Association of Ki-67 Expression and Response of Neoadjuvant Chemotherapy in Invasive Breast Cancer Patients in Bandung

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Abstract

Objective: To analyze the association of Ki-67 expression and response of neoadjuvant chemotherapy in patients with invasive breast cancer.

Methods: A retrospective observational study on the association of Ki-67 expression and response of neoadjuvant chemotherapy in patients with invasive breast cancer was conducted. This study included twenty-five female patients with invasive breast cancer who met the inclusion criteria. Parameters analyzed were age, tumor size, and immunohistochemical expression of Ki-67. Size of the tumor at pre- and post-neoadjuvant chemotherapy were obtained in cm^3 and compared between 3 groups of Ki-67 expression levels. One way ANOVA was used to perform the statistical analysis.

Results: A significant difference in changes of tumor size for Ki-67 level >20% compared to <14% and 14–20% was seen. Based on the result, neoadjuvant chemotherapy was proven to have similar effects in patients with Ki-67 expression of <14% and 14–20% but less effective in patients with Ki-67 expression of >20%.

Conclusions: Low to modest expression of Ki-67 was a better biomarker to predict the response of neoadjuvant chemotherapy in patients with invasive breast cancer compared to high expression of Ki-67. However, the cut-off value of 20% could be ideal to predict the outcome of neoadjuvant chemotherapy in patients with invasive breast cancer.

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Introduction

Breast cancer is the leading cancer in women both in developed and developing countries.[1] Incidences of breast cancer are increasing in the developing countries because of increasing life expectancy, urbanization, and adoption of western lifestyles. In Indonesia, breast cancer is the number one cancer for women in 2014.[2] According to this condition, more attention should be given to breast cancer to be able to benefit more patients.

Neoadjuvant chemotherapy is defined as the administration of systemic drugs before doing surgical intervention that is also the standard treatment to treat locally advanced breast cancer as well as a standard option for primary operable disease.[3] Ki-67 is a protein strictly associated with proliferation of the cell. Since the discovery of this protein, it has been widely introduced to be a proliferation marker for tumor cells.[4] Many cancers are associated with an increased level of Ki-67 expression in cancer cells that they are used as a biomarkers for cancer cells.[5,6,7] Furthermore, it would be

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interesting to find out the interaction between Ki-67 expression and the effect of neoadjuvant chemotherapy. As neoadjuvant chemotherapy is such effective choice of therapy and Ki-67 being and uprising biomarkers in the breast cancer field, this study aimed to analyze the association between Ki-67 expression level and response of neoadjuvant chemotherapy in patients with invasive breast cancer.

Methods

This study was a retrospective observational study on the association of Ki-67 expression and response to neoadjuvant chemotherapy in patients with invasive breast cancer. The ethical clearance was sought from the Health Research Ethics Committee of Faculty of Medicine Universitas Padjadjaran under the Registration No. 0116080891. Total sampling approach was applied for this study.

The inclusion criteria used included twenty five female patients with a diagnostic code of C50, underwent one cycle of chemotherapy prior to surgical intervention, and had tissue sample immunohistochemically stained for Ki-67. Exclusion criteria were patients whose primary diagnosis was not C50.

The tumor size was used as an indicator to measure the neoadjuvant chemotherapy response because of the limited choice available in the medical record. cPR and pPR were not recorded for the patients. One-way ANOVA were used to determine association of Ki-67 expression and the response of neoadjuvant chemotherapy.

Ki-67 expressions were then categorized into three groups, i.e. low (expression of <14%), modest (expression between, 14–20%), and high (expression of >20%). One way ANOVA test followed by LSD test for post hoc analysis was used to analyze the mean difference of tumor size (before and after chemotherapy) towards Ki-67 expression category.

Results

Twenty five patients participated in this study with all patients received the FAC regimen consisting of 5-fluorouracil, doxorubicin and cyclophosphamide as the standard choice of neoadjuvant chemotherapy for invasive breast cancer in Dr. Hasan Sadikin General Hospital, Bandung. The mean age of patients was 50.28 years (Table 1).

Table 1 Characteristics of Patients

Characteristics	Mean or Frequency
Age (yrs)	50.28
Tumor size, pre-chemotherapy (cm^3)	
Small (<100)	3
Medium (100–300)	14
Large (>300)	8
Ki-67 expression	
Low (<14%)	6
Modest (14–20%)	13
High (>20%)	6

Patients with a Ki-67 expression of 14–20% contributed approximately half of the subjects (n=13), which was double of the subjects with Ki-67 expression of <14% (n=6) and >20% (n=6). The majority of the tumor sizes before chemotherapy were found between 101–300 cm^3 which is the medium category for tumor size and about one-third of the subjects had a tumor size of more than 300 cm^3.

The changes of the tumor size were shown in cm^3 (Table 2). The overall distribution of the tumor size looks similar between the low and modest category while the patient of the high category has a higher average tumor size. These finding suggest tumor size reduction in the low and modest category post-neoadjuvant chemotherapy. In contrast, those patients with high Ki-67 expression showed insignificant reduction of tumor size after their treatment.

The posthoc test result showed a specific significance value when each category of Ki-67 expression was compared against each other. There was no significant difference when low Ki-67 expression and modest Ki-67 expression were compared ($p=0.516$), which suggest that the neoadjuvant chemotherapy has a similar effect among patients within these 2 groups of population. However, when those 2 categories were compared to patients with high Ki-67 expression, both groups showed a significant difference and suggested a significant decrease of effectiveness ($p<0.05$).

Discussion

After analyzing the data, the significance of changes in tumor size for the Ki-67 expression

Table 2 Changes of Tumor Size by Ki-67 Expression

Ki-67 Expression	Tumor Size			p Value
	Pre-Chemo (Mean ± SD)	Post-Chemo (Mean ± SD)	Δ(delta) pre- and post-chemo (Mean ± SD)	
Low (<14%)[a]	556.83±641.11	329±375.17	229.17±266.20	a vs b : 0.516
Modest (14–20%)[b]	362.54±330.97	216.04±242.00	145±101.92	b vs c : 0.011
High (>20%)[c]	2,161.67±5,065.42	2,152.33±5,069.70	17.33±56.34	a vs c : 0.018

>20 is still difficult to explain due to insufficient evidence to reach the conclusion. However, data supports the conclusion of several other results that Ki-67 could be used as a good predictive marker for assessing neoadjuvant chemotherapy outcome.

Low to modest expression of Ki-67 was a better biomarker to predict the response to neoadjuvant chemotherapy in patients with invasive breast cancer compared to the high expression of Ki-67.

A previous study determined that Ki-67 can be used to predict neoadjuvant chemotherapy response, but the cut-off value for the Ki-67 expression is 25%. Hence, value higher than 25% for Ki-67 expression can be used as a predictor of response towards neoadjuvant chemotherapy.[7] In comparison to this study, the data collected was unable to reach such precision of Ki-67 expression. In addition, 76% of the patient in this data has Ki-67 expression that is <20% which is much lower than the suggested cut-off value of Ki-67 expression as a predictor to assess the response to neoadjuvant chemotherapy. To a certain extent, this study also supports the result of the previous study from the perspective of Ki-67 expression that is below 25% which is not within the range to suitably predict the response of neoadjuvant chemotherapy.

Another previous studies also stated that Ki-67 has the potential to be used as a predictive and prognostic marker. However, the studies did not specify the exact cut-off value for Ki-67 expression for its predictive and prognostic value to be more evident as well as prominent after using the standard Ki-67 cut off value suggested by the St. Gallen's International Expert Consesus.[8,9] These results are similar to previous studies where it is stated that the idea of a relatively high Ki-67 expression value to be valid. In addition, another study investigated the optimal cut-off point for Ki-67 as a prognostic factor concluded that the ideal point is at 20% as the hazard ratio of that cut off point is the highest compared to the others.[10] Pathologic response is also a very common and useful way to determine the effectiveness of cancer treatments, they are used in both of the research that is being compared above. But due to the retrospective nature of this study with no data available about the pathologic responses after the treatment, it is unable to include into this study which compromises its validity. Furthermore, the suggested cut-off point by St. Gallen Consensus of 14% is slowly being proven to be not the ideal cut-off point by many study. This study which uses the suggested value of 14% also was not able to discover anything significant at that value.

The limitation of this study is that IHC test is not routinely done in Dr. Hasan Sadikin General Hospital, Bandung for all invasive breast cancer patients which leads to a very small sample size for this study, thereby limiting the credibility of this study.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. CA Cancer J Clin. 2012;62(1):10–29.
2. World Health Organization. Cancer country profiles 2013. [cited 2016 Apr 1]. Available from: http://www.who.int/cancer/country-profiles/en/.
3. Lotsch J, Sipila R, Tasmuth T, Kringel D, Estlander AM, Meretoja T, *et al*. Machine-learning-derived classifier predicts absence of persistent pain after breast cancer surgery

with high accuracy. Breast Cancer Res Treat. 2018;72(12):399–411.

4. Burcombe RJ, Makris A, Richman PI, Daley FM, Noble S, Pittam M, *et al*. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. Br J Cancer. 2005;92(1):147–55.
5. Ingolf JB, Russalina M, Simona M, Julia R, Gilda S, Bohle RM, *et al*. Can ki-67 play a role in prediction of breast cancer patients' response to neoadjuvant chemotherapy? Biomed Res Int [serial on the internet]. 2014 Mar [cited 2017 Aug 7];2014(1):[about 8p.]. Available from: https://www.hindawi.com/journals/bmri/2014/628217/.
6. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, *et al*. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat. 2013;139(2):539–52.
7. Kim KI, 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):40–6.
8. Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, *et al*. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer [serial on the internet]. 2011 Nov [cited 2018 Jan 17];11(486):[about 13p.]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262864/.
9. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A brief summary of the consensus discussion. Breast Care (Basel). 2015;10(2):124–30.
10. Tashima R, Nishimura R, Osako T, Nishiyama Y, Okumura Y, Nakano M, et al. Evaluation of an optimal cut-off point for the ki-67 index as a prognostic factor in primary breast cancer: a retrospective study. PLoS One [serial on the internet]. 2015 Jul [cited 2017 Dec 12];10(7):[about 10p.]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0119565.