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Changes in Ki67 expression and clinical response to neoadjuvant chemotherapy in locally advanced breast cancer (LABC)

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ABSTRACT

Background: Locally Advanced Breast Cancer (LABC) is still the most common stage found in breast cancer patients in Indonesia. Neoadjuvant Chemotherapy (NAC) is the initial therapy and the main pillar of LABC treatment. NAC could provide less extensive surgery and improve patient's overall survival to those who achieve a complete pathological response. Ki67 expression is a tumor biomarker representing tumor cell proliferation and has been extensively investigated as a promising predictive and prognostic factor in breast cancer. This study aims to examine the association between Ki67 expression with clinical response of NAC.

Methods: The study was designed as a case-control study in breast cancer patients who received standard anthracycline-based NAC. Clinical and immunohistochemical characteristics before and after NAC were obtained retrospectively. Changes in Ki67 and NAC responses were analyzed. Data were analyzed using SPSS version 23 for Windows

Results: A total of 66 subjects were analyzed. About 33 subjects were in good clinical response and 33 subjects were in poor clinical response. Chi-square analysis showed that no significant differences were found in the pre-treatment Ki67 expression between good and poor clinical response group, whereas a low post-treatment Ki67 expression (Ki67 <20%) was correlated with a good clinical response to NAC (p=0.027). Further analysis also showed that a decrease of Ki67 expression greater than 12.5% after treatment was significantly correlated with good clinical response (p=0.007; OR=4.67; 95%CI=1.45-15.08). In multivariate analysis, a decrease in Ki67 was significantly correlated to response in NAC (p=0.037).

Conclusion: Decreased in Ki67 greater than 12.5% was correlated with good clinical response of Anthracycline-based NAC in LABC.

Keywords: Locally Advanced Breast Cancer, Ki67, Neoadjuvant Chemotherapy, Anthracycline.
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INTRODUCTION

Locally advanced breast cancer (LABC) is the most common stage found in breast cancer patients in Indonesia. Neoadjuvant chemotherapy acted as the initial therapy and the main pillar of treatment for locally advanced breast cancer. Achieving a complete response towards therapy is the primary goal of neoadjuvant chemotherapy. It can improve overall survival and disease-free survival, especially in the triple-negative subtype group and patients with human epidermal growth factor receptor 2/neu (HER2/neu) expression.[1,2] Anthracycline-based chemotherapy has still become a widely used regimen as neoadjuvant and adjuvant therapy in breast cancer. Data obtained in a research center in Italy stated that the overall response rate of anthracycline-based neoadjuvant chemotherapy or in combination with taxane was up to 72%, while the overall response rate in previous studies conducted in Indonesia was ranged from 40–50%.[3-5] Several factors are referred to as predictive and prognostic factors in neoadjuvant chemotherapy. Tumor size and lymph node involvement have been associated with neoadjuvant chemotherapy response in locally advanced breast cancer. In addition, several other factors such as tumor histological grading, age, menopausal status, tumor receptor status (e.g., HR, HER2/neu, Ki67), and the number of chemotherapy cycles also influence the chemotherapy response.[3,6]

Ki67 expression is a tumor biomarker that represents tumor cell proliferation and this protein is expressed in all phases of the cell cycle, except the G0 phase. Assessment of Ki67 expression in tumor residues after neoadjuvant chemotherapy is considered to provide a good description of the cancer cell proliferation index. A study by Chen et al. suggested that Ki67 expression prior to treatment may predict neoadjuvant chemotherapy response in breast cancer but only in a luminal subtype.[7] The study also stated that the decrease of Ki67 expression after

neoadjuvant chemotherapy was associated with a reduction in tumor size in the breast cancer group with luminal subtypes and luminal-HER2 types.[7] Wu et al. in 2018 reported a 44.8% change in Ki67 expression before and after neoadjuvant chemotherapy.[8] High Ki67 expression after neoadjuvant chemotherapy has been associated with a poor prognosis.[9] Currently, there is no study examining the Ki67 expressions with the clinical response of NAC in LABC patients. Based on those mentioned above, this study aims to investigate the level of Ki67 expression with the clinical response of LABC patients before and after NAC treatment.

MATERIALS AND METHODS

Study Participants

A case-control study was conducted to determine the relationship between changes in Ki67 expression before and after neoadjuvant chemotherapy on the clinical response of anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer. This study also assessed the relationship between early Ki67 expression (pre-treatment) and the response rate of anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer. In this study, we recruited a total of 66 patients at Dr. Soetomo General Hospital, Surabaya, Indonesia from the study priod. We evaluated the post-chemotherapy clinical response based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria and classified the patients into complete response, partial response, progressive disease, and stable disease.[10] In this study, we defined good clinical responses as patients with complete and partial responses.

In contrast, poor clinical response is defined as patients with stable disease and progressive disease. Further, we divided the patients into 2 groups: the case group and the control group. The case group consisted of patients who received Anthracycline-based NAC for at least three courses and good clinical response. In comparison, the control group consisted of patients who underwent anthracycline-based NAC for at least three courses and resulted in poor clinical response.

Neoadjuvant chemotherapy

Sixty-six patients with histologically confirmed breast cancer were given a neoadjuvant chemotherapy regimen. Prior to each course of chemotherapy session, all patients were checked for measurements of tumor size and complete blood test, including hemoglobin, leukocyte count, platelet count, neutrophil count, blood urea nitrogen, and serum creatinine levels. Only patients who received ≥3 courses of treatment with CAF or CEF were included, which included intravenous administration of Cyclophosphamide (600 mg/m^2), Epirubicin or Doxorubicin (60 mg/m^2), and 5-Fluorouracil (600 mg/m^2) each 21 days.

The Ki67 expression and the changes of Ki67 level

We examined the expression of the Ki67 level using immunohistochemistry. The expression of Ki67 in this study was divided into high Ki67 expression and low Ki67 expression following the European Society for Medical Oncology (ESMO) and PERABOI (Indonesian Society of Surgical Oncology) guidelines 2020.[11,12] The expression of less than equal to 20% was defined as low Ki67 expression and the expression of more than 20% was defined as high Ki67 expression. We also analyzed the changes of the Ki67 level and described the changes of the Ki67 level as the difference of Ki67 expression before NAC and Ki67 expression after NAC. We utilized the cut-off of 12.5% for the changes of Ki67 level following the cut-off value reported in the previous study.[9]

Statistical Analysis

Discrete variables were tested using the Chi-square test. Statistical significance was determined when the P-value was less than 0.05. The statistical analysis was performed using the SPSS version 23.0 for Windows.

RESULTS

The average age of 66 respondents was 47.9 ± 7.6 years. There were 33 subjects in the good and 33 in the poor chemotherapy clinical response group (mean age of 48.3 ± 7.9 years and mean age of 47.5 ± 7.4, respectively). There was no significant difference in age between good and poor clinical response groups (P >0.05). The highest number of subjects was found in the age group >40 years (81.8%) (Table 1).

Table 1 shows the association between subject characteristics and the changes in Ki67 expression before and after neoadjuvant chemotherapy in locally advanced breast cancer. In this analysis, there were no statistical differences between these groups in terms of age, tumor size, histopathological characteristic, histological grade, hormonal status, expression of HER2/neu, subtype, and numbers of NAC courses (p>0.05), except for lymph node involvement (N2-N3) (P = 0.038; OR = 0.322; 95% CI 0.108-0.959) with the changes in Ki67 level group (Table 1).

The association between various characteristics and the clinical response after NAC is depicted in Table 2. Our data showed that the group with good clinical response to chemotherapy was not different from the group with poor clinical response to chemotherapy in terms of age, tumor size, lymph nodes, histopathology, histological grading, hormonal status, HER2/neu, and subtype of clinical response to neoadjuvant chemotherapy in locally advanced breast cancer (Table 2).

The association between chemotherapy response and Ki67 expression before and after NAC is depicted in Table 3. Following the European Society for Medical Oncology (ESMO) and PERABOI (Indonesian Society of Surgical Oncology) guidelines 2020, the expression of Ki67 in this study was divided into high Ki67 expression and low Ki67 expression.[11,12] The cut-off value to categorize the expression group was 20%. Before NAC treatment, low Ki67 expression was found in 15 subjects (15/66; 22.7%) and high Ki67 expression was found in 51 subjects (52/66; 77.3%); while after NAC treatment, low Ki67 expression was found in 18 subjects (18/66; 27.3%) and high Ki67 expression was found in 48 subjects (48/66; 72.7%). Our data showed a significant association between the level of Ki67 expression with patients' clinical response after NAC administration (P = 0.027; OR = 3.64; 95% CI 1.12-11.85). We also found that the proportion of patients with a good clinical response is increased in patients with low Ki67 expression after NAC administration (good response:

13/18; 72.7% vs. 5/18; 27.8%). There was no significant association found between the Ki67 expression level before NAC administration and patients' clinical response (p>0.05) (Table 3).

The relationship between chemotherapy response and changes in Ki67 expression before NAC and Ki67 expression after neoadjuvant chemotherapy is depicted in Table 4. We found that the group with decreased >12.5% in Ki67 expression between pre-treatment and post-treatment Ki67 were correlated with good clinical response (P = 0.007; OR = 4.67; 95% CI 1.45-15.08). In multivariate analysis, decreased >12,5% in Ki67 were strongly correlated to response in NAC rather than low post-treatment Ki67 expression (P = 0.037; OR = 3.66; 95% CI 1.08-12.40) (Table 4).

Table 1. Subject's Characteristics Based on the changes of Ki67 level

Characteristics	Total (N=66)	Ki67 Level (N=66)		p	OR (95% CI)
		Decreased > 12.5% (n=20)	Decreased ≤ 12.5% (n=46)		
Age (Years), n (%)					
≤ 40	12 (18.2)	1 (8.3)	11 (91.7)	0.088	0.167 (0.020-1.398)
> 40	54 (81.8)	19 (35.2)	35 (64.8)		
Size (cm), n (%)					
< 5	12 (18.2)	4 (33.3)	8 (66.7)	0.801	1.188 (0.313-4.512)
≥ 5	54 (81.8)	16 (29.6)	38 (70.4)		
Nodal status, n (%)					
N0-1	42 (63.6)	9 (21.4)	33 (78.6)	0.038*	0.322 (0.108-0.959)
N2-3	24 (36.4)	11 (45.8)	13 (54.2)		
Histopathology, n (%)					
Ductal	54 (81.8)	15 (27.8)	39 (72.2)	0.579	-
Lobular	4 (6.1)	2 (50.0)	2 (50.0)		
Mixed	8 (12.1)	3 (37.5)	5 (62.5)		
Grading, n (%)					
Grade I	12 (18.2)	3 (25.0)	9 (75.0)	0.884	-
Grade II	17 (25.8)	5 (29.4)	12 (70.6)		
Grade III	37 (56.0)	12 (32.5)	25 (67.6)		
ER Status, n (%)					
Negative	31 (46.9)	9 (29.0)	22 (71.0)	0.833	0.893 (0.311-5.561)
Positive	35 (53.1)	11 (31.4)	24 (68.5)		
PR Status, n (%)					
Negative	30 (45.5)	6 (20.0)	24 (80.0)	0.096	0.393 (0.128-1.201)
Positive	36 (55.5)	14 (38.8)	22 (61.1)		
HER2 status, n (%)					
Negative	37 (56.0)	12 (18.2)	25 (37.87)	0.671	1.260 (0.434-3.660)
Positive	29 (44.0)	8 (27.6)	21 (72.4)		
Subtype, n (%)					
Luminal A	7 (10.6)	4 (57.1)	3 (42.9)	0.242	-
Luminal B	38 (57.6)	9 (23.7)	29 (76.3)		
HER2 overexpression	12 (18.2)	3 (25.0)	9 (75.0)		
TNBC	9 (13.6)	4 (44.4)	5 (55.6)		
Chemotherapy, n (%)					
3 Courses	21 (31.8)	5 (23.8)	16 (76.2)	0.433	0.625 (0.192-2.034)
4-6 Courses	45 (68.2)	15 (33.3)	30 (66.7)		

PR: Progesterone Receptor; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple-Negative Breast Cancer; OR: Odds Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05.

Table 2. Subject's characteristics and response post-NAC

Characteristics	Clinical Response (N=66)		p	OR (95% CI)
	Good Response (n=33)	Poor Response (n=33)		
Age (Years), n (%)				
≤ 40	5 (41.7)	7 (58.3)	0.520	1.508 (0.430-5.350)
40	28 (51.9)	26 (48.1)		
Size (cm), n (%)				
< 5	8 (66.7)	4 (33.3)	0.339	0.431 (0.120-1.600)
≥ 5	25 (46.3)	29 (53.7)		
Nodal status, n (%)				
N0-1	19 (45.2)	23 (54.8)	0.306	1.695 (0.620-4.670)
N2-3	14 (58.3)	10 (41.7)		
Histopathology				
Ductal	25 (46.3)	29 (53.7)	0.410	-
Lobular	3 (75.0)	1 (25.0)		
Mixed	5 (62.5)	3 (37.5)		
Grading				
Grade I	6 (50.0)	6 (50.0)	0.120	-
Grade II	12 (70.6)	5 (29.4)		
Grade III	15 (40.5%)	22 (9.5)		
ER Status				
Negative	14 (45.2%)	17 (54.8)	0.459	1.635 (0.616-4.34)
Positive	19 (54.3%)	16 (45.7)		
PR Status				
Negative	13 (48.1%)	14 (51.9)	0.482	1.650 (0.620-4.410)
Positive	20 (57.1%)	15 (42.9)		
HER2 Status				
Negative	17 (47.2%)	19 (52.8)	0.524	1.376 (0.520-3.670)
Positive	16 (55.2%)	13 (44.8)		
Subtype				
Luminal A	2 (40.0%)	3 (60.0)	0.189	-
Luminal B	22 (56.4%)	17 (43.6)		
HER2 overexpression	7 (58.3%)	5 (41.7)		
TNBC	2 (20.0%)	8 (80.0)		

PR: Progesterone Receptor; ER: Estrogen Receptor; HER2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple-Negative Breast Cancer; OR: Odds Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05.

DISCUSSION

Currently, breast cancer still becomes the most common cancer in women. The prognosis is depended on various factors, such as the stage when initial treatment is given, age, lymph node involvement, hormone receptor status, and the tumor size.[1-5] One of the parameters currently used to predict breast cancer prognosis is Ki67, a tumor biomarker is representing tumor cell proliferation. This protein is expressed in all phases of the cell cycle, except the G0 phase. This study found that the decreased Ki67 expression of more than 12.5% was significantly related to the better clinical response to NAC with anthracycline-based regimens. Our result was similar to a previous study by Chen C et al., which reported that patients whose Ki67 expression decreased during neoadjuvant chemotherapy had excellent outcomes, even better than patients who initially had lower Ki67 expression prior to chemotherapy administration.[9]

In this study, we found a significant association between lymph node involvement with the decrease level of Ki67. However, our analyses showed that the group with decreased Ki67 expression >12.5% did not significantly differ from the group with decreased Ki67 expression ≤12.5% in terms of age, tumor size, histopathology, histological grading, hormone receptor status, HER2/neu, and the number of cycles of NAC. Many studies reported that various clinical and pathological factors might be used as predictive factors for determining the response to NAC and the impact of chemotherapy response on overall survival. Other factors such as

Table 3. Association between Ki67 expression before and after NAC with clinical response

Characteristics	Total (N=66)	Clinical Response (N=66)		P	OR (95% CI)
		Good Response (N=33)	Poor Response (N=33)		
Ki67 before NAC, n (%)					
High > 20%	51 (77.3)	26 (51.0)	25 (49.0)	0.769	0.841 (0.265-2.660)
Low ≤ 20%	15 (22.7)	7 (46.7)	8 (53.3)		
Ki67 after NAC, n (%)					
High > 20%	48 (72.7)	20 (41.7)	28 (58.3)	0.027*	3.640 (1.120-11.850)
Low ≤ 20%	18 (27.3)	13 (72.7)	5 (27.8)		

NAC: neoadjuvant chemotherapy; OR: Odds Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05.

Table 4. Association between the changes in Ki67 expression with clinical response

Ki67 Response	Total (N=66)	Clinical Response (N=66)		P	OR (95% CI)
		Good Response (N=33)	Poor Response (N=33)		
Decreased >12.5%	20 (30.3)	15 (75.0)	5 (25.0)	0.007*	4.670 (1.450-15.08)
Decreased ≤12.5%	46 (69.7)	18 (39.1)	28 (60.9)		

OR: Odds Ratio; CI: Confidence Interval; *Statistically significant if p-value less than 0.05.

tumor size and lymph node involvement have been associated with neoadjuvant chemotherapy response in locally advanced breast cancer. However, patients with good predictive factors may show resistance to chemotherapy or experience early relapse due to the possible presence of certain cellular characteristics at the molecular level.[3,6,13]

We found that the group with good clinical response to chemotherapy did not significantly differ from the group with poor clinical response to chemotherapy regarding age, tumor size, lymph nodes, hormonal status, HER2/neu, and subtypes. This result was supported by previous studies conducted in Surabaya, Indonesia, which showed that age, histopathology, and subtype were unrelated to chemotherapy response.[4,5] Various studies have shown a positive correlation between Ki-67 expression and the proliferative cell fraction in tumors. Therefore, many clinicians have investigated the relationship between decreased Ki67 expression and chemotherapy response in patients with breast cancer. Based on the optimal cut-off value of changes in Ki67 expression before and after neoadjuvant chemotherapy in a previous study by Chen C et al., we found that the group with good clinical response to chemotherapy had a decrease in Ki67 expression >12.5%.[9]

Age is one of the most important risk factors for breast cancer. In this study, the prevalence of patients with breast cancer was higher in patients more than 40 years old than in patients less than 40 years. The incidence of breast cancer is said to increase significantly with age and reaches its peak at the age of menopause and then gradually decreases or remains constant. In a case-control study, subjects over 50 years were associated with a higher incidence of breast cancer. Still, breast cancer in younger women appeared in a larger size, advanced stage, positive lymph nodes, and lower survival rate.[14]

Based on the tumor characteristics, we found in this study that the majority of the subjects had tumor sizes greater than 5 cm and high tumor grading. This finding agrees with the previous study in Southeast Asia, which reported that Malay and Indian women were more likely to have unfavorable tumor characteristics such as bigger tumor size, poorly differentiated tumors, and high-grade tumors, contributing to poorer overall survival.[14] Luminal B was the most common subtype found in this study, followed by HER2 overexpression subtype, TNBC subtype, and Luminal A being the least common subtype. The prevalence pattern of breast cancer subtypes in Indonesia was different from the pattern in other regions in the world. Studies in the United States revealed that the most common breast cancers subtypes were luminal A type, followed by triple-negative subtype, luminal B type, HER2 overexpression type.[15] However, our result is in accordance with data from the Indonesian Cancer Registry, which states that the most prevalent subtype of breast cancer in Indonesia is Luminal B. In addition, this study also found the distribution of groups of patients with high pre-chemotherapy Ki67 expression in 51 subjects (77.2%) which indicates that the population in Indonesia has high Ki67 levels in accordance with a previous study.[16]

In the setting of neoadjuvant chemotherapy, three parameters of Ki67 expression, namely pre-treatment Ki67 expression, post-treatment Ki67 expression, and the changes of Ki67 expression itself, could be obtained and assessed. Until now, which value of Ki67 correlated in response to NAC is still a

matter of debate. Also, a standard cut-off point to classify Ki-67 expression as high or low has not been found. This resulted in different studies using different cut-off points for the classification of the Ki67 level.[17] According to the 2019 ESMO guidelines and the 2020 PERABOI protocol adopted in Indonesia, the cut-off value used to distinguish between low and high groups is 20%.[11,12]

Good chemotherapy response has been associated with good relapse-free survival (RFS), disease-free interval (DFI), and overall survival (OS). A study by Chen C et al. showed that the optimal cut-off of Ki67 expression before chemotherapy was >55%, the optimal postoperative Ki67 cut-off was 25%, and the optimal cut-off of Ki67 changes during neoadjuvant chemotherapy was 12.5%.[9] A decrease in Ki67 expression >12.5% was used as a predictor for negative RFS.[9]

In this study, high Ki67 expression before NAC administration could not predict the response to neoadjuvant chemotherapy in LABC. This is in line with the study of Del Prete S et al., which showed that Ki67 level pre-chemotherapy was not significantly associated with chemotherapy response because chemotherapy response was not only related to the proliferation of cancer cells.[3] However, conflicting results were obtained from a number of other studies which reported that pre-chemotherapy Ki67 expression consistently became a significant predictor of therapeutic response and prognosis. It has been reported that high pre-chemotherapy Ki67 expression is a stronger predictor of good therapeutic response and a poor marker of prognosis.[9] This is based on the premise that tumors with higher cell proliferation rates may respond better to chemotherapy than tumors with lower proliferation rates. It can be concluded that patients who experienced a decreased in Ki67 expression after chemotherapy were the group that benefited the most from receiving NAC. Those findings are similar to our results in this study that showed low post-treatment Ki67 expression and changes in Ki67, which decreased >12,5% in Ki67 expression, both correlated with a good clinical response to NAC.

Many other studies have also shown a positive relationship between the changes in Ki67 expression and chemotherapy response. Changes in Ki67 are considered to predict the NAC response, especially in breast cancer with positive hormonal status (luminal type) and luminal subtypes that have HER2/neu expression, but not HER2 overexpression and TNBC subtypes. Therefore, it is necessary to provide more aggressive adjuvant therapy such as adjuvant chemotherapy and postoperative radiation in the HER2 overexpression and TNBC groups.[7]

Various studies also stated that patients with low Ki67 expression after chemotherapy had comparable long-term outcomes to patients with a complete pathological response. This is in line with the results of a study by Ding Y et al., which showed that Ki67, which was still high in post-chemotherapy residual tumors, had a greater risk of having DFS and lowered OS compared to the group with low Ki67.[18] Therefore, the study by Li Y et al. stated that Ki67 levels after neoadjuvant chemotherapy were of more importance.[19] This is based on the premise that even though the tumor showed decreased Ki67 expression after neoadjuvant chemotherapy but remained in the high-expression group, there was still sufficient proliferative activity to ensure tumor survival and lead to local or distant metastasis.[19] In multivariate analysis, decreases>12,5% in Ki67 were strongly correlated to response in NAC than low post-treatment Ki67 expression. Another study stated that a change in Ki67 expression from >20% on biopsy (pre-NAC) to <20% on post-NAC had a better outcome in terms of DFS when compared with patients with high Ki67 (>20%) at the surgery. This also shows that the decreased in Ki67 after chemotherapy has a significant role in determining the response to chemotherapy and also the long-term outcome in patients.[20]

We found that the patients with a decreased Ki67 expression of ≤12.5% or even an increase in Ki67 expression after receiving NAC had worse outcomes concerning DFS and OS, which was in concordance with the previous study.[21] Several possible mechanisms could explain the increased expression of Ki67 after neoadjuvant chemotherapy. Chemotherapy mainly kills tumor cells that are actively proliferating, indirectly encouraging residual tumor cells in the G0 phase to metabolize actively or enter into another division cycle. In this case, Ki67 could be re-expressed in tumor cells. On the other hand, the association between high Ki67 expression and the development of chemotherapy resistance may also explain the increased Ki67 expression after neoadjuvant chemotherapy in breast cancer.[18,22]

According the recent findings, the author suggest that a further longitudinal prospective study need to be carried out in order to determine the causality effect of the changes in Ki67 expression and clinical response to neoadjuvant chemotherapy among LABC patients due to the limitation of case-control study approach.

CONCLUSION

Ki67 was found to be useful in determining the clinical response to NAC in patients diagnosed with LABC. Changes in Ki67 expression with cut-off points >12.5% were strongly correlated to the response in NAC with Anthracycline-based regimens.

CONFLICTS OF INTEREST

No competing interests were declared.

ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Dr. Soetomo Hospital, Surabaya, with number 0311/LOE/301.4.2/I/2021 by following the guidelines of the Declaration of Helsinki prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

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

REFERENCES

1. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical

benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–172.
2. Sasanpour P, Sandoughdaran S, Mosavi-Jarrahi A, Malekzadeh M. Predictors of Pathological Complete Response to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients. Asian Pac J Cancer Prev. 2018;19(9):2423–2427.
3. Del Prete S, Caraglia M, Luce A, Montella L, Galizia G, Sperlongano P, et al. Clinical and pathological factors predictive of response to neoadjuvant chemotherapy in breast cancer: A single center experience. Oncol Lett. 2019;18(4):3873–3879.
4. Minerva B, Ali I, Tanggo EH, Danardono E. Neutrophil lymphocyte ratio and clinical response after neoadjuvant chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil regiment in locally advanced breast cancer. Eurasian J Biosci. 2020;14(1):2473–2478.
5. Mulluzi AS, Ishardyanto H, Ali I, Kahar H. Platelet To Lymphocyte Ratio Relationship With Neoadjuvant Chemotherapy Of Caf Regiment Response In Locally Advanced Breast Cancer Patients. Indian J Public Heal Res Dev. 2021;12(1):223–229.
6. Sjöström J, Blomqvist C. Predictive factors for response to cytotoxic treatment in advanced breast cancer: a review. Acta Oncol. 1996;35(Suppl 5):84–90.
7. Chen R, Ye Y, Yang C, Peng Y, Zong B, Qu F, et al. Assessment of the predictive role of pre-treatment Ki-67 and Ki-67 changes in breast cancer patients receiving neoadjuvant chemotherapy according to the molecular classification: a retrospective study of 1010 patients. Breast Cancer Res Treat. 2018;170(1):35–43.
8. Wu Y-T, Li X, Lu L-J, Gan L, Dai W, Shi Y-L, et al. Effect of neoadjuvant chemotherapy on the expression of hormone receptors and Ki-67 in Chinese breast cancer patients: A retrospective study of 525 patients. J Biomed Res. 2017;32(3):191–197.
9. Chen C, Zhang Y, Huang Z, Wu J, Huang W, Zhang G. Decrease in the Ki67 index during neoadjuvant chemotherapy predicts favorable relapse-free survival in patients with locally advanced breast cancer. Cancer Biol Med. 2019;16(3):575–586.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–247.
11. PERABOI. Panduan Penatalaksanaan Kanker. Edisi Ke-2. Jakarta: PERABOI; 2020.
12. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol Off J Eur Soc Med Oncol. 2019;30(8):1194–1220.
13. Zubair Z, Masood S, Khattak S, Syed AA. Predictive Factors Involved in Determining response to Neoadjuvant Chemotherapy in High Grade Serous ovarian cancer and impact of response on 5 years disease free survival and overall survival. Pakistan J Med Heal Sci. 2020;14(3):638-643.
14. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast cancer (Dove Med Press). 2019;11:151–164.
15. Acheampong T, Kehm RD, Terry MB, Argov EL, Tehranifar P. Incidence Trends of Breast Cancer Molecular Subtypes by Age and Race/Ethnicity in the US From 2010 to 2016. JAMA Netw open. 2020;3(8):e2013226.
16. Widiana IK, Irawan H. Clinical and Subtypes of Breast Cancer in Indonesia. Asian Pacific J Cancer Care. 2020;5(4):281–285.
17. Kim K Il, Lee KH, Kim TR, Chun YS, Lee TH, Park HK. Ki-67 as a predictor of response to neoadjuvant chemotherapy in breast cancer patients. J Breast Cancer. 2014;17(1):40–46.
18. Ding Y, Ding K, Qian H, Yu X, Zou D, Yang H, et al. Impact on survival of estrogen receptor, progesterone receptor and Ki-67 expression discordance pre- and post-neoadjuvant chemotherapy in breast cancer. PLoS One. 2020;15(4):e0231895.
19. Li L, Han D, Wang X, Wang Q, Tian J, Yao J, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol. 2017;13(11):1021–34.
20. Montagna E, Bagnardi V, Viale G, Rotmensz N, Sporchia A, Cancello G, et al. Changes in PgR and Ki-67 in residual tumour and outcome of breast cancer patients treated with neoadjuvant chemotherapy. Ann Oncol Off J Eur Soc Med Oncol. 2015;26(2):307–313.
21. Cabrera-Galeana P, Muñoz-Montaño W, Lara-Medina F, Alvarado-Miranda A, Pérez-Sánchez V, Villarreal-Garza C, et al. Ki67 Changes Identify Worse Outcomes in Residual Breast Cancer Tumors After Neoadjuvant Chemotherapy. Oncologist. 2018;23(6):670–678.
22. Wiranata S, Anjani IAW, Saputra IPGS, Sadvika IGAS, Prabawa IPY, Supadmanaba IG, et al. Pre-treatment Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as a Stage Determination in Breast Cancer. Open Access Maced J Med Sci. 2020;8(B):1058- 1063.