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Ki-67 as a Predicting Factor of Neoadjuvant Chemotherapy Clinical Response for Local Advanced Breast Cancer in Indonesia

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ABSTRACT

Background: Breast cancer is one of the most common health problems in Indonesia where 42.7% of patients have been diagnosed with Local Advanced Breast Cancer (LABC). Neoadjuvant chemotherapy (NAC) is aimed to decrease the tumor size to be operable and decrease mortality. Ki-67 is highly expressed in the cell proliferation phase, while chemotherapy agents work effectively by targeting this proliferation. This study evaluates the utility of Ki-67 in LABC patients of the Asian-Indonesian population.
Methods: This is a retrospective cohort study. Ki-67 data was from the medical record based on the immunohistochemistry staining with >20% cut off point. Clinical response was measured based on the WHO criteria after the third chemotherapy cycle.
Result: The majority of subjects in this study were 50 years old, with T4 tumor size, N1 lymph node involvement, NST histopathological type, grade 2, ER-positive, PR-positive, HER2-negative, high Ki67 expression, and luminal B subtype. 52.1% of all subjects showed 'poor' clinical responses to NAC. There was no significant association between subjects' characteristics and the NAC Clinical response. Moreover, there was no significant association between Ki-67 and chemotherapy clinical response (p=1).
Conclusion: There is no statistically significant association between Ki-67 expression and NAC clinical response of LABC patients in Indonesia.
Key words: Ki-67, neoadjuvant chemotherapy, local advanced breast cancer, clinical response, Indonesia

INTRODUCTION

Breast cancer is one of the most frequent diseases of women in Indonesia, which is found in 48,998 Indonesian women (1). Moreover, breast cancer has caused 19,750 deaths each year in Indonesia, resulting in the most common cancer mortality cause among Indonesian women (1). Nevertheless, 80% of breast cancer patients came to seek medical help in the advanced stage (2).

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Among breast cancer cases, Local Advanced Breast Cancer (LABC) leads to a major challenge. Despite aggressive multimodality treatments, most of the LABC patients experienced relapses and were led to a higher mortality rate (3). Currently, neoadjuvant chemotherapy (NAC) followed by surgery such as mastectomy or breast-conserving surgery is the treatment of choice for patients with LABC (4). NAC is administered in order to decrease the tumor size to be more operable and decrease the mortality rate (3). However, only 22% of patients showed complete response to NAC (3). Hence, a predictive factor is needed to help the caregiver in considering the effectiveness of NAC which would be given to the patient.

A study by Lee et al states that there are predictive factors of tumor response to chemotherapy including ages, TNM stages, tumor grades, ER, PR, HER2, and Ki-67 (3). Ki-67 is one of a potential predictive factor which has been proved being correlated to worse disease-free survival and overall survival of breast cancer patients (5). Ki-67 is directly correlated to cell proliferation rate (5). Ki-67 tends to be expressed lower in the G1 phase and early S phase, but increases to the peak level in the cell mitotic phase (5,6). Ki-67 will appear increasingly in the condensed chromosomes of the cytoplasm while the nuclear membrane of each cell separates in the mitosis process (6). Besides, chemotherapy agents work effectively as anti-tumor targeting to cell proliferation phase (7). Hence, it is hypothesized that higher ki-67 may predict higher chemotherapy effectiveness. The potential role of Ki-67 in predicting the LABC response to NAC is still controversial. A previous study that included patients from Asia and Europe showed a significant association between expression of Ki-67 and NAC pathologic complete response (8). On the other hand, a study in German concluded that Ki-67 was not associated with NAC response (9). Moreover, Ki-67 was reported to be varied based on the demographical and race factors. For example, a study by Guth et al and Mannel et al stated that Ki-67 is found to be expressed higher in African-American people compared to Caucasians (10,11).

MATERIAL AND METHOD

The study design was a retrospective cohort study. Data were obtained from medical records in an Indonesian tertiary hospital and Indonesian Oncological Surgeons Association cancer registry from January 2013 to December 2018. The inclusion criteria of this study were LABC patients who had undergone NAC in January 2013 - December 2018 period. Subjects with incomplete data in their medical records were excluded from this study.

The minimum number of subjects in this study in one group was 48 subjects. This sample size was calculated based on a formula to compare 2 independent proportions.

The Independent variable of this study is the Ki-67 expression of the subject. Ki-67 data was obtained from the medical record stating the cell percentage of positive Ki-67 immunohistochemistry staining on paraffin blocks. More than 20% cut off point value was considered as a high expression of Ki-67, otherwise, it would be stated as a low expression of Ki-67 (12). Meanwhile, the non-independent variable of this study is the NAC clinical response based on the WHO criteria which was measured after the third chemotherapy administration and stated in the medical records. Then the clinical response recorded in this study was simplified into the following classification: 'good' clinical response (consisted of complete and partial responses) and 'poor' clinical response (consisted of stable disease and progressive response) (13). Subjects of this study were categorized into 2 groups based on these 2 clinical responses. Besides independent and non-independent variables of each subject, the author also analyzes other variables such as age, TNM stage, clinical stadium, histopathological grade, ER/PR expression, HER2 expression, types of chemotherapy used.

Data analysis was carried out using the IBM© SPSS® version 20. Bivariate analysis was performed using the Chi-square or Fisher's exact test. Moreover, we planned to conduct a multivariate analysis on subjects' characteristics that may be associated with the NAC clinical response. P-values of less than 0.05 were considered statistically significant.

RESULTS

There were 94 subjects in our study: 47 subjects in the 'good' clinical response group and 47 subjects in the 'poor' clinical response group, all of which were included in the data analysis. More subjects in the geriatric age category (49.4%) obtained 'poor' clinical response compared to younger age subjects. Subjects with grade 2 (52.9%) and grade 3 (56.3%) resulted in worse clinical response than subjects with grade 1. The majority of patients with ER-positive (56.8%) and PR-positive (54.5%) showed a poor clinical response. Moreover, the majority of subjects with luminal A and luminal B subtypes obtained a poor clinical response. Meanwhile, the majority of HER2-enriched (55.6%) and

triple-negative subjects (66.7%) showed a good clinical response. In the majority, LABC patients had the following characteristics: 50 years old of average age, T4 tumor size, N1 lymph node involvement, NST histopathological type, grade 2, ER/PR positive, HER2 negative, high Ki-67, and Luminal B molecular subtype. However, all of the subjects' characteristics resulted in no significant differences between the two groups. There was not any variable that results in a p-value lower than 0.25 in the first bivariate analysis. Hence, we had no variable to be included in the multivariate analysis. The detailed data of the subject's characteristics analysis is provided in *table 1*.

Based on the chemotherapy regimens used to treat LABC of our subjects, 82 (87.2%) subjects got cyclophosphamide, doxorubicin, and fluorouracil regimen; 5 (5.3%) subjects got cisplatin and paclitaxel; 3 (3.2%) subjects got cyclophosphamide, epirubicin, and fluorouracil regimen; and 4 (4.3%) subjects got the other chemotherapy regimens. 39 (41.5%) subjects showed high Ki-67 expression and 28 (29.8%) subjects showed low Ki-67 expression. In this study, there were 45 (47.9%) subjects who showed 'good' clinical response after 3 cycles of NAC. This contained 0 (0%) subjects with complete response and 45 (47.9%) subjects with partial response. However, there were 49 (52.1%) subjects who showed 'poor' clinical response consisted of 37 (39.4%) subjects with stable disease and 12 (12.8%) subjects with the progressive response. Moreover, this study resulted in no significant statistical difference between high and low expression Ki-67 in terms of NAC clinical response (p=1). The detailed analysis is shown in *table 2*.

DISCUSSION

The characteristics of subjects in this study are different compared to other studies in Western and other Asian countries. The detailed data of subjects' characteristics are provided in *table 1*. The average age of LABC patients in India is 44 years old and in Bandung city is 47 years old (14). Meanwhile, the median ages of LABC patients in the UK are 62 years old and 60 years old in the USA (15). However, the average age of LABC patients in this study was 50 years old. In Indonesia, the majority of patients came with already advanced-stage breast cancer caused by factors such as low health education, hesitancy to seek medical care, and alternative treatment preference. This may explain why the majority of subjects (90.4%) of this study were in the T4 stage. This is different from the previous study in Canada where the majority of patients (42.7-44.7%)

Table 1 - Characteristics of subjects

Variable	Total	Percentage
Age Category		
<18 years	0	0%
19-59 years	85	90.4%
>59 years	9	9.6%
Tumor Size and Extension (T)		
1	0	0%
2	0	0%
3	9	9.6%
4	85	90.4%
Regional Lymph Node Involvement (N)		
0	26	27.7%
1	49	52.1%
2	14	14.9%
3	5	5.3%
Histopathological type		
NST	67	71.3%
Lobular	5	5.3%
Ductal	13	13.8%
Others	9	9.6%
Grade		
1	9	9.6%
2	53	54.4%
3	32	34%
ER		
Positive	74	78.7%
Negative	20	21.3%
PR		
Positive	66	70.2%
Negative	28	29.8%
HER2		
Positive	39	41.5%
Negative	55	58.5%
Ki67		
High	66	70.2%
Low	28	29.8%
Molecular Subtype		
Luminal A	26	27.7%
Luminal B	53	56.4%
HER2	9	9.6%
Triple negative	6	6.4%
Chemotherapy		
Cyclophosphamide, doxorubicin, fluorouracil	82	87.2%
Cisplatin, paclitaxel	5	5.3%
Cyclophosphamide, epirubicin, fluorouracil	3	3.2%
Others	4	4.3%
Clinical Chemotherapy Response based on WHO		
Complete response	0	0%
Partial response	45	47.9%
Stable disease	37	39.4%
Progressive response	12	12.8%
Chemotherapy Response		
'Good'	45	47.9%
'Poor'	49	52.1%

Table 2 - Association between Ki-67 expression and bone metastasis

Variable	'Good' clinical response	'Poor' clinical response	p-value
High Ki-67	32 (48.5%)	34 (51.5%)	1
Low Ki-67	13 (46.4%)	15 (53.6%)	

were in the T2 and T3 stages (16). The other different subjects' characteristics of this study are the majority molecular subtype, which is Luminal B in 56.4% of subjects. On the other hand, Luminal A was the most found molecular subtype in a previous study (17). In this study, the majority of subjects got cyclophosphamide, doxorubicin, and fluorouracil chemotherapy regimens. Partial response was the most resulted clinical response based on WHO criteria in this study (47.9% of subjects). However, after all, clinical responses were classified into two categories in this study, the majority of subjects (52.1%) showed 'poor' clinical response. This contradicts previous studies by Gao et al and Das et al which resulted in 'good' clinical response as the majority outcome in the range of 74-83% of the subjects (18,19). The best method to evaluate the tumor response toward chemotherapy is the Miller-Payne score. Pathological response evaluation on based Miller-Payne classification is the potential to be an independent factor for distant disease free survival and local recurrence free survival (20). However, this study was only evaluating the clinical response, hence the association between Ki-67 expression and the pathological response was unknown in this study.

Based on the analysis result in this study which is provided in table 2, there is no significant association between Ki-67 and chemotherapy clinical response (p=1). Theoretically, the high expression of Ki-67 is associated with the high proliferating cells. Meanwhile, chemotherapy agents are effectively targeting the cancer cells which are in the proliferation phase (7). Hence, the result of this study is not in line with our theoretical-based hypothesis. Previous studies showed the inconsistent result to prove the association between Ki-67 expression and chemotherapy response. The result of our study contradicts a previous study by Prihantono et al and Rezano et al which stated that highly expressed Ki-67 resulted in significant tumor size decrement after chemotherapy, with a threshold of 14-20% Ki-67 expression (21,22). However, both studies had not conducted any multivariate analysis to evaluate the independence of association between Ki-67 expression and chemotherapy response. Moreover, a study by Tao et al which included 6739 patients from Asia and Europe showed that high expression of Ki-67 was significantly associated with NAC pathologic complete response (8). Moreover, a study by Chen et al in China showed that Ki-67 expression above the 14% threshold led to better chemotherapy response (23). However, a study by Ingolf et al in German including 77 patients supports our finding in this study by concluding that Ki-67 was not associated with NAC response (9).

This study was conducted in a tertiary referral hospital in Indonesia. Hence, other non-clinical factors that we did not analyze such as treatment delay due to referral system management errors and economic factors might play roles in the clinical response outcomes. This is supported by a study in Nigeria which stated that economical problems resulted in the decrement of chemotherapy compliance (24). Another study by Cabreara et al in Mexico concluded 40% of pathological complete responses resulted from patients who started NAC 28 days after the biopsy, while those who started NAC in more than 28 days after biopsy only resulted in pathological complete responses in 27% of patients (p=0.0001) (25). This study found that 77.8% of >59 years old patients got 'poor' responses compared to 44.9% in adult patients with no significant statistical association. Besides, tumor size and extension, lymph node involvement, histopathological type, tumor grade, ER/PR, HER-2 amplification status, and molecular subtype are not associated with NAC Clinical response (*table 3*). This is supported by Won et al in Korea who concluded that there was no statistically significant association between tumor size and lymph node involvement with chemotherapy response (26). Another study by Vasudevan et al in India found a statistically significant association between T2 and N0 tumors with pathological complete response (27). Grade 2 and 3 tumor patients resulted in worse clinical response compared to grade 1 (52.9% vs. 56.3%) with an insignificant association (p=0.472). The higher-grade resulted in increased proliferation of the tumor cells. Theoretically, the higher grade of the tumor would get a better chemotherapy response because chemotherapy invades actively proliferating tumor cells. A study by Fernandez et al in Mexico concluded that a higher grade of tumor resulted in better chemotherapy response (28). Other studies showed that HER2 and triple-negative patients got better chemotherapy response compared to the other molecular subtypes (29,30). Nevertheless, there were only a few subjects with HER2 amplification and triple-negative breast cancers which caused no statistically significant association in this study.

The absence of pathological response analysis is also a weakness of this study. Hence, we suggest a future study to investigate the association between Ki-67 expression and pathological response after NAC administration to LABC patients. Moreover, further study to evaluate the causes on why the majority of subjects resulted in poor clinical response to NAC therapy is required.

Table 3 - Association between characteristics of subjects and clinical response to chemotherapy

Variable	'Good' clinical response	'Poor' clinical response	p-value
Age Category			
<18 years	0 (0%)	0 (0%)	
19-59 years	43 (50.6%)	42 (49.4%)	0.162
>59 years	2 (22.2%)	7 (77.8%)	
Tumor Size and Extension (T)			
1	0	0%	1.000
2	0	0%	
3	4 (44.4%)	5 (55.6%)	
4	45 (47.9%)	49 (52.1%)	
Regional Lymph Node Involvement (N)			
0	13 (50%)	13 (50%)	
1	23 (46.9%)	26 (53.1%)	
2	8 (57.1%)	6 (46.2%)	0.551
3	1 (20%)	4 (80%)	
Histopathological type			
NST	34 (50.7%)	33 (49.3%)	
Lobular	2 (40%)	3 (60%)	0.103
Ductal	8 (61.5%)	5 (32.8%)	
Others	1 (11.1%)	8 (88.9%)	
Grade			
1	6 (66.7%)	3 (33.3%)	
2	25 (42.7%)	28 52.9%)	0.472
3	14 (43.8%)	18 (56.3%)	
ER			
Positive	32(43.2%)	42 (56.8%)	
Negative	13 (65%)	7(35%)	
PR			
Positive	30 (45.5%)	36 (54.5%)	0.621
Negative	15 (53.6%)	13 (46.4%)	
HER2			
Positive	18 (46.2%)	21(53,8%)	0.943
Negative	27 (49.1%)	28 (50,9%)	
Molecular subtype			
Luminal A	12 (46.2%)	14 (53.8%)	
Luminal B	24 (45.3%)	29 (54.7%)	0.745
HER2	5 (55.6%)	4 (44.4%)	
Triple-negative	4 (66.7%)	2 (33.3%)	

In conclusion, there is no significant statistical association between Ki-67 expression and clinical response to NAC of Indonesian LABC patients. Moreover, other factors such as age, tumor size and extension (T), lymph node involvement (N), histopathological type, tumor grade, ER/PR, HER-2 amplification status, and molecular subtype of LABC are not predictive factors of NAC response of LABC patients.

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Conflict of interest and source of funding

The authors affirm neither conflict of interest nor funding source in this study.

Ethical approval

This study had been approved by the Ethics Committee of Medical Faculty No. KET-1327/ UN2.F1/ ETIK/PPM.00.02/2019.

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