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Correlation between CA 15-3 and Miller Payne Histopathological Response in Locally Advanced Breast Cancer Undergoing FAC Regiment Neoadjuvant Chemotherapy

Kiki Akhmad Rizki,[1] Raden Yohana Azhar,[1] Birgitta M. Dewayani,[2] Aulia Novariza Fahman[3]

[1]Division of Oncology Surgery, Department of Surgery, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

[2]Department of Anatomical Pathology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

[3]Department of General Surgery, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Response to chemotherapy for breast cancer can be assessed using the CA 15-3 tumor marker, or through histopathological means such as Miller Payne assessment. This study aimed to explore the correlation between CA 15-3 level and histopathological response in locally advanced breast cancer. This is a cross-sectional study measuring CA 15-3 before and after neoadjuvant chemotherapy using the FAC regiment. This study took place in Dr. Hasan Sadikin Hospital Bandung, Indonesia, from January to August 2022. Data on histopathological responses before chemotherapy and after surgery were also collected. Thirty-nine patients were admitted as subjects. Most patients had invasive carcinoma of no special type (79.5%) and luminal B HER 2 molecular subtype (38.5%). A significant decrease in CA 15-3 level after chemotherapy (from 23.54±18.38 ng/mL to 16.30±6.51 ng/mL) was observed. No significant correlation between CA 15-3 level and Miller Payne histopathological responses were found in the subjects.

Keywords: Breast cancer, chemotherapy, histopathology

Introduction

According to the Global Burden of Cancer Study (GLOBOCAN) released by the International Agency for Research on Cancer (IARC) in 2020, it was known that breast cancer is the malignancy with the highest percentage of new cases, which is 2,261,419 cases (11.7% of all new cancer cases) and has a mortality rate of 6.9%. As many as 65,858 new breast cancer cases were diagnosed in Indonesia in 2020, making it the most diagnosed malignancy.[1]

Locally advanced breast cancer is defined as a collection of invasive manifestations. The early manifestations and radiological imaging of this breast cancer involve the lymph nodes as well. This breast cancer has a size of more than 5cm, it may also adhere to the skin or the chest wall. Lymph node metastases adhering to the surrounding tissue may also be found in this type of cancer. One of the modalities to treat locally advanced breast cancer is neoadjuvant chemotherapy. This chemotherapy is given to patients with high-grade malignancy who have never received local-regional procedures through surgery or radiation.[2]

Proskurina et al.[3] found that combined chemotherapy using conventional anthracyclins such as 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) is more effective in combatting breast malignancy compared to the use of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).

In patients diagnosed with breast cancer, tumor markers may serve several purposes in the management and early detection of disease progression. The most commonly used tumor marker for breast cancer is CA 15-3. This tumor marker can be used as a diagnostic, prognosis, therapy monitoring, and recurrence prediction tool after surgery and chemotherapy.[4,5] The American Society of Clinical Oncology 2007

Corresponding Author:
Aulia Novariza Fahman
Department of General Surgery, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
Email: maumaubau@yahoo.co.id

(ASCO) discovered that CA 15-3 is increased as much as 75-90% in advanced stages and when metastasis is present. The increased level of this tumor marker can predict an unfavorable prognosis and the incidence of metastasis.[6]

The Miller-Payne system can be used to assess neoadjuvant chemotherapy response at the histological level. Histopathological response evaluation is currently an important independent prognostic factor because the evaluation of the residual tumor is based on the decreased amount of tumor cells. This evaluation can also predict overall survival and disease-free interval in patients with large breast cancer and advanced stage.[7,8] The Miller Payne evaluation system is presented in Table 1.

Few studies have looked into the benefit of CA 15-3 correlating with histopathological response after neoadjuvant chemotherapy. This research aims to find the correlation between CA 15-3 level with the histopathological response using Miller Payne system in locally advanced breast cancer patients undergoing FAC regiment neoadjuvant chemotherapy.

Methods

This is a cross-sectional study to find the correlation between CA 15-3 level and histopathological response before and after chemotherapy. CA 15-3 before FAC neoadjuvant chemotherapy and 21±7 days after the fourth cycle of chemotherapy will be compared. Histopathological response data are collected before the start of neoadjuvant chemotherapy and after surgery.

This study uses patients diagnosed with locally advanced breast cancer as subjects. Patients who visited the surgical oncology clinic in Dr. Hasan Sadikin General Hospital, Bandung in the period between October 2021 to August 2022 were considered as subjects. Locally advanced breast cancer patients undergoing FAC regiment neoadjuvant chemotherapy and consented to be part of this study were included as subjects. Patients with comorbid such as diabetes mellitus and chronic kidney disease were omitted from participating in this study. Patients with bilateral breast cancer, cirrhosis, hepatitis, benign tumor or breast infection, colon cancer, ovarian cancer, lung cancer, and pancreatic cancer were also excluded. Patients with a previous history of chemotherapy or who are currently undergoing chemotherapy along with radiation were excluded from this study as well.

Comparative tests such as paired t-test and ANOVA are used to analyze the variables. Correlation is determined by Jaspen (M) Correlation for correlation between CA 15-3 with Miller Payne grade and Pearson correlation test for correlation between CA 15-3 with the other variables.

This research abides by ethical considerations. Patients were given information about this study and were asked for consent. This study has received clearance from the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung (Number: LB.02.01/X.6.5/124/2022).

Results

Thirty-nine patients were admitted as the study subjects. Characteristics of the patients are presented in Table 2. Most of the subjects are aged between 50–59 years old. The most common histopathological type is no special type, accounting for more than 2 two-thirds of the subject population. Most patients fell into grade III of Miller Payne's histopathological system after surgery.

The comparison between CA 15-3 levels before and after chemotherapy showed a significant difference as presented in Table 3 ($p<0.005$). CA 15-3 levels in invasive lobular and no special types before and after chemotherapy displayed a significant difference only in the no special type group. Comparing CA 15-3 levels before and after chemotherapy with the tumor subtypes yields a significant difference in the Luminal B, HER 2 Positive, and HER 2 Type groups.

Table 1 Miller Payne System

Response criteria	
Grade I	No change, no significant reduction in tumor cell
Grade II	Minor loss of tumor cells (≤30%)
Grade III	Loss of tumor cells between 30% and 90%
Grade IV	Reduction of tumor cells >90%
Grade V	No identifiable malignant cells, ductal carcinoma in situ (DCIS) may be present

Table 2 Characteristics of Subjects

Variable	n	Percentage (%)
Age (years)[b]	48 (26–76)	
20–29	1	2.6
30–39	8	20.5
40–49	11	28.2
50–59	15	38.5
60–69	3	7.7
70–79	1	2.6
Histopathology type		
Invasive Ductal	1	2.6
Invasive Lobular	5	12.8
No Special Type	31	79.5
Mucinous	1	2.6
Secretory	1	2.6
Tumor Subtype		
Luminal A	4	10.3
Luminal B, HER 2 Positive	5	12.8
Luminal B, HER 2 Negative	15	38.5
HER 2 Types	10	25.6
Triple Negative	5	12.8
CA 15-3 levels		
Before chemotherapy (ng/ml)[b]	17.7 (4.5–74.3)	
After Chemotherapy (ng/ml) [a]	16.30 ±6.51	
Miller Payne Histopathology		
I	5	12.8
II	9	23.1
III	14	35.9
IV	9	23.1
V	2	5.1

[a]Average ± SD; [b]Median (min.–max.)

This study also calculates the correlation between the difference between both levels of CA 15-3 with Miller Payne grade. It was found that there is a decrease in levels of CA 15-3 but there is no correlation between decreased CA 15-3 levels with Miller Payne grade (r count < r tables). This result is presented in Table 4.

Discussion

Tumor markers are used in assisting early diagnosis and classification, determining prognosis, monitoring the success of therapy, as well as monitoring the recurrence of the disease. Most serological tumor markers cannot be used for asymptomatic screening of patients and very few can be used for diagnosis due to their low sensitivity and specificity. To increase sensitivity in some types of malignancies used a relatively specific combination of tumor markers.[9] All breast cancer patients examined for tumor markers were associated with local and systemic therapy.[10]

The tumor marker that is often used for breast cancer is CA 15-3. This marker is overexpressed in >90% of breast cancers. CA 15-3 promotes tumor invasion and metastasis through activation of the mitogen-activated protein kinase signaling pathway and decreased

Table 3 Comparison of CA 15-3 Before and After Chemotherapy in Different Variables

	CA 15-3 Before Chemotherapy (Average±SD)	CA 15-3 After Chemotherapy (Average±SD)	P
CA 15-3 level	23.54±18.38	16.30±6.51	0.002
Histopathology type			
Invasive Ductal	10.6	9.4	
Invasive Lobular	26.06±4.25	15.62±1.25	0.123
No Special Type	21.94±3.25	15.93±1.19	0.022
Mucinous	24.8	18.7	
Secretory	72.4	35.7	
Subtype tumor			
Luminal A	17.75±6.73	13.70±1.85	0.539
Luminal B, HER 2 Positive	22.08±3.32	16.90±2.65	0.006
Luminal B, HER 2 Negative	16.71±2.31	13.70±1.18	0.164
HER 2 Type	37.15±8.17	20.84±2.67	0.022
Triple Negative	22.90±10.63	16.50± 2.80	0.534

Table 4 Correlation between Miller Payne Grade and Decreased CA 15-3 Levels

Miller Payne Grade[a]	CA 15-3 Before Chemotherapy[b]	CA 15-3 After Chemotherapy[b]	Difference in CA 15-3 Levels[b]	r count	r tables
3 (1–5)	23.54±18.38	16.30±6.51	7.24±13.92	0.073	0.325

[a]Median (Min-Max); [b]Mean±SD

regulation of E-cadherin. Thus, CA 15-3 is more associated with metastatic risk and has a negative correlation with progressive free disease.[11] Hasan et al.[12] explained that CA 15-3 level show a high increase in breast cancer cases and significantly help in the diagnosis of breast cancer. Although, the assessment is not a gold standard but is efficient in predicting susceptibility to breast cancer and detection of breast cancer prognosis.

At the beginning of the disease, CA 15-3 sensitivity levels are very low, however, it will increase according to the clinical degree of breast cancer, highest in cases of metastases. Research conducted by Jia et al. reported that CA 15-3 concentration will increase in 10% from patients with stage I disease, 20% with stage II disease, 40% with stage III disease, and 75% with stage IV disease.[13] This is also in line with research conducted by Chin et al showing that in cases of metastatic breast cancer, the sensitivity of CA 15-3 is superior.[14] Another study also reported that CA 15-3 is useful as an early screening for high-risk patients as well as mammograms. Research conducted by Sototetti et al.[15] assessing CA 15-3 levels before and after chemotherapy in advanced stages of breast cancer concluded that elevated CA 15-3 are predictive of a poor response to chemotherapy. Several other studies have shown that the use of CA 15-3 together can increase sensitivity in about 90% of people with breast cancer who are already metastatic.[16]

In the study by Yang et al.[11] CA 15-3 level before therapy was lower in the triple-negative subtype compared to other subtypes. In this study, CA 15-3 before therapy in the triple-negative subtype tends to be low compared to Luminal B – HER 2 positive and HER 2. However, when compared to Luminal A and Luminal B – HER 2 negatives, the CA 15-3 level on triple negative is slightly higher. As for this study, the results were slightly different because the division of subtypes carried out in this study was different from the research of Yang et al.[11] In the study conducted by Shao et al. it was explained that Luminal B has aggressive clinical properties so that CA 15-3 tends to be higher in the positive

Luminal B population. However, another study by Araz et al.[17,18] suggested that the Luminal type did not determine CA 15-3 levels.

In the study by Gupta et al.,[19] pre-therapeutic CA 15-3 levels were significantly higher than post-therapy CA 15-3 levels. This is in line with the results of this study. We found that there was a significant decrease in the average CA 15-3 levels before and after chemotherapy with a P value of 0.002. CA 15-3 levels before and after chemotherapy also had a strong correlation with an r of 0.780 and a P value of <0.001. This shows that in general the samples in this study had a good response to chemotherapy.

Another objective assessment in addition to tumor markers is the evaluation of the histopathological response. There are several systems for evaluating histopathological responses, one of which is the Miller Payne system. In the Miller Payne system, the response is evaluated based on a reduction in tumor cellularity between the biopsy specimen and the mastectomy. In addition, Miller Payne can establish a prognosis in patients who experience a non-complete response. This is an advantage of Miller Payne because it can better predict the prognosis of neoadjuvant post-chemotherapy patients. In the Miller Payne system of 5 grades, Grades I-IV are categorized as a partial pathological response (pPR) and grade V as a pathological complete response (pCR). Residual ductal carcinoma in situ stand-alone is classified as a complete response.[8]

The relationship between CA 15-3 levels and MP histopathological responses was studied. There was no significant difference in the average levels of CA 15-3 after chemotherapy in all grades of Miller Payne. This shows the absence of an influence of CA 15-3 levels on the patient's histopathological response. After that, a correlation test of the differences between CA 15-3 level with Miller Payne grade was carried out and it was found that there was a decrease after chemotherapy but there was no statistically significant correlation (r count<r tables). The results showed that CA 15-3 were not associated with histopathological responses. This is in line with the results of research from Lin et al.20 which reported that CA 15-3 levels are not related to pathological variables, one of which is histopathology. This finding suggests that using the Miller-Payne system is beneficial in confirmation of therapeutic response.

In conclusion, we found that chemotherapy significantly decreases CA 15-3 levels after chemotherapy but discovered no correlation between the tumor marker and histopathological response when evaluated with the Miller Payne system. There are several limitations in this study such as the presence of factors that are difficult to control such as the emergence of other diseases in the middle of research that have been previously excluded at the beginning, the possibility of the emergence of new metastases in the middle of the study can also be a confounding factor in the study.

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