21.063, p=0.001), and an increase in TLC of 100 cells/m3 was significantly associated with an increase in the occurrence of SD by 6.94 compared to the occurrence of PD (aRR 6.94, 95%CI 1.419–33.929, p=0.017).

Discussion

This study aimed to examine the relationship between BMI and TLC and the response to anthracycline-based neoadjuvant chemotherapy in LABC patients. There were 94 patients as a sample of the study. They were patients at Ulin Hospital and were diagnosed by an oncology surgeon as LABC patients. The patients underwent anthracycline-based neoadjuvant chemotherapy at Ulin Hospital Banjarmasin from July 2021 to December 2021.

After reviewing the result of the response to anthracycline-based neoadjuvant chemotherapy, the tumor size of most patients had decreased and only 23% of the patients had PD or increasing tumor size >20% (at least 5 mm) from the initial lesion. This indicates that anthracycline-based neoadjuvant chemotherapy provides beneficial results for LABC patients at Ulin Hospital Banjarmasin, where the majority of patients experience a change for the better.

Chemotherapy is a type of treatment that aims to destroy cancer cells. Neoadjuvant therapy aims to reduce tumor size and control micrometastasis. The results of neoadjuvant chemotherapy in most patients showed the presence of PR where the tumor size of most patients was reduced by at least 30% of the initial lesion.

Based on the results of bivariate and multivariate analysis, it was found that there was a significant relationship between the patient's BMI and the response to anthracycline-based neoadjuvant chemotherapy in LABC patients. An increase in BMI of 1 kg/m^2 was significantly associated with an increase in the incidence of PR by 1.26 times (26% increase in incidence) compared to the occurrence of PD, and an increase in the incidence of SD by 1.29 (29% increase in incidence) compared to the incidence of PD. This BMI value is a representation of a person's nutritional status.

Patients with lower BMI are unable to meet the nutrition needs of their bodies. As a result, the body will find it difficult to perform metabolism,

and balance water, minerals, and acid-base in body fluids. This condition slows down the regeneration of the body tissues and slows down the replacement of the damaged cells. Poor nutritional status causes an increased risk of other comorbidities and can increase symptoms caused by side effects of chemotherapy.[19]

The result of the study on nutritional status/BMI is consistent with that of Alpizar et al.[23] who stated that the patient's malnourished condition significantly affected the efficacy of therapy as it decreased the response to chemotherapy and increased toxicity.Normal nutritional status can reduce the side effects of chemotherapy. Meanwhile, the condition of patients with obese BMI did not indicate a significant difference in their effect on chemotherapy response when compared to patients with normal BMI. This happens because most patients with obese BMI tend to be in the category of mild obesity so the level of nutritional adequacy in patients with obese BMI is not significantly different from patients with normal BMI.

The result of the study on BMI also supports the statement of Pradjatmo et al.,[21] that good nutritional status of cancer patients will have a positive effect on patients when receiving surgery, chemotherapy, or radiotherapy. Weight loss or poor nutritional status reduces the immunological response to tumor cells and resistance to infection, increases susceptibility to complications and decreases the response to postoperative therapy, chemotherapy, and radiotherapy.

Based on the results of bivariate and multivariate analysis, TLC was significantly associated with the response to anthracycline-based neoadjuvant chemotherapy for LABC patients. Each addition of 100 cells/mm^3 TLC value was significantly associated with an increase in the incidence of PR by 6.83 times compared to the occurrence of PD, and was significantly associated with an increase in the incidence of SD by 6.94 times compared to the occurrence of PD. These results mean that the higher the patient's TLC value, the higher the chemotherapy response status obtained.

TLC parameter is a parameter of nutrition and prediction of disease prognosis. The TLC parameter measures the number of lymphocytes and leukocytes present in the patient's body. Lymphocytes are one of the main components in the immune system and are indispensable in the immune response to cancer. The higher the lymphocyte count of a patient, the better the response of the patient's immunity to cancer they are suffering from.

The result of this study on TLC corroborates the result of Conesa's study which examined differences in the number of lymphocytes before and after chemotherapy in breast cancer patients. Low lymphocyte count values are associated with poor condition of advanced breast cancer patients before and after chemotherapy.[22]

After the doxorubicin/epirubicin neoadjuvant chemotherapy treatment, TLC levels in the patient's body were still in the abnormal range, which was below 800 cells/mm^3. Even though the increase in TLC was followed by an increase in the response status to chemotherapy, the low TLC in LABC patients should be a concern. The low TLC value is in line with the research of Zehua et al. where 371 rectal cancer patients were examined. Based on the study, it was found that the circulating lymphocyte count decreased during neoadjuvant therapy, including chemoradiotherapy or chemotherapy alone in locally advanced rectal cancer.[18] According to Rocha and Fortes,[24] responses to changes in immunity, such as decreased TLC, increase the frequency and severity of infections. This results in an increase in mortality and morbidity.

Based on the results of this study and previous studies, it is important to monitor the patient's nutritional status (in this case assessed from BMI) and TLC during the anthracycline-based neoadjuvant chemotherapy for LABC patients. These two parameters are shown to be significantly related to the response to anthracycline-based neoadjuvant chemotherapy. Changes in BMI and TLC during chemotherapy will be important as well, considering that these changes will also affect the outcome of the chemotherapy response.

The limitation of this study is that there is no adjustment to other confounding variables that could also affect the response to neoadjuvant chemotherapy, such as age, disease stage, receptor subtype, and others. It is hoped that future studies will also consider these confounding variables.

To this date, there have been limited studies on the effect of TLC on the response of anthracycline-based neoadjuvant chemotherapy in LABC patients although the measurement of TLC parameters is one of the parameters which will cost lower compared to other parameters. This is one of the strengths of this research.

Based on the findings and the discussion above, it can be concluded that there is a significant relationship between BMI and TLC and the response to anthracycline-based

neoadjuvant chemotherapy in LABC patients. Suggestions that can be given based on the results of this study are as further research needs to be conducted on the relationship between BMI and TLC of patients with response to anthracycline-based neoadjuvant chemotherapy in LABC patients, taking into account other factors that may influence the response to anthracycline-based neoadjuvant chemotherapy. There should be further research to examine the nutritional improvement program that is carried out concurrently with the administration of anthracycline-based neoadjuvant chemotherapy in patients with LABC to evaluate the effect of this intervention on the speed and status of the chemotherapy response.

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