Bali Medical Journal (*Bali Med J*) 2019, Volume 8, Number 3 (P2B2 PABI XVI Manado, Special Issue 2019): S569-S575
P-ISSN.2089-1180, E-ISSN: 2302-2914

Published by DiscoverSys

The relationship of hormonal receptor, HER-2, and KI-67 changes after administration of anthracycline-based neoadjuvant chemotherapy with the results of histopathological grading in stage III breast cancer patients at Saiful Anwar Malang Regional Public Hospital 2018

Risal Wintoko[1*], Hery Susilo[2]

ABSTRACT

Background: Breast cancer is cancer, with the highest incidence in women worldwide. It also has a very high mortality due to late treatment. The immunohistochemical examination is an important factor in determining breast cancer subtypes and subsequent therapy. However, neoadjuvant chemotherapy (NACT) has been reported to change the expression of immunohistochemical examinations of *Estrogen Receptor* (ER), *Progesterone Receptor* (PR), *Human Epidermal Growth Factor Receptor-2* (HER-2), and Ki-67. This study aims to determine the relationship between hormonal, HER-2, and KI-67 changes after NCAT.

Method: The immunohistochemical examinations were conducted on ER, PR, HER-2, Ki-67 and histopathological grading from 59 cases of stage III breast cancer after NACT administration. We analyzed the relationship between the changes in the expression of immunohistochemical examinations on the biopsy tissue specimens before NACT administration and from the tissue mastectomy after NACT administration associated with its histopathological grading with spearman correlation analysis using SPSS version 25 for Windows.

Results: There were changes in the results of the expression of immunohistochemical examinations of ER, PR, HER-2, KI-67 and histopathological grading by 23.7%, 22.03%, 32.2%, 32.2% and 40.68% in stage III breast cancer patients who received NACT. There was a relationship with a weak correlation between the changes in immunohistochemical examinations of ER, PR, HER-2 and KI-67 with the changes in histopathological grading. The correlation coefficients between ER, PR, HER-2, Ki-67 and the histopathological grading were r=0.265, r=0.317, r=0.352 and r=0.335.

Conclusions: Patients with stage III breast cancer who were treated with NACT experienced changes in the expression of immunohistochemical examinations of ER, PR, HER-2 and KI-67 and would experience changes in histopathological grading, causing changes in the breast cancer subtypes.

[1]Department of Surgery, Faculty of Medicine, Universitas Brawijaya, Malang Indonesia
[2]Department of Surgery, Oncology Division, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

Keywords: ER, PR, HER-2, KI-67 and histopathological grading
Cite this Article: Wintoko, R., Susilo, H. 2019. The relationship of hormonal receptor, HER-2, and KI-67 changes after administration of anthracycline-based neoadjuvant chemotherapy with the results of histopathological grading in stage III breast cancer patients at Saiful Anwar Malang Regional Public Hospital 2018. *Bali Medical Journal* 8(3): S569-S575. DOI: 10.15562/bmj.v8i3.1555

INTRODUCTION

According to global data, breast cancer is cancer with the highest incidence in women worldwide which is equal to 24.5% of all cancers in women with a proportion of 25-94 among 100.000 incidents.[1] In Indonesia, it is the second-highest number of cancer after cervical cancer, the ratio between breast cancer and cervical cancer is 5:8 and in a short time is expected to be cancer with the highest incidence in women.[2] Data from National Cancer Management Committee (KPKN) Indonesia up to February 2017 showed that the number of breast cancer patients increased compared to cervical cancer patients.[2] This is because early detection of cervical cancer is more accessible by using Visual Acetic Acid Inspection (IVA) and Pap smear methods, and cervical cancer can be prevented by using Human Papilloma Virus (HPV) vaccine.[3]

The mortality from breast cancer is quite high since many patients come with late conditions. Many studies have shown that with early detection, it can save thousands of lives every year. Based on data from Dharmais National Cancer Center Hospital, the number of breast cancer patients who come in the early stages (stage I and II) is 13.42%, stage III is 17% and many more (29.98%) come with an advanced stage (stage IV). Most patients begin with recurrence, which is equal to 39.66%. Diagnostic delay can be caused by patient delay, doctor delay, or hospital delay.[4]

Breast cancer consists of various complex

*Corresponding to:
Risal Wintoko; Department of Surgery, Faculty of Medicine, Universitas Brawijaya, Malang Indonesia;
risalwintoko.dr@gmail.com

Received: 2019-07-14
Accepted: 2019-11-14
Published: 2019-12-01

and heterogeneous subtypes that have different clinical properties. These various subtypes require individualized treatment. In addition to treatment based on conventional prognosis factors such as menopause status, age and stage, current treatment is also based on biomolecular examination.[5] Several modalities for breast cancer therapy indicate possible variations in the procedure. For instance, development of surgical technique, radiation therapy, hormonal therapy, target cell therapy and chemotherapy to alternative or complementary treatment.[4]

Locally advanced breast cancer (LABC) is stage III breast cancer, its presentations or incidents in Indonesia are still quite high and vary from various educational centres, ranging from 40-80%.[6-8] Included in the stage III breast cancer is stage IIIA, IIIB and IIIC breast cancer. Stage III therapy is recommended in the form of neoadjuvant chemotherapy, neoadjuvant hormonal therapy and neoadjuvant radiation.[4] The role of surgical modality in LABC is limited, especially in stage IIIA, and in several studies, the administration of neoadjuvant chemotherapy at the stage is still a benchmark. The recommended surgery after neoadjuvant chemotherapy is Modified Radical Mastectomy (MRM) or standard radical mastectomy (Halsted mastectomy). Postmenopausal patients with positive hormone receptors can be given hormonal neoadjuvant therapy. The grading can be done in 4 months after administration. If it is not responsive or progressive, then the neoadjuvant chemotherapy is given.[4]

Neoadjuvant Chemotherapy (NACT) is the administration of chemotherapy before surgery. NACT aims to reduce tumour size (tumour shrinkage) and control micrometastasis. The administration of NACT can prevent tumour multiplication and allow significant regression of the primary tumour so that the surgery can be performed. NACT is given to locally advanced stage or stages III breast cancer.[9] The most frequently used and most cost-effective NACT is anthracycline-based NACT since this regimen is quite sensitive and cheap.

Immunohistochemical examination (IHK) is an examination method by using antibody as a marker for detecting antigens in the tissue sections or other cell preparation forms. IHK is a standard in determining breast cancer subtypes. Its determination will play a role in helping to determine the type and prediction of the response to its systemic and prognostic therapies. The standard IHK done for breast cancer is hormonal receptors, namely *estrogen receptor* (ER) and *progesterone receptor* (PR), *Human Epidermal Growth Factor Receptor-2* (HER-2) and Antigen KI-67 (Ki-67). Hormonal receptors play a role in the administration of hormonal therapy in breast cancer while HER-2 plays a role in the administration of the targeting therapy.[10]

Immunohistochemical examinations before and after NACT administration show significant changes from hormonal receptors (ER and PR) and HER-2 expressions.[11] NACT will significantly reduce HER-2 and Ki-67 expressions. However, it does not alter the hormonal receptors (ER and PR) substantially in patients with stage III breast cancer.[12] From the background above the writers are very interested in researching changes in immunohistochemical examinations (ER, PR, HER-2 and Ki-67) after the administration of anthracycline-based neoadjuvant chemotherapy with the results of histopathological grading in patients with stage III breast cancer. Based on those mentioned above, the immunohistochemical examination is very important for hormonal therapy and targeting therapy that is known to be quite expensive, and if there is a change from this IHK examination, it is possible that the treatment still can be used. So, this study aims

METHODS

This research was a descriptive-analytic observational research with a prospective cohort approach aimed to find out the relationship of hormonal receptors (estrogen receptor and progesterone receptor), HER-2, and Ki-67 changes after the administration of anthracycline-based NACT with the results of histopathological grading changes in patients with stage III breast cancer at Saiful Anwar Regional Public Hospital Malang. This research was conducted at the Integrated Oncology Surgical Polyclinic of Saiful Anwar Regional Public Hospital Malang and Laboratory of Anatomy Pathology, Faculty of Medicine, Brawijaya University, conducted between January and December 2018.

The population of the research subjects was locally advanced stage or stage III breast cancer patients who fulfilled the inclusion criteria and had undergone examination procedures such as incisional biopsy/core biopsy, anthracycline-based NACT and had undergone definitive operative procedures for breast removal or breast cancer mastectomy that needed to have outpatient treatment in the Integrated Oncology Surgical Polyclinic of Saiful Anwar Regional Public Hospital Malang. In this research, there was 1 research group that was in accordance with the inclusion criteria and exclusion criteria. Each patient was given informed consent and obtained ethical clearance

from the Health Research Ethics Commission of Saiful Anwar Regional Public Hospital Malang. From the preliminary data of the medical record of Saiful Anwar Regional Public Hospital Malang, it was found that the number of new breast cancer patients during 2017 was 196 patients in which 114 of them were patients with stage III breast cancer.

The inclusion criteria used in this study were women aged 30 – 70 years, patients with locally advanced stage (stage III) breast cancer and undergone tissue biopsy or core biopsy procedures, received NACT and definitive surgical procedures or mastectomy, willing to take part in the research-proven by signing an informed consent and approval sheet, not in a state of trauma, infection, obesity, and metabolic diseases, and undergo *anthracycline* regiment *neoadjuvant chemotherapy*

Independent variables in this research were hormonal receptors (*estrogen receptor* and *progesterone receptor*), HER-2 and Ki-67 changes after the administration of anthracycline-based chemotherapy. Dependent variables in this research were the changes in the results of histopathological grading based on *Nottingham Grading System Score* in stage III breast cancer patients. Data were analyzed using SPSS version 25 for Windows.

Table 1. Baseline characteristics of respondents

Variables	Frequency (N=59)	Percentages (%)
Age		
≤ 40	5	8.47
41-50	23	38.98
51-60	24	40.69
≥ 61	7	11.86
Stage		
III A	7	11.86
III B	50	84.75
III C	2	3.39
Subtype		
Luminal A	11	18.64
Luminal B	33	55.94
HER-2	7	11.86
Triple Negative	8	13.56
Chemotherapy Response		
Partial Response	57	96.61
Complete Response	2	3.39
Histopathological Response		
I	10	16.95
II	16	27.12
III	33	55.93
ER		
Positive	41	69.49
Negative	18	50.51
PR		
Positive	38	64.41
Negative	21	35.59
HER-2		
Negative/+	32	54.24
++	7	11.87
+++	20	33.89
		72.88
Ki-67		
High	43	
Low	16	27.12

RESULTS

There were 94 stages III breast cancer patients who underwent therapy at the Oncology Surgical Polyclinic of Saiful Anwar Regional Public Hospital Malang. From the total 94 patients, 28 patients were excluded from the research because the writers had to replace the anthracycline-based chemotherapy regiment due to its non-optimal response (stable disease and progressive disease) and 7 patients refused to join the research.

Based on the characteristics of the research samples above, it can be seen that most of the breast cancer patients are aged between 51-60 years of 24 patients (40.69%), stage III B is 50 patients (84.75%), luminal B type is 33 patients (55.94%), *partial response* in 57 patients (96.61%), positive ER is 42 patients (69.49%), positive PR is 38 patients (64.61%), negative HER-2 is 32 (54.24%) patients, *high proliferation* Ki-67 is 43 patients (72.88%), and the highest histopathological grading is stage III with 33 patients (55.93%) (Table 1).

Based on Figure 1 above, there were changes in the immunohistochemical examinations of ER, PR, HER-2 and Ki-67 and histopathological grading after NACT administration in patients with stage III breast cancer. The changes in the immunohistochemical examinations were ER of 23.7%, PR of 22.03%, HER-2 of 32.2%, Ki-67 of 32.2%, and the change in histopathological grading was 40.68% after the administration of anthracycline-based neoadjuvant chemotherapy in stage III breast cancer patients (Figure 1).

In the immunohistochemical examination of ER, there were changes after NACT administration from positive to negative by 12 patients (20.34%), stable 45 patients (76.27%) and negative to positive by 2 patients (3.39%) (Table 2). In the immunohistochemical examination of PR, there were changes after NACT administration from positive to negative by 10 patients (16.95%), stable 46 patients (77.97%) and negative to positive by 3 patients (5.08%). In the immunohistochemical examination of HER-2, there were changes after NACT administration from positive to negative by 18 patients (30.5%), stable 40 patients (67.80%) and negative to positive by 1 patient (1.7%) (Table 2). In the immunohistochemical examination of Ki-67, there were changes after NACT administration from positive to negative by 19 patients (32.2%), and stable 40 patients (67.80. In the histopathological

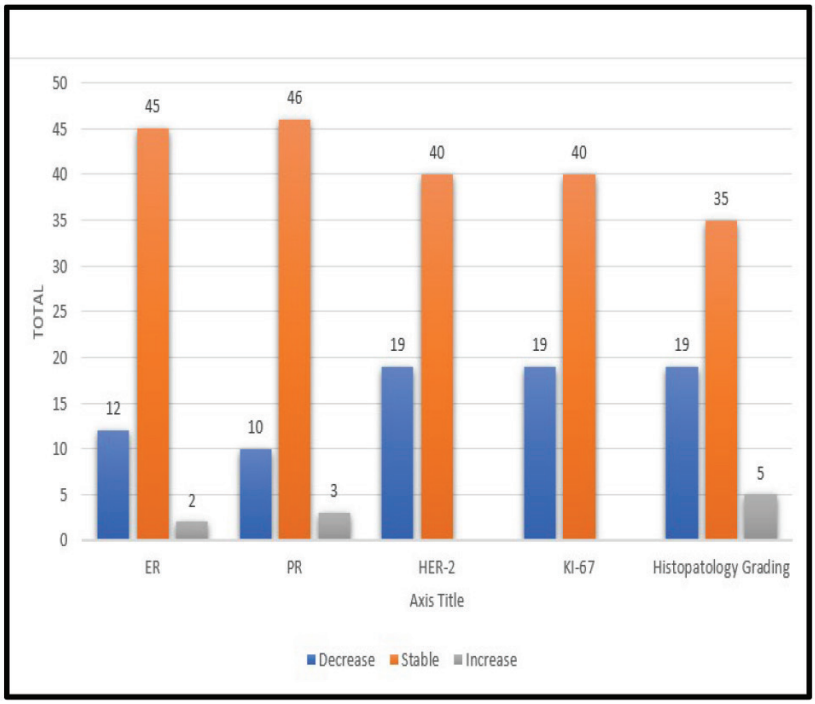

Figure 1. The results of immunohistochemical examinations of ER, PR, Her-2 and Ki-67

Table 2. Cross-tabulation of changes in immunohistochemical examination of ER, PR, and HER-2 with changes in histopathological grading

Variables	Histopathological Grading (N=59)			Total	r	P
	Decrease (%)	Stable (%)	Increase (%)			
ER						
Decrease	6 (50.00)	5 (41.67)	1 (8.33)	12	0.265	0.000
Stable	13 (28.89)	30 (66.67)	2 (4.44)	45		
Increase	0 (0.00)	0 (0.00)	2 (100.00)	2		
PR						
Decrease	6 (60.00)	4 (40.00)	0 (0.00)	10	0.317	0.001
Stable	12 (26.09)	31 (67.39)	3 (6.52)	46		
Increase	1 (33.33)	0 (0.00)	2 (66.67)	3		
HER-2						
Decrease	11 (57.89)	7 (36.84)	1 (5.26)	19	0.352	0.014
Stable	8 (20.00)	28 (0.00)	4 (10.00)	40		
KI-67						
Decrease	10 (52.63)	9 (47.37)	0 (0.00)	19	0.355	0.035
Stable	9 (22.50)	26 (65.00)	5 (12.50)	40		

grading examination, there were changes after NACT administration namely increased by 5 patients (8.47%), decreased by 19 patients (32.20%), and stable by 35 patients (59.32%) (Table 2).

The grading of the relationship between the changes in the immunohistochemical examination of ER and changes in histopathological grading after NACT administration was obtained from the *chi-square* analysis with a *p*-value = 0.000, because of the *p*-value = 0.000 < 0.05 (α=5%). The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.265, so it can be concluded that there was a weak correlation between the changes in ER and the changes in histopathological grading (Table 2).

The grading of the relationship between the changes in the immunohistochemical examination of PR and the changes in histopathological grading after the administration of anthracycline-based NACT was obtained from the *chi-square* analysis with a *p*-value = 0.001 because the *p*-value = 0.001 < 0,05 (α=5%). The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.317, so it can be concluded that there was a weak correlation between the changes in PR and the changes in histopathological grading (Table 2).

The grading of the relationship between the changes in the immunohistochemical examination of HER-2 and the changes in histopathological grading based on the results of the *chi-square* analysis with a *p*-value = 0.014, because the *p*-value = 0.014 < 0.05 (α=5%). The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.352, so it can be concluded that there was a weak correlation between the changes in HER-2 and the changes in histopathological grading (Table 2).

The grading of the relationship between the changes in the immunohistochemical examination of Ki-67 and the changes in histopathological grading based on the results of the *chi-square* analysis with a *p*-value = 0.035, because the *p*-value = 0.035 < 0.05 (α=5%). The correlational relationship by using Spearman correlation analysis obtained a correlation coefficient value of r=0.335, so it can be concluded that there was a weak correlation between the changes in Ki-67 and the changes in histopathological grading (Table 2).

DISCUSSION

Breast cancer is the most common cancer in women worldwide. Based on the estimation from International Agency for Breast Cancer (IARC) in 2012, the incidence of breast cancer was 43.1 per 100,000 women with a mortality of 12.9 per 100,000 women. In Indonesia, the estimation reaches 134 per 100,000 women. Locally advanced breast cancer is stage III A, III B, and III C breast cancer. The recommended treatment modality is NACT or Neoadjuvant hormonal therapy (chosen based on the immunohistochemical examinations taken during biopsy of breast tumour tissue before), followed by surgery therapy or radiation therapy.[13]

Published by DiscoverSys | *Bali Med J* 2019; 8(3): S569-S575 | doi: 10.15562/bmj.v8i3.1555

NACT is chemotherapy done before surgery in cases of stage III breast cancer that aims to reduce tumour size and control micrometastasis. In NACT, the most commonly used regimen is anthracycline-based. The NACT grading is given at least after 2-3 cycles at 21 days intervals. The chemotherapy response is graded in a locoregional and systemic manner.[14] The effects of chemotherapy can cause spontaneous death of the cancer cells, inhibit the formation of blood vessels, inhibit the division or replication of cancer cells and prevent the cell division by changing the structure of cancer cells.[14] NACT will affect changes in the immunohistochemical examinations of ER, PR, HER-2 and Ki-67, and will also affect differences in its histopathological grading. With the changes in ER, PR, HER-2, Ki-67 and the changes in histopathological grading the response from subsequent treatment can be graded. In this case, the researchers would like to find out whether or there is a relationship or not between changes in immunohistochemical examination ER, PR, HER-2 and Ki-67 with variations in histopathological grading.

Immunohistochemical examinations of ER, PR, HER2 and Ki-67 are useful for molecular classification so that it is useful in determining the therapy to be given to breast cancer patients. This classification is based on the similarity of protein expression profiles. This gene expression-based classification is associated with effective treatment of breast malignancy.[15]

NACT is used for therapy in stage III breast cancer and the tendency to treat breast cancer based on the presence of ER, PR and HER-2 receptors.[16,17] The changes in the status of the immunohistochemical examinations of ER, PR and HER-2 between the biopsy result tissue and mastectomy result tissue have been reported after NACT administration, but these results have not been consistent.[16,17] The changes in the status of immunohistochemical examinations of ER, PR or HER-2 will have consequences for therapeutic, prognostic, and financial financing of necessary treatment for patients and health care providers. With the increased use of NACT, it is essential to know whether there are changes in the examinations of ER, PR and HER-2 and the possible consequences for subsequent additional systemic therapy. NACT is able to change the expression and status of ER, PR, and HER-2 receptors.[16,17]

From the findings of this research, it was found that there was a link with the weak correlation between the changes in the expressions of the immunohistochemical examinations of ER and PR with the changes in histopathological grading after NACT administration in stage III breast cancer. This research was in accordance with Guangchao et al.'s in 2015 which stated that there were significant changes in ER and PR receptors after NACT administration, namely the changes in immunohistochemical examination of ER by 28.6% and PR by 22.9%.[18] Another research conducted by Bala Basak et al., also stated that there was a significant change in immunohistochemical ER and PR examinations after NACT administration by 12.5% and 21.2%.[19]

The changes in hormonal receptors from positive to negative were more common in breast cancer with positive HER-2 than negative HER-2. In addition, the conversion of hormonal receptor status observed occurred more frequently in tumours with poor differentiation than good differentiation.[20] The relatively high proportion of Ki-67 index was found in breast tumours with positive to negative hormonal receptor changes compared to breast cancer which had a negative hormonal receptor status.[20]

A study conducted by Chen *et al.* in 2012 reported that patients with positive to negative hormonal receptor changes after NACT administration did not benefit from hormonal therapy compared to patients whose hormonal receptor status remained stable.[21] In contrast, Hirata et al., 2009 reported that there were no significant differences in the level of Progressive Free Survival (PFS) and Overall Survival (OS) between patients given the hormonal therapy with hormonal receptors that turned negative, and patients given the hormonal therapy with hormonal receptor that turned negative, and patients given the hormonal therapy with hormonal receptor which remained positive after NACT administration.[22]

From the findings of this research, it was found that there was a link with weak correlation between the changes in the expressions of immunohistochemical examination of HER-2 with the changes in histopathological grading after NACT administration in stage III breast cancer. The change in HER-2 expression was 32.2% of the total sample examined, and 57.89% experienced decrease in its histopathological grading. This was also in line with Neubauer et al.'s, 2008 research, which stated that there was a change in HER-2 expression after NACT administration by 15%, where 85% was a change from the expression of positive HER-2 to negative HER-2.[23] In contrast, Avci N. et al., 2015 stated that the presence of NACT would give a quite significant change in the expression of immunohistochemical examination of HER-2 in breast cancer patients by 61.9%.[12]

The changes in HER-2 expression were also related to the prognosis of breast cancer. The comparison of the results of HER-2 expression

after NACT administration from the research was 32.25%, in which 57.8% of the change in HER-2 expression was accompanied by a decrease in the tissue histopathology grading. Thus, it can be concluded that changes in HER-2 expression and the changes in the tissue histopathology grading had a better response to NACT administration. In other words, the changes in HER-2 expression and the changes in histopathological grading affected the success of neoadjuvant chemotherapy response of stage III breast cancer.

From the findings of this research, it was found that there was a weak correlational relationship between the changes in Ki-67 expression and the changes in histopathological grading. The change in Ki-67 expression in this research was 32% after NACT administration. This research was in accordance with a study by Ramteke P et al. in 2017 which stated that there was a change in Ki-67 expression after NACT administration by 17%.[24] Meanwhile, according to Guangchao Jin et al., 2015, the change in Ki-67 expression after NACT administration was 54.3%.[18]

Ki-67 as a proliferative marker is a nuclear antigen in humans and forms an integrated part with both normal cell division and malignant cell division. Because the characteristic of cancer is uncontrolled and continuous cell proliferation, the Ki-67 proliferation index is used to grade and manage breast cancer.[25] The Ki-67 value is a prognostic indicator, a guide to select the therapies and a method of measuring responses on the ongoing treatment.[25] Grading of Changes in Ki-67 expression is related to Histopathological changes, where cancer cells that have high Ki-67 expression will have good response to chemotherapy (partial response and complete response) so that it will change the grading of tumour tissue histopathology.[25] The same thing was conveyed by Yin HF et al. who stated that changes in cell proliferation and changes in tissue histopathology degrees were the most important factors that were effective in grading the effectiveness of neoadjuvant chemotherapy.[26]

Qi-Xing Tan et al., 2014 reported that there were significant changes in the expression of immunohistochemical examinations of ER, PR in breast cancer with neoadjuvant chemotherapy.[27] The changes in hormonal receptor status were found more frequently in tumours with positive HER-2 status, poor differentiation and a relatively high proportion of Ki-67 index.[27] Progressive Free Survival and Overall Survival grading in patients with positive to negative hormonal receptor changes with chemotherapy will be worse than patients with constantly positive hormonal receptors after chemotherapy, while tumours with negative to positive hormonal receptor changes will have better prognosis.

Recently, the American Society of Clinical Oncology (ASCO) published clinical practise guidelines that recommend re-biopsy of breast cancer metastasis to reevaluate expression of immunohistochemical examinations of ER, PR and HER-2. Nonetheless, the evidence is still lacking about whether there is a change for chemotherapy regimens to be carried out based on changing biomarkers in the setting of adjuvant therapy. The panel consensus is used as biomarker testing of the metastatic tumours to the appropriate direct treatment.[28]

Lindstrom LS *et al.* stated that there was no ASCO guideline about whether the exclusion of the biopsy specimens must be retested after *neoadjuvant chemotherapy* therapy, and whether the adjuvant chemotherapy should be changed if there are changes. As a result, the practice is different throughout the world. The neoadjuvant chemotherapy is increasingly used before surgical resection of breast cancer, with a treatment regimen guided by hormonal receptor status and HER-2 expression from biopsy samples of breast tumours. Even though several previous studies have shown that biomarker expression can change after neoadjuvant chemotherapy in breast cancer, however many possibilities can explain the differences between hormonal receptors and HER-2 expression and amplification of ERBB-2 and Ki-67 genes after neoadjuvant chemotherapy.

ETHICAL CLEARANCE

This research had been approved by the Ethics Committee prior to the study conducted.

CONFLICT OF INTEREST STATEMENT

The authors declare that there was no conflict of interest in this research.

FUNDING

The authors are responsible for the study funding without the involvement of grant or any other resource of funding

AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, preparation, drafting, review, and approval of this manuscript.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN. 2018;68:394–424
2. Basic Health Research (Riset Kesehatan Dasar/Rikesdas) of the Ministry of Health. Health Research and Development Agency, Indonesian Ministry of Health: South Jakarta. 2013
3. Gondhowiardjo S, Sekarutami SM, Poetiray EDC. Breast Cancer Treatment: The Role of Surgery and Irradiation. In: The Multidisciplinary Cancer Management of SolidTumors. Faculty of Medicine University of Indonesia; Jakarta. 2004:225-238
4. Tong CWS, Wu M, Cho WCS, To KKW. Recent Advances in the Treatment of Breast Cancer. Front Oncol. 2018;8:227.
5. Fumagalli D, Bedard PL, Nahleh Z, Michiels S, Sotiriou C, Loi S,, et al. A common language in neoadjuvant breast cancer clinical trials: proposals for standard definitions and endpoints. Lancet Oncol. 2012;13(6):e240-8.
6. Akhsan A, Aryandono T. Prognostic factors of locally advanced breast cancer patients receiving neoadjuvant and adjuvant chemotherapy. Asian Pac J Cancer Prev. 2010;11(3):759-61.
7. Lestari AAW, Prabawa IPY, Wiranata S, Supadmanaba IGP. High eosinophilic lymphocyte ratio (ELR) related with subtype of breast cancer in Sanglah General Hospital. Annals of Oncology. 2018;29(suppl_9).
8. Wiranata S, Adiputra PAT, Lestari AAW, Prabawa IPY, Supadmanaba IPY. Platelet Lymphocyte Ratio (PLR) Related with Clinicopathological Characteristics of Balinese Women Breast Cancer Patient. Annals of Oncology. 2019;30(suppl_6).
9. Suyatno, Pasaribu ET. Surgical Oncology Diagnosis and Therapy. 2nd edition. Sagung Seto: Jakarta. 2014: 60-65
10. Zaha DC. Significance of immunohistochemistry in breast cancer. World J Clin Oncol. 2014;5(3):382-92.
11. Kaya AO, Buyukberber S, Yamac D, Coskun U, Yildis R, Yaman E, et al. Change in Hormon Receptor and Her-2 Status After Neoadjuvant Chemotherapy in Breast Cancer. 2010. Turkiye Klinikleri J Med Sci. 2010;30(2):469-473
12. Avci N, Deligonul A, Tolunay S, Cubukcu E, Fatih Olmez O, Ulas A, et al. Neoadjuvant chemotherapy-induced changes in immunohistochemical expression of estrogen receptor, progesterone receptor, HER2, and Ki-67 in patients with breast cancer. J BUON. 2015;20(1):45-9.
13. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003;21(22):4165-74
14. Rosai J, Ackerman. Clasification of Tumours pathology and genetic of tumours of Breast. In: Surgical pathology. 10th Ed. Toronto: Elsevier. Word Health Organization, Lyon: IARC Press. 2012
15. van de Ven S, Smit VT, Dekker TJ, Nortier JW, Kroep JR.. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev. 2011;37(6): 422-430.
16. Zhang N, Moran MS, Huo Q, Haffty BG, Yang Q. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. Cancer Invest. 2011;29(9):594-598.
17. Jin G, Han Y, Liu C, Chen L, Ding B, Xuan S, et al. Evaluation of biomarker changes after administration of various neoadjuvant chemotherapies in breast cancer. Int J Clin Exp Pathol. 2015;8(1): 914-921.
18. Basak Oven Ustaalioglu B, Aker Vardar F, Bilici A, Gurleyik G, Erkol B, Kefeli U, et al. Clinical importance of discordance of hormone receptors and Her2/neu status after neoadjuvant chemotherapy in breast cancer. J BUON. 2014;19(4):879-886.
19. 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- 155.
20. Chen S, Chen CM, Yu KD, Zhou RJ, Shao ZM. Prognostic Value of a Positive-to-negative Change in Hormone Receptor Status after Neoadjuvant Chemotherapy in Patients with Hormone Receptor-positive Breast Cancer. Ann Surg Oncol. 2012;19(9): 3002-3011.
21. Hirata T, Shimizu C, Yonemori K, Hirakawa A, Kouno T, Tamura K, et al. Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer. Br J Cancer. 2009;101(9):1529-36.
22. Neubauer H, Gall C, Vogel U, Hornung R, Wallwiener D, Solomayer E, et al. Changes in tumour biological markers during primary systemic chemotherapy (PST). Anticancer Res 2008;28(3B):1797-804
23. Ramteke P, Seenu V, Prashad R, Gupta SD, Iyer V, Deo S, et al. Alteration in steroid hormone and Her-2/neu receptor status following neoadjuvant chemotherapy in locally advanced breast cancer: Experience at a tertiary care centre in India. Indian J Cancer. 2016;53(3):366-371.
24. Mannell A. The role of Ki-67 in breast cancer. S Afr J Surg. 2016;54(2):10-13.
25. Yin HF, Wang YH, Qin XQ, Zhang H, Li T, Ye JM, et al. Effect of neoadjuvant chemotherapy on histologic grade and expression of biological markers in breast cancer. Zhonghua Zhong Liu Za Zhi. 2009;31(11):858-62.
26. Tan QX, Qin QH, Yang WP, Lian B, Wei CY. Prognostic value of hormone receptor status conversion following neoadjuvant chemotherapy in a series of operable breast cancer patients. Int J Clin Exp Pathol. 2014;7(7):4086-94.
27. Van Poznak C, Somerfield MR, Bast RC, Cristofanilli M, Goetz MP, Gonzalez-Angulo AM. Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2015;33(24):2695-704
28. Lindström LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012;30(21):2601-8.