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Correlation between Serum Interleukin-6 Levels and Clinical Response to Anthracycline-Based Neoadjuvant Chemotherapy Regimen in Locally Advanced Breast Cancer Patients

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ABSTRACT

Background: Neoadjuvant chemotherapy is the initial therapy and the main pillar of treatment for locally advanced breast cancer (LABC). Currently, there is marker that widely accepted as a predictive factor for chemotherapy response in LABC. Elevated serum interleukin-6 (IL-6) levels and tumor sites have been proposed as prognostic markers for breast cancer. In this study, we aimed to examine the association between serum IL-6 levels with clinical response after the administration of neoadjuvant chemotherapy.

Methods: This study is an observational analytic study with a cohort prospective character to determine the relationship between IL-6 serum levels and clinical response to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer (LABC) patients at Dr. Soetomo General Hospital during April 2021 to September 2021 with a total sample of 38 patients.

Results: Fourteen patients (77.8%) had a positive response in the low IL-6 level group and 4 patients (22.2%) had a negative response. In high IL-6 level group, 4 patients (40%) had a positive response and 16 patients (80%) had a negative response. The cut off of 15.495 pg/mL was used as cut off value for IL-6 to predict the clinical response to chemotherapy. The sensitivity, specificity, PPV, NPV, and accuracy of IL-6 to predict the clinical response after chemotherapy were 80.0%, 77.8%, 80.0%, 77.8%, and 78.9%, respectively.

Conclusion: There is a relationship between serum IL-6 levels and clinical response to anthracycline-based neoadjuvant chemotherapy regimens in locally advanced breast cancer (LABC) patients.

Keywords: interleukin-6, clinical response, locally advanced breast cancer

INTRODUCTION

Breast cancer is the most common cancer in women and the leading cause of cancer-related death. Breast cancer cases are increasing every year and as many as 2.2 million women in the world suffer from breast cancer each year. In Indonesia, a total of 17,792 new breast cancer patients was reported and the aged standard in the incidence rate of female breast cancer was 48.9 per 100,000 (GLOBOCAN 2012, https://gco.iarc.fr/). In Indonesia, locally advanced breast cancer (LABC) is the most common stage found in breast cancer patients.

Neoadjuvant chemotherapy is the initial therapy and the main pillar of treatment for LABC. Achieving a pathological complete response is the main goal of neoadjuvant chemotherapy. According to the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), an anthracycline-based regimen with a combined regimen of

cyclophosphamide, adriamycin (doxorubicin hydrochloride), fluorouracil (CAF) or cyclophosphamide, epirubicin, fluorouracil (CEF) can be used as first-line chemotherapy for LABC.[1-3] However, a descriptive analytic study by Audrina et al in 2011-2013 showed that 52% of patients who receiving neoadjuvant chemotherapy had a stable disease response. That study has implications for many studies that discuss the factors that influence the response of chemotherapy.[4] Factors such as tumor size and nodule, tumor biologic factors, and tumor histological grading, as well as inflammatory mediators have been investigated by various studies and are said to play a role in the response to chemotherapy in breast cancer.[5,6]

Interleukin-6 (IL-6) is an inflammatory mediator released by various cells in the tumor microenvironment. Elevated levels of IL-6 in serum and tumor sites have been demonstrated in several cancers including breast cancer. Despite few studies, serum IL-6 values have also been proposed as a negative prognostic marker for breast cancer. IL-6 can also modulate tumor therapeutic resistance such as multidrug resistance (MDR). Elevated serum IL-6 levels may exert a resistance effect on Doxorubicin chemotherapy.[7-9]

Currently, there was no tumor biologic factors that can be used clinically as predictive factors of chemotherapy response in LABC with high accuracy. Several researchers have tried to find predictive factors of chemotherapy response in LABC, but the results were not satisfying.[10] IL-6 can attract the attention of oncologists as a predictor factor of chemotherapy response. Research conducted by Mittal et al., showed that increased levels of IL-6 will give a poor response to chemotherapy.[8] Therefore, in this study we aimed to examine the association between IL-6 levels with clinical response in LABC patients treated with anthracycline-based neoadjuvant chemotherapy.

MATERIALS & METHODS

Study participants

The study was designed as a cohort prospective study in order to determine the relationship between IL-6 levels and clinical response after anthracycline-based neoadjuvant chemotherapy. We measured the IL-6 serum levels one day before administering the neoadjuvant chemotherapy. The measurement of serum IL-6 levels was carried out at the Clinical Pathology Laboratory, Dr. Soetomo General Hospital (Surabaya, Indonesia). In addition, patients' information such as name, age, gender, address, and telephone number were recorded. Each patient was explained about the study and asked to sign the informed consent as an agreement to participate in the study. Ethical approval was obtained from the Ethics Committee of Dr. Soetomo General Hospital (Surabaya, Indonesia) following the guidelines of the Declaration of Helsinki.

Neoadjuvant chemotherapy

Thirty-eight patients were given anthracycline-based neoadjuvant chemotherapy, consisted of cyclophosphamide, doxorubicin, and 5-Flourouracil (CAF regimen). The CAF regimen administration was given every 3 weeks until the third cycle on the ninth week. The dose of the CAF regimen was based on body mass index (BMI), with a dose of cyclophosphamide 500 mg/m^2 i.v., doxorubicin 50 mg/m^2 i.v., and 5-Flourouracil 500 mg/m^2. Furthermore, the clinical response to chemotherapy will be measured 14 days after the third cycle of chemotherapy was done at the Oncology Polyclinic, Dr. Soetomo General Hospital (Surabaya, Indonesia).

Statistical Analysis

The statistical analysis was performed using the SPSS statistical software package version 23.0 (IBM Corp., Armonk, NY, USA). Discrete variables were tested using the Chi-square test. Statistical significance was determined when the P value was less than 0.05.

RESULT

Subject's characteristics and clinical response after chemotherapy

A total of 38 women were included in this study, with mean age 48.89 ± 9.71years. Clinical response to chemotherapy is an evaluation of the change in tumor size that is measured objectively through physical examination according to the RECIST 1.1 criteria. The clinical response to chemotherapy was divided according to the RECIST 1.1 criteria into four categories that consist of progressive disease, stable disease, partial response, and complete response. In this study, the clinical response to chemotherapy was divided into 2, positive response (partial response and complete response) and negative response (progressive disease and stable disease). We found that there were 20 patients and 18 patients with negative response and positive response, respectively. Clinical responses of research subjects are shown in Table 1.

Table 1: Clinical response of subject based on RECICT 1.1

Subject Characteristic		Frequency	Percentage (%)
Clinical Response	Positive	18	47.4
	Negative	20	52.6
	Total	**38**	**100**

We analyzed the association between subject's characteristics and clinical response after neoadjuvant chemotherapy (Table 2). There were 21 subject aged <50 years (55.3%), consisting of 9 patients (9/21; 42.9%) had a positive response and 12 patients (12/21;57.1%) had a negative response. There were 17 patients aged >50 years, consisted of 9 patients (9/17;52.9%) had a positive response and 8 patients (8/17;47.1%) had a negative response. Based on the Chi-Square test analysis, it was found that there was no significant association between age and clinical response to chemotherapy (P= 0.536).

In this study the most frequent breast cancer subtype was luminal subtypes (26/38; 68.4%) followed by non-luminal subtypes (12/38; 31.6%). Our results showed that in luminal subtype patients, 14 patients (14/26; 53.8%) had a positive response and 12 patients (12/26; 46.2%) had a negative response. In the non-luminal subtype group, there were 4 patients (4/12; 33.3%) with positive response and 8 patients (8/12;66.7%) with negative response. Chi-Square test analysis showed that there was no significant association between tumor subtypes and the clinical response to chemotherapy with (P=0.239).

Table 2: Subject's characteristics and clinical response

Subject Characteristics		Clinical Response		Total	Mean	P Value
		Response (+)	Response (-)			
Age	< 50 years	9	12	21	48.89 ± 9.71	0.536
		42.9%	57.1%	100%		
	> 50 years	9	8	17		
		52.9%	47.1%	100%		
Subtype	Luminal	14	12	26	-	0.239
		53.8%	46.2%	100%		
	Non-Luminal	4	8	12		
		33.3%	66.7%	100%		
Histopathology	Ductal Carcinoma	15	18	33	-	0.544
		45.5%	54.5%	100%		
	Non-Ductal Carcinoma	3	2	5		
		60.0%	40.0%	100%		
Grading	Grade I	1	1	2	-	0.228
		50.0%	50.0%	100%		
	Grade II	12	8	20		
		60.0%	40.0%	100%		
	Grade III	5	11	16		
		31.3%	68.8%	100%		

Histopathological examination showed that ductal carcinoma was the most common type (33/38; 86.8%), followed by non-ductal carcinoma (5/38; 13.2%). The results showed in patients with ductal carcinoma, 15 patients (15/33; 45.5%) had

positive response and 18 patients (18/33; 54.5%) had negative response. In non-ductal carcinoma group, there were 3 patients (3/5; 60.0%) with positive response and 2 patients (2/5; 40.0%) with negative response. Based on the Chi-Square test analysis, we found that there was no significant association between tumor histopathology and clinical response to chemotherapy (P=0.544).

Based on the tumor grade, our results showed that grade II was the most common grade (20/38; 52.6%), followed by grade III (16/38; 42.1%), and grade I (2/38; 5.3%). Half of the subjects in grade I (1/2; 50.0%) had positive response and the other (1/2;50.0%) had negative response. In subjects with grade II tumor, there were 12 patients (12/20;60.0%) had positive response and 8 patients (8/20; 40.0%) had negative response. Five patients with grade III (5/16;31.3%) had positive response and the remaining 11 patients (11/16;68.8%) had negative response. Based on the Chi-Square test analysis, it was found that there was no statistical relationship between tumor grading and clinical response to chemotherapy (P = 0.228).

Interleukin-6 level of subjects

In this study, we found that 38 patients had a mean value of 59.33 ± 105.4 with a maximum level of IL-6 was 492 pg/mL and a minimum level of 2.85 pg/mL. The profile of IL-6 levels of subjects in this study is shown in Table 3.

The cut-off value of IL-6 levels in this study was based on a Receiver Operating Characteristic (ROC) curve analysis with IL-6 as the independent variable and clinical response to chemotherapy as the dependent variable. From the ROC curve analysis, it was obtained that value of 15,495 pg/mL as the cut off value for IL-6 (area under the curve/ AUC = 0.821) (Figure 1). From the cut off value, we divided the IL-6 level into high IL-6 expression and low IL-6 expression. We found that there were 20 patients (20/38; 52.6%) with high IL-6 level and 18 patients (18/38; 47.4%) with low IL-6 level. Table 4 shows the frequency of high and low IL-6 expression levels in this study. The sensitivity, specificity, PPV, NPV, and accuracy of IL-6 to predict the clinical response after chemotherapy were 80.0%, 77.8%, 80.0%, 77.8%, and 78.9%, respectively.

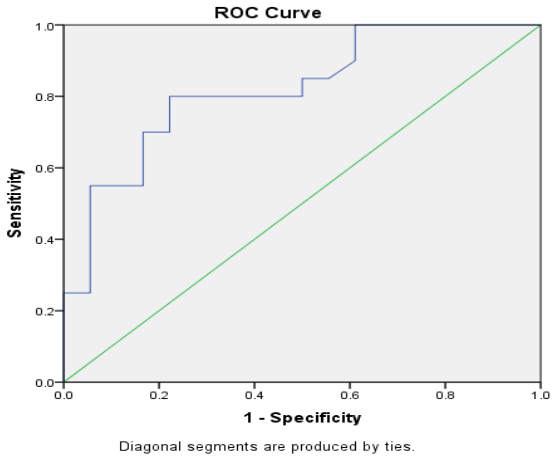

Figure 1: Receiver Operating Characteristic (ROC) curve analysis of interleukin-6 levels and clinical response to anthracycline-based neoadjuvant chemotherapy

Table 3: The profile of interleukin-6 in subjects

Subject Characteristic	Total (n)	Max	Min	Mean	Std. Deviation
Interleukin-6	38	492	2,85	59.33 ± 105.4	105.414

Table 4: Interleukin-6 level of subjects in this study

Subject Characteristic		Frequency	Percentage (%)
Interleukin-6	Low	18	47.4
	High	20	52.6
	Total	**38**	**100**

Relationship between interleukin-6 and clinical response

The relationship between IL-6 to the clinical response of chemotherapy in LABC patients was tested using Chi-Square test. We found that there was a statistically significant relationship between IL-6 levels to the clinical response to chemotherapy (P = 0.001). This study also calculated the association of the risk of elevated IL-6 levels with the patient's clinical response. From the analysis, it was found that the group of patients with high levels of IL-6 had a 3,889 times higher risk to develop negative clinical response (RR = 3.889; P = 0.001; 95% CI = 1.564-9.667).

Table 5: Relationship between interleukin-6 and clinical response to chemotherapy

Subject Characteristic		Clinical Response		Total	P value	OR
		Response (+)	Response (-)			
IL-6 level	Low	14	4	18	0.001	3.889 (1.564-9.667)
		77.8%	22.2%	100%		
	High	4	16	20		
		20.0%	80.0%	100%		

DISCUSSION

LABC is the most common stages that diagnosed from breast cancer patients, and the incidence of LABC in Indonesia is estimated to be more than 50% of all cases. Previous studies in Surabaya, Indonesia reported that breast cancer patients who came in stage III was as high as 74%.[3,4] Neoadjuvant chemotherapy is used to treat LABC, inflammatory breast cancer, and big tumor downstaging to allow for breast conservation therapy. Neoadjuvant chemotherapy such as an anthracycline-based regimen is the initial therapy and the main pillar of locally advanced breast cancer treatment with the main goal of achieving a pathological complete response in order to increase overall survival and disease free survival.[1-3] Several factors such as primary tumor size and nodule, tumor biologic factors, tumor histological grading, and inflammatory mediators have been investigated as factors that might have association with clinical response to chemotherapy in breast cancer patients.[5,6] Age is one of the most important risk factors associated with breast cancer. The age group >50 years is thought have an influence to the risk of breast cancer incidence. However, in this study, we found that age was not associated with the clinical response after chemotherapy. Our result was in concordance with previous study conducted by Wibisono et al., which reported that the age was not a factor associated with the clinical response to chemotherapy in breast cancer patients.[11] The results of this study are also supported by research conducted by Cuello-López et al. which reported that age was not a factor associated with chemotherapy response.[12]

Based on tumor subtypes, luminal subtypes had higher positive response rates than non-luminal type, although the results of the analysis showed no significant association with the clinical response to chemotherapy. Similar results were found in the study conducted by Kunnuru et al. showed that patients with luminal type had a higher percentage of complete response and partial response when compared with TNBC and HER2 subtypes.[13] Another study conducted by Yarso et al. also showed that patients with the luminal subtype had almost the same neoadjuvant chemotherapy response rates as patients with the HER-2 subtype, but both still had a better response than breast cancer patients with the triple negative subtype.[14] The contradictive results in this study can be caused by various factors, including the relatively small number of samples in this study and differences in the study population, as well as the sampling period.[14,15] In addition, previous study also reported that the subtype was not a predictive factor in response to neoadjuvant chemotherapy.[16]

Based on histopathology, we found that ductal carcinoma had higher rate of negative response than other histological type, although there was no statistically significant relationship with the clinical response to chemotherapy. Breast cancer with histopathology of invasive lobular carcinoma has been reported to be less responsive to neoadjuvant chemotherapy than histopathology of invasive ductal carcinoma.[17] In this study, there was no statistically significant association between tumor histopathology and clinical response to chemotherapy. Our result was in concordance with previous studies conducted at Dr. Soetomo General Hospital which reported that age, histopathology and subtype were not related to chemotherapy response. Low grade invasive breast carcinomas, such as tubular carcinoma, lobular carcinoma, invasive cribriform

carcinoma, papillary carcinoma, and mucinous carcinoma with low proliferation rate did not get a significant response from neoadjuvant chemotherapy, so neoadjuvant chemotherapy is not the treatment of choice for these types of cancer.[18-20]

Based on tumor grading, most of them were classified as grade II and most had a positive response. The same results were also found in the study of Purnawaty et al., where the distribution of neoadjuvant chemotherapy response to anthracycline-based chemotherapy for grade II (moderate differentiated) tumor grading showed a significantly better response compared to grade III (poorly differentiated) and tumor grading. grade I (well differentiated) with a total sample of 119 patients. In this study, we also found no significant association between tumor grading and clinical response to chemotherapy. Previous study by Wang et al. reported that the distribution of neoadjuvant chemotherapy response to anthracycline-based chemotherapy to grade III (poorly differentiated) tumors showed a significantly better response than grade I (well differentiated) and grade II tumors (moderately differentiated). All patients who received a complete response had a grade III tumor grade. In this study, tumor grading was a predictive factor for the response to neoadjuvant chemotherapy. However, patients who have good predictive factors can still show resistance to chemotherapy, due to the possibility of certain cellular characteristics at the molecular level. [15,21] Cellular mechanisms of cellular resistance include cell membrane activity that affects drug absorption, transport and efflux of drugs, expression of enzymes that metabolize chemotherapy drugs and inactivate chemotherapy drugs in the body, as well as genetic mutations in the body, activation of STAT3, increased expression of multidrug genes, mdr1, and upregulation of C/EBPβ and C/EBPδ (transcription factor protein). [22,23]

In this study, we used ROC curve analysis to examine the optimal cut off value of IL-6 to predict the clinical outcome. Further, we found that IL-6 may be used as a potential biomarker to predict the clinical outcome post the administration of neoadjuvant chemotherapy. Our result was in accordance with the study of Mittal et al., which reported that subjects with low IL-6 level had complete or partial response in more than half the cases. In addition, patients with breast cancer had significantly higher serum IL-6 levels than healthy women. Elevated serum IL-6 levels were also associated with poor prognosis and low survival rates in breast cancer patients, probably due to the increased tumor growth by up-regulating antiapoptotic and angiogenic proteins in tumor cells.[8] On the other hand, it has been shown that STAT3 is highly active in more than 50% of breast cancers in which IL-6 is one of the main activators.[9] IL-6 also has a role in the development of drug resistance. The classic IL-6 signaling pathway is the IL-6/JAK/STAT3 signaling pathway, which involves the PI3K/Akt and MAPK/ERK signaling pathways.[7] The higher level of IL-6 can also estimate the increasing risk of resistance towards Doxorubicin which can be indicated by the decreased response to chemotherapy in breast cancer patients.[24]

The role of IL-6 in the regulation of chemotherapy resistance has been reported in some cases. A study conducted by Chang et al. revealed that non-squamous lung cancer (NSCLC) showed higher serum IL-6 levels in patients with chemotherapy resistance. The authors hypothesized that tumor cells respond to genotoxic stress by secreting IL-6 and TIMP1 to counteract the cytotoxicity of doxorubicin.[25]

There were several limitations in this study. First, the number of subjects in this study was relatively small. Further study with higher number of subjects might be needed to provide stronger evidence. Second, the subjects were collected from one hospital. Therefore, the result in this study might not be able to represent Indonesian population in general.

CONCLUSION

There is a statistically significant relationship between serum IL-6 levels and clinical response to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer (LABC) patients. LABC patient with high IL-6 levels had higher chance of developing negative response to neoadjuvant chemotherapy.

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