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Original Article

IMPACT OF THE COMBINATION OF DOXORUBICIN, CYCLOPHOSPHAMIDE, AND DOCETAXEL ON CA 15-3 BIOMARKER LEVELS IN BREAST CANCER PATIENTS: A COMPARATIVE STUDY BETWEEN DELAYED AND NON-DELAYED CHEMOTHERAPY

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ABSTRACT

Objective: A significant issue in breast cancer diagnosis is the delay in both diagnosis and treatment, known as a delay factor. This study compares CA 15-3 biomarker levels in breast cancer patients undergoing eight cycles of Anthracycline (Doxorubicin) and Cyclophosphamide followed by Taxane (Docetaxel) (AC-T), focusing on differences between those receiving delayed versus non-delayed chemotherapy.

Methods: This retrospective cross-sectional study included 36 breast cancer patients from a total population of 191 who received chemotherapy from August 2022 to April 2024. Eligible patients were women with HER2-negative breast cancer treated with a combination regimen of AC for 4 cycles followed by T for 4 cycles per hospital protocol. Patients were categorized into delayed factors group if diagnosed at advanced stages (IIIB, IIIC, IV) and if chemotherapy was initiated later, while those diagnosed and treated at early stages (0-IIIA) were classified as non-delay factors. Clinicopathological data and CA 15-3 levels (pre-and post-neoadjuvant and adjuvant chemotherapy) were extracted from the Management Information System of Dr. M. Djamil Hospital in Padang, West Sumatera, Indonesia.

Results: Neoadjuvant therapy led to an average CA 15-3 increase of-4.70 µ/ml in delayed factor patients and a decrease of 5.15 µ/ml in non-delayed factor patients (p=0.001). Adjuvant therapy resulted in an average CA 15-3 increase of-14.82 µ/ml in delayed factor patients and a decrease of 13.30 µ/ml in non-delayed factor patients (p=0.030). A negative value indicates that the CA 15-3 level is higher post-chemotherapy compared to pre-chemotherapy.

Conclusion: The administration of the AC-T combination, both as neoadjuvant and adjuvant therapy over eight cycles, demonstrated a more favorable impact on CA 15-3 biomarker levels in non-delayed patients compared to those experiencing delays.

Keywords: Anthracycline, Cyclophosphamide, Taxane, Eight cycles, CA 15-3, delayed, non-delayed, Breast cancer

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INTRODUCTION

Breast cancer patients, regardless of early or advanced stage, are treated with both neoadjuvant and adjuvant chemotherapy. One commonly used chemotherapy regimen for breast cancer patients is the AC-T combination [1–4]. AC-T has become a cornerstone in chemotherapy for breast cancer treatment. This combination has demonstrated significant benefits in reducing breast cancer recurrence and mortality [5–11].

The efficacy of chemotherapy and subsequent cancer progression can be assessed by monitoring biomarkers; one of them is CA 15-3 biomarker levels [12–16]. CA 15-3 is a mucin glycoprotein that is a product of the Mucin1 (MUC-1) gene, expressed in epithelial cells, and is associated with breast, colorectal, ovarian, lung, and pancreatic cancers [17]. The European Group on Tumor Markers advises utilizing CA 15-3 levels for evaluating prognosis, early detection of disease progression in 60-80% of metastatic breast cancer cases, and for monitoring the response to treatment [18, 19]. Increased CA 15-3 levels are utilized to assess the likelihood of breast cancer recurrence and serve as an indicator for evaluating therapeutic response in advanced stages [20–23].

An important phenomenon in breast cancer is the delay in diagnosis and therapy, commonly referred to as delayed treatment. In this context, patients diagnosed and treated at advanced stages (IIIB, IIIC, IV) are classified as delayed, while those diagnosed and treated at early stages (0–IIIA) are considered non-delayed [2, 24].

Studies assessing CA 15-3 biomarker levels based on chemotherapy use have been conducted previously [25–27]. However, this study did not include a comparison of CA 15-3 biomarker levels in patients undergoing delayed and non-delayed neoadjuvant and adjuvant therapy. Comparative studies have been conducted to evaluate CA 15-3 levels in stages II and IV breast cancer patients [28], but did not comprehensively evaluate CA 15-3 levels in early and advanced-stage patients. There is a need for a comprehensive comparative study to assess CA 15-3 biomarkers in early-stage (IA, IIA, IIB, IIIA) and advanced-stage (IIIB, IIIC, IV) patients receiving neoadjuvant and adjuvant AC-T chemotherapy. Such a study would better elucidate the impact of delayed and non-delayed on CA 15-3 levels."

This comparative study aims to compare the levels of CA 15-3 biomarkers between delayed and non-delayed of eight cycles of AC-T combination chemotherapy in breast cancer patients.

MATERIALS AND METHODS

This cross-sectional retrospective study has received ethical approval from Dr. M. Djamil Hospital in Padang, West Sumatera, Indonesia (Ethics Committee Number: DP.04.03/D. XVI. XI/71/2024).

Case selection

This study involved 36 breast cancer patients from a total population of 191 who received chemotherapy from August 2022 to April 2024. The restricted sample was selected as an optimal representation of the population that met strict inclusion criteria, designed to minimize variability and increase the precision and reliability of comparative data. The inclusion criteria were met by female patients diagnosed with HER2-negative breast cancer, who received 4 cycles of AC (doxorubicin and cyclophosphamide) followed by 4 cycles of T (docetaxel), in accordance with the hospital's chemotherapy protocol. Patients who received neoadjuvant and adjuvant therapy are types of therapy that will be

included in the criteria of this study. In this study, "delay factors" were defined as conditions where patients were diagnosed at an advanced stage (IIIB, IIIC, IV) and began chemotherapy. Patients diagnosed and treated at an early stage (0-IIIA) were classified as "non-delay factors". Clinicopathological data were obtained from the Management Information System of Dr. M. Djamil Hospital in Padang, West Sumatera, Indonesia. This data included age, marital status, laterality, progression and spread of breast cancer based on tumor size (tumor stage), lymph node involvement (nodul status), the state of cancer spreading from its original location to other parts of the body (metastatic status), breast cancer staging (tumor, nodul, metastatic stage), expression levels of certain genes that may contribute to cancer growth and development (ER, PR), percentage of actively dividing tumor cells (Ki-67), breast cancer subtypes categorized by molecular and biological characteristics of cancer cells (luminal A, luminal B, basal-like), triple-negative breast cancer (TNBC), surgical interventions, neoadjuvant and adjuvant chemotherapy, and whether chemotherapy was delayed or not. The levels of the tumor biomarker CA 15-3 pre-and post-neoadjuvant and adjuvant therapies (pre-and post-chemotherapy) were recorded in patients who met the inclusion criteria.

Statistical analysis

Data were analyzed using SPSS version 27.0.1. Fisher's Exact Test and the Likelihood Ratio Test were utilized to assess the significance of differences in baseline CA 15-3 biomarker levels across various clinicopathological characteristics. The Paired Samples Test and Wilcoxon Signed-Rank Test were used to assess the significance of changes in CA 15-3 levels pre-and post-chemotherapy. The Mann-Whitney U Test was used to compare changes in CA 15-3 levels after eight cycles of neoadjuvant and adjuvant AC-T therapy between delayed and non-delayed factors. A p-value below 0.05 was deemed statistically significant.

RESULTS

Baseline CA 15-3 biomarker levels based on clinicopathological characteristics

The clinicopathological characteristics of breast cancer patients and baseline CA 15-3 levels are presented in table 1. Baseline CA 15-3 levels refer to the values obtained pre-neoadjuvant and adjuvant AC-T chemotherapy. The mean baseline CA 15-3 level for patients under 50 years old (41.45 µ/ml) is higher compared to those aged 50 years and older (18.13 µ/ml). Single patients have a higher mean baseline CA 15-3 level (63.74 µ/ml) compared to married patients (27.00 µ/ml). Tumors on the right side result in a higher mean baseline CA 15-3 level compared to tumors on the left side or bilateral cases. T3 stage tumors show the highest mean baseline CA 15-3 level at 53.43 µ/ml, which is higher than other tumor stages. N2 stage tumors, with a mean baseline CA 15-3 level of 50.36 µ/ml, also show higher levels compared to other nodal statuses. Patients with M1 status have the highest mean baseline CA 15-3 level of 89.39 µ/ml. Stage IV patients also show a mean baseline CA 15-3 level of 89.39 µ/ml, indicating an increase in baseline CA 15-3 levels pre-chemotherapy. ER and PR negative patients have higher mean baseline CA 15-3 levels compared to those who are ER and PR positive. The mean baseline CA 15-3 level is higher in Ki-67 ≥20% (32.99 µ/ml) compared to<20% (17.89 µ/ml). Luminal B and basal-like molecular subtypes have higher mean baseline CA 15-3 levels compared to luminal A. Grade II tumors show the highest mean baseline CA 15-3 level (49.41 µ/ml) compared to other histological grades. Patients who underwent modified radical mastectomy (MRM) have a mean baseline CA 15-3 level of 32.11 µ/ml, which is higher than those who did not have surgery. Patients receiving eight cycles of adjuvant AC-T therapy have higher mean baseline CA 15-3 levels compared to those receiving neoadjuvant therapy. Patients with delayed chemotherapy have higher mean baseline CA 15-3 levels compared to those without delay. Statistical tests using Fisher's Exact Test and the Likelihood Ratio show that there are no significant differences in mean baseline CA 15-3 levels among the various clinicopathological characteristics, as indicated by p-values>0.05.

CA 15-3 biomarker levels in neoadjuvant AC-T therapy

CA 15-3 values pre-chemotherapy and post-chemotherapy for eight cycles of neoadjuvant AC-T can be seen in fig. 1. Neoadjuvant therapy in patients with delayed factors showed a mean CA 15-3 level of 19.66 µ/ml pre-chemotherapy and an increase to 24.36 µ/ml post-chemotherapy, indicating a significant difference in mean CA 15-3 levels (p=0.009). In contrast, patients with non-delayed factors who received neoadjuvant therapy had a mean CA 15-3 level of 22.19 µ/ml pre-chemotherapy and 17.04 µ/ml post-chemotherapy. This decrease was statistically significant (p=0.021) between pre-chemotherapy and post-chemotherapy values in the non-delayed group.

CA 15-3 biomarker levels in adjuvant AC-T therapy

The CA 15-3 values pre-chemotherapy and post-chemotherapy for eight cycles of adjuvant AC-T can be seen in fig. 2.

Adjuvant therapy in patients with delayed factors showed a mean CA 15-3 level of 75.23 µ/ml pre-chemotherapy and an increase to 90.05 µ/ml post-chemotherapy. The Wilcoxon signed-rank test indicated that this increase was not statistically significant (p=0.093). In contrast, patients with non-delayed factors who received adjuvant therapy had a mean CA 15-3 level of 15.74 µ/ml pre-chemotherapy and 2.44 µ/ml post-chemotherapy. This decrease was statistically significant (p<0.001) between pre-chemotherapy and post-chemotherapy values.

Changes in CA 15-3 biomarker levels after eight cycles of AC-T therapy in delayed and non-delayed factors

The changes in mean CA 15-3 levels after eight cycles of neoadjuvant and adjuvant AC-T therapy are shown in table 2.

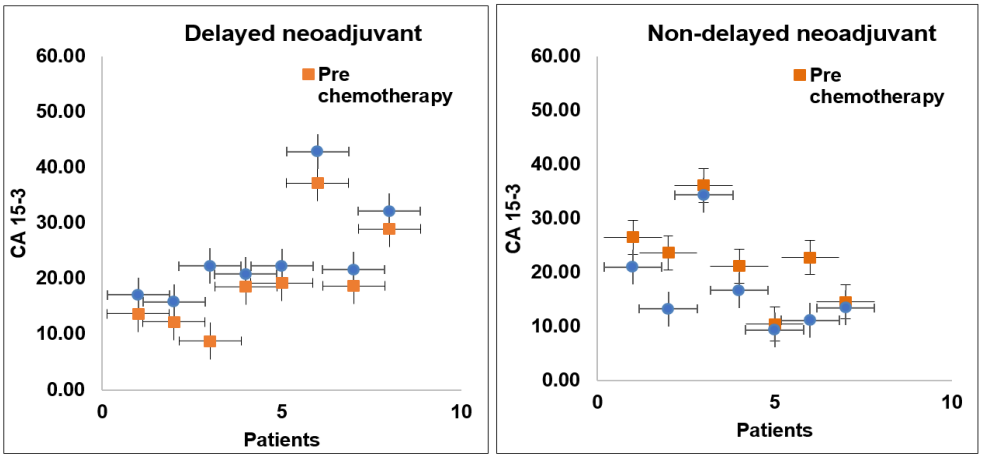

Fig. 1: CA 15-3 value in neoadjuvant AC-T administration

Table 1: Clinicopathologic characteristics of patients and baseline CA 15-3 values

Clinicopathologic characteristic	N (%)	CA15-3 Baseline (μ/ml)						p value
		Min	Max	Mean	SD	Normal n (%)	Elevated n (%)	
Age								
<50 y	20(55.6)	4.10	327.11	41.45	79.36	16(80.0)	4(20.0)	1.000[a]
≥50 y	16(44.4)	6.48	36.12	18.13	7.58	15(93.8)	1(6.3)	
Marital state								
Married	32(88.9)	4.10	327.11	27.00	55.44	28(87.5)	4(12.5)	0.466[a]
Single	4(11.1)	11.69	201.29	63.74	91.82	3(75.0)	1(25.0)	
Laterality								
Right	15(41.7)	4.10	327.11	49.22	90.81	12(80.0)	3(20.0)	0.221[b]
Left	16(44.4)	6.48	36.12	18.04	8.33	15(93.8)	1(6.3)	
Bilateral	5(13.9)	10.42	36.15	18.38	10.34	4(80.0)	1(20.0)	
Tumor stage								
T1	2(5.6)	8.78	36.12	22.45	19.33	1(50.0)	1(50.0)	0.348[b]
T2	3(8.3)	4.10	13.67	10.41	5.47	3(100.0)	0(0.0)	
T3	22(61.1)	6.78	201.29	25.54	39.89	20(90.9)	2(9.1)	
T3	9(25.0)	6.48	327.11	53.43	103.03	7(77.8)	2(22.2)	
T4	2(5.6)	8.78	36.12	22.45	19.33	1(50.0)	1(50.0)	
Nodul status								
N0	9(25.0)	4.10	36.15	18.79	11.53	7(77.8)	2(22.2)	0.215[b]
N1	6(16.7)	6.78	26.54	15.36	7.43	6(100.0)	0(0.0)	
N2	15(41.7)	6.48	327.11	50.36	90.33	13(86.7)	2(13.3)	
N3	6(16.7)	11.51	28.94	17.05	6.40	6(100.0)	0(0.0)	
Metastatic status								
MX	3(8.3)	12.23	23.38	16.09	6.31	3(100.0)	0(0.0)	0.361[b]
M0	26(72.2)	4.10	36.15	17.11	8.53	24(92.3)	2(7.7)	
M1	7(19.4)	8.78	327.11	89.39	125.12	4(57.1)	3(42.9)	
TNM stage								
IA	1(2.8)	36.12	36.12	36.12	N/A	0(0.0)	1(100.0)	0.109[b]
IIA	1(2.8)	4.10	4.10	4.10	N/A	1(100.0)	0(0.0)	
IIB	7(19.4)	9.23	36.15	18.41	9.54	6(85.7)	1(14.3)	
IIIA	11(30.6)	6.78	26.54	17.35	6.72	11(100.0)	0(0.0)	
IIIB	4(11.1)	6.48	18.54	12.43	4.92	4(100.0)	0(0.0)	
IIIC	5(13.9)	11.51	28.94	16.72	7.10	5(100.0)	0(0.0)	
IV	7(19.4)	8.78	327.11	89.39	125.12	4(57.1)	3(42.9)	
ER								
Positive	17(47.2)	6.48	201.29	30.09	45.00	14(82.4)	3(17.6)	1.000[a]
Negative	19(52.8)	4.10	327.11	31.97	71.86	17(89.5)	2(10.5)	
PR								
Positive	18(50.0)	6.48	201.29	28.93	43.93	15(83.3)	3(16.7)	1.000[a]
Negative	18(50.0)	4.10	327.11	33.24	73.72	16(88.9)	2(11.1)	
Ki-67 (%)								
<20	10(27.8)	6.48	37.18	17.89	11.63	8(80.0)	2(20.0)	1.000[a]
≥20	26(72.2)	4.10	327.11	32.99	64.18	23(88.5)	3(11.5)	
Molecular characteristics								
Luminal A	10(27.8)	6.48	37.18	17.89	11.63	8(80.0)	2(20.0)	0.754[b]
Luminal B	10(27.8)	13.48	201.29	37.51	57.75	9(90.0)	1(10.0)	
Basal like	16(44.4)	4.10	327.11	35.31	78.19	14(87.5)	2(12.5)	
TNBC								
Yes	18(50.0)	4.10	327.11	33.24	73.72	16(88.9)	2(11.1)	1.000[a]
No	18(50.0)	6.48	201.29	28.93	43.93	15(83.3)	3(16.7)	
Grade								
I	1(2.8)	11.69	11.69	11.69	N/A	1(100.0)	0(0.0)	0.371[b]
II	16(44.4)	6.48	327.11	49.41	87.24	13(81.3)	3(18.8)	
III	11(30.6)	4.10	36.12	16.85	8.93	10(90.9)	1(9.1)	
Missing	8(22.2)	6.78	37.18	16.43	10.08	7(87.5)	1(12.5)	
Surgery								
MRM	31(86.1)	4.10	327.11	32.11	64.52	27(87.1)	4(12.9)	1.000[a]
No surgery	5(13.9)	16.38	37.18	24.32	8.17	4(80.0)	1(20.0)	
Chemotherapy								
Neoadjuvant	15(41.7)	8.78	37.18	22.84	8.62	13(86.7)	2(13.3)	0.376[a]
Adjuvant	21(58.3)	4.10	327.11	38.40	77.98	18(85.7)	3(14.3)	
Chemotherapy administration status								
Delayed	16(44.4)	6.48	327.11	47.44	87.99	13(81.3)	3(18.8)	0.637[a]
Non-delayed	20(55.6)	4.10	36.15	18.00	8.96	18(90.0)	2(10.0)	

Min: minimal; Max: maximal; SD: standard deviation; TNM: tumor, node, metastasis; ER: estrogen receptor; PR: progesteron receptor; TNBC: triple negative breast cancer; MRM: modified radical mastectomy; N/A: not applicable; a: Fisher's Exact Test; b: Likelihood Ratio. $p<0.05$ indicates a significant difference.

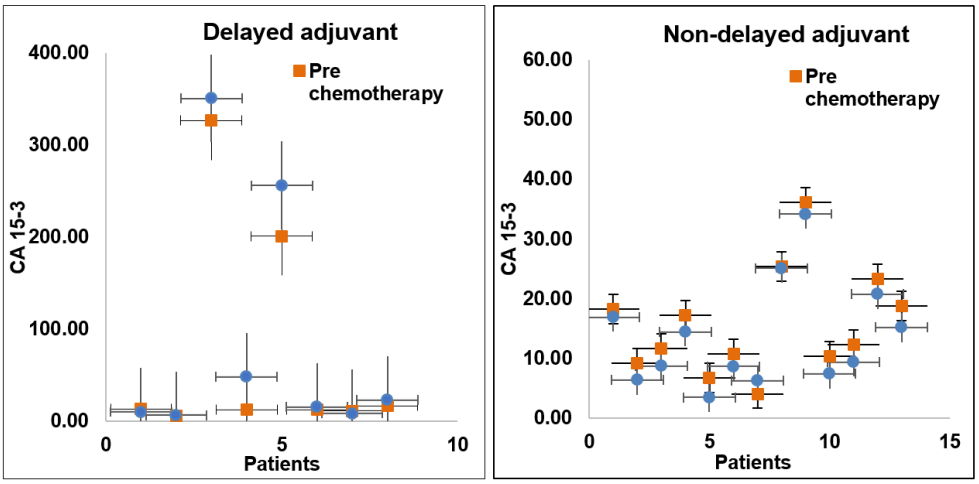

Fig. 2: CA 15-3 value in adjuvant AC-T administration

Table 2: Changes in CA 15-3 values based on the status of administration of doxorubicin, cyclophosphamide, and docetaxel combination chemotherapy for 8 cycles

Chemotherapy administration status		CA 15-3 (µ/ml)				Average change value of CA 15-3 (µ/ml)	p value
		Pre-chemotherapy		Post-chemotherapy			
		Mean	SD	Mean	SD		
Neoadjuvant	Delayed (n=8)	19.66	9.29	24.36	8.93	-4.70 (increased)	0.001
	Non-delayed (n=7)	22.19	8.28	17.04	8.53	5.15 (decreased)	
Adjuvant	Delayed (n=8)	75.23	121.41	90.05	135.00	-14.82 (increased)	0.030
	Non-delayed (n=13)	15.74	8.78	2.44	8.82	13.30 (decreased)	

$p<0.05$ indicates a significant difference.

Patients with delayed factors who received neoadjuvant therapy experienced an average increase in CA 15-3 levels of-4.70 µ/ml. In contrast, patients with non-delayed factors who received neoadjuvant therapy showed an average decrease in CA 15-3 levels of 5.15 µ/ml. The difference in the change in average CA 15-3 levels after eight cycles of neoadjuvant AC-T was statistically significant, with a p-value of 0.001. Patients with delayed factors who received eight cycles of adjuvant AC-T showed an average increase in CA 15-3 levels of-14.82 µ/ml. In contrast, patients with non-delayed factors experienced an average decrease in CA 15-3 levels of 13.30 µ/ml. The difference in the change in average CA 15-3 levels after adjuvant therapy was statistically significant, with a p-value of 0.030. A negative value indicates that the CA 15-3 level is higher post-chemotherapy compared to pre-chemotherapy.

DISCUSSION

We describe how the administration of neoadjuvant and adjuvant AC-T combination therapy over eight cycles affects CA 15-3 biomarker levels in patients, considering delayed and non-delayed factors. Delay factors refer to cases where patients were diagnosed at advanced stages (IIIB, IIIC, IV) and initiated chemotherapy, whereas those diagnosed and treated at early stages (0–IIIA) were classified as non-delay factors [2, 24]. Chemotherapy delay is defined as a commencement beyond the ideal timeframe of 4 to 6 w post-diagnosis or surgery, as per clinical guidelines. Patients were categorized accordingly: non-delayed treatment began within 4 to 6 w, while delayed treatment commenced after 6 w [29–32].

This study involved 36 breast cancer patients, a number determined by strict inclusion criteria designed to ensure homogeneity and reliability of the data. Although the sample size may appear limited, it reflects the real-world challenge of recruiting patients who meet specific eligibility criteria for detailed biomarker analysis in a specialized clinical setting. The statistical methods applied in this study were chosen to maximize the robustness of the analysis despite the relatively small sample size. Fisher's Exact Test and Likelihood Ratio Test were employed to evaluate the significance of differences in baseline CA 15-3 levels across clinicopathological characteristics, ensuring reliability in categorical comparisons. Paired Sample Tests and Wilcoxon Signed Rank Tests were used to analyze pre-and post-chemotherapy CA 15-3 level changes, accommodating non-normal data distributions effectively. Additionally, the Mann-Whitney U test was utilized to compare CA 15-3 level changes between delayed and non-delayed groups after eight cycles of AC-T chemotherapy in both neoadjuvant and adjuvant settings. To address concerns about statistical power, a post-hoc power analysis can further validate whether the sample size was sufficient to detect clinically meaningful differences. Although the cohort size is limited, the statistical significance of the findings ($p<0.05$) and the use of non-parametric tests mitigate the risk of Type I and Type II errors associated with small sample sizes. Previous studies have demonstrated that similar approaches are effective in analyzing biomarker trends in small cohorts, supporting the reliability of these results [33–35].

The mean baseline CA 15-3 levels in all patients who met the inclusion criteria in this study did not show significant differences among various characteristics. The average pre-chemotherapy CA 15-3 levels did not reflect the response to therapy, as most patient characteristics showed values still within the normal range. CA 15-3 levels in the early stages of treatment often do not show significant changes and are therefore not suitable for assessing initial responses to chemotherapy. CA 15-3 levels tend to be more relevant for monitoring disease progression at advanced stages or after several treatment cycles, rather than before therapy initiation [36, 37]. Although CA 15-3 is an important biomarker in breast cancer therapy monitoring, its levels often remain within normal limits at the beginning of treatment or pre-chemotherapy, showing changes only when disease progression occurs or in response to further therapy [37].

The difference in mean CA 15-3 levels in pre-and post-neoadjuvant chemotherapy for patients with treatment delays was statistically significant. CA 15-3 levels tended to rise progressively with ongoing therapy, particularly in patients with advanced-stage breast cancer or disease progression. An increase of more than 20% in CA 15-3 levels after therapy serves as a positive predictive indicator for

disease progression in patients undergoing systemic therapy [21]. There was a significant difference in the mean CA 15-3 levels between pre-and post-neoadjuvant chemotherapy in patients without treatment delays. A decrease in mean CA 15-3 levels was observed after neoadjuvant administration in patients without treatment delays. This decrease suggests that administering neoadjuvant therapy without delay can lower CA 15-3 levels in patients, potentially reflecting a positive clinical response to the therapy. CA 15-3 is one of the markers used to monitor response to therapy in breast cancer patients, particularly in cases where therapy is administered in a timely manner without delay. A reduction in CA 15-3 levels after chemotherapy is often associated with a decrease in tumor burden, a better response to treatment, and a reduced risk of further progression [36, 37].

Patients with treatment delays who received adjuvant therapy did not show a significant difference in mean CA 15-3 levels between pre-and post-chemotherapy. Although there was an increase in mean CA 15-3 levels, these findings indicate that in the delayed treatment group, the therapeutic response was not strong enough to produce a significant change in this biomarker level. The non-significant increase in CA 15-3 levels may be influenced by several factors, such as tumor characteristics, disease stage, or individual response to therapy. Some studies suggest that CA 15-3 levels are more frequently correlated with disease progression in advanced stages or metastasis, and increases in CA 15-3 levels may not always directly reflect therapy response failure [36, 38]. In patients without treatment delays who received pre-and post-adjuvant chemotherapy, a significant difference was observed. A decrease in mean CA 15-3 levels was particularly noted in patients with early-stage breast cancer. Patients with lower CA 15-3 levels after adjuvant chemotherapy tend to have better clinical outcomes and a lower likelihood of disease recurrence [38]. A decrease of more than 20% in CA 15-3 levels after chemotherapy can predict a longer progression-free survival and a better therapy response [36, 39]. Adjuvant therapy administered without delay often results in a significant decrease in CA 15-3 levels, reflecting treatment success and better disease control [40]. The AC-T combination is an effective standard regimen for both early and advanced breast cancer. A decrease in CA 15-3 levels often indicates the success of this therapy, especially in cases with no delay [41].

The mean CA 15-3 levels in AC-T neoadjuvant therapy show a significant difference between delayed and non-delayed treatment groups. Non-delayed neoadjuvant therapy yields better results in terms of CA 15-3 biomarker reduction. The decrease in CA 15-3 levels in the non-delayed group reflects a positive response to chemotherapy. A significant reduction in CA 15-3 levels after chemotherapy is often associated with a decrease in tumor burden and improved clinical outcomes, especially in patients receiving timely therapy. Conversely, the increase in CA 15-3 levels in the delayed therapy group may suggest that the tumor burden is more resistant to chemotherapy or that the therapy is not sufficiently effective in reducing biomarker levels. Delays in administering chemotherapy can negatively impact therapy effectiveness and patient clinical outcomes, particularly in cases of advanced breast cancer [28].

Administration of AC-T adjuvant therapy shows a significant difference in mean CA 15-3 levels between delayed and non-delayed treatment groups. Non-delayed adjuvant therapy yields better outcomes in reducing the CA 15-3 biomarker compared to delayed adjuvant administration. Delays in administering adjuvant therapy can negatively impact treatment response and clinical outcomes. The increase in CA 15-3 levels after chemotherapy in patients with delayed factors may be due to reduced therapy effectiveness resulting from the delay. Timely administration of adjuvant therapy can effectively reduce CA 15-3 levels, which is a crucial marker for assessing tumor burden and response to therapy in breast cancer patients [21, 42]. An increase in CA 15-3 levels in delayed patients may be associated with tumor resistance to chemotherapy or disease progression during the waiting period before starting adjuvant therapy. This also suggests that high post-chemotherapy CA 15-3 levels often serve as a poor indicator of long-term response to therapy [36].

In adjuvant therapy, research indicates that higher CA 15-3 levels are frequently linked to residual tumor burden or ongoing micrometastatic activity. Delays in treatment can allow this activity to persist, potentially leading to a worse prognosis. Conversely, initiating therapy promptly helps mitigate micrometastatic progression, thereby decreasing recurrence risks and improving local tumor management. In the context of neoadjuvant therapy, elevated CA 15-3 levels are associated with more advanced disease progression, which can diminish the tumor's responsiveness to treatment. A reduction in CA 15-3 levels following initial therapy, however, signals improved tumor reactivity to chemotherapy and a faster decline in tumor burden. Moreover, CA 15-3 has been recognized as a critical prognostic and predictive biomarker in breast cancer management. Combining CA 15-3 with other markers, such as carcinoembryonic antigen (CEA) or cell-free DNA (cfDNA), further enhances diagnostic sensitivity in assessing therapeutic efficacy and monitoring disease progression. The clinical implications of delayed adjuvant chemotherapy include a poorer long-term prognosis, characterized by an increased risk of systemic recurrence. In the neoadjuvant setting, delays are associated with suboptimal tumor response, complicating tumor reduction, compromising survival outcomes, and reducing the likelihood of successful surgical resection. These findings underscore the role of CA 15-3 as a critical marker for determining the optimal timing of therapy. Furthermore, its significance can be compared to other biomarkers, such as carcinoembryonic antigen (CEA) or HER2, which also demonstrate correlations between therapeutic initiation timing and clinical outcomes [43, 44]. In the future, nanotechnology approaches are expected to enhance the effectiveness of chemotherapeutic agents, including commonly used regimens like AC-T. Advances in nanotechnology also offer improvements in bioimaging and targeted drug delivery systems, potentially refining the interpretation and monitoring of biomarkers such as CA 15-3 [45].

CONCLUSION

There was a difference in CA 15-3 biomarker levels between patients who experienced treatment delays in neoadjuvant and adjuvant AC-T therapy over eight cycles and those without delays. Patients with treatment delays showed an increase in CA 15-3 levels, while patients without delays showed a decrease. Administration of the AC-T combination therapy, both neoadjuvant and adjuvant, for eight cycles in patients without delays had a better impact on CA 15-3 biomarker levels compared with patients who experienced delays.

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AUTHORS CONTRIBUTIONS

All authors have contributed to and approved the manuscript for publication.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest related to this research.

REFERENCES

1. Dipiro J, Schwinghammer T, Dipiro C. Chapter 19. Pharmacotherapy handbook. 9th ed. section 4. McGraw-Hill Companies; 2015.
2. Kementerian Kesehatan RI. Pedoman nasional pelayanan Kedokteran tata Laksana kanker payudara. Jakarta: Kementerian Kesehatan Republik Indonesia; 2019. p. 15-20.
3. NCCN. Guidelines for patients inflammatory-breast-patient. National comprehensive cancer network foundation; 2023. Available from:

https://www.nccn.org/patients/guidelines/content/PDF/inflammatory-breast-patient.pdf.
4. Voorwerk L, Slagter M, Horlings HM, Sikorska K, van de Vijver KK, de Maaker M. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med. 2019 Jun;25(6):920-8. doi: 10.1038/s41591-019-0432-4, PMID 31086347.
5. Alsaloumi L, Shawagfeh S, Abdi A, Basgut B. Efficacy and safety of capecitabine alone or in combination in advanced metastatic breast cancer patients previously treated with anthracycline and taxane: a systematic review and meta-analysis. Oncol Res Treat. 2020;43(12):694-702. doi: 10.1159/000510356, PMID 32950984.
6. Dipiro J, Yee G, Posey M, Haines S, Nolin T, Ellingrod V. Pharmacotherapy: a pathophysiologic approach. 11th ed. Annals of Pharmacotherapy. McGraw-Hill; 2020.
7. Gao S, Li T, Guo Y, Sun C, Xianyu B, Xu H. Selenium-containing nanoparticles combine the NK cells mediated immunotherapy with radiotherapy and chemotherapy. Adv Mater. 2020;32(12):e1907568. doi: 10.1002/adma.201907568, PMID 32053267.
8. Liu Y, Fan L, Wang ZH, Shao ZM. Nab-paclitaxel followed by dose-dense epirubicin/cyclophosphamide in neoadjuvant chemotherapy for triple-negative breast cancer: a phase II study. Oncologist. 2023 Jan;28(1):86-e76. doi: 10.1093/oncolo/oyac223, PMID 36426808.
9. Lu Q, Lee K, Xu F, Xia W, Zheng Q, Hong R. Metronomic chemotherapy of cyclophosphamide plus methotrexate for advanced breast cancer: real-world data analyses and experience of one center. Cancer Commun (Lond). 2020;40(5):222-33. doi: 10.1002/cac2.12029, PMID 32390331.
10. Mobus V, Luck HJ, Ladda E, Klare P, Schmidt M, Schneeweiss A. Phase III randomised trial comparing intense dose-dense chemotherapy to tailored dose-dense chemotherapy in high-risk early breast cancer (GAIN-2). Eur J Cancer. 2021 Oct;156:138-48. doi: 10.1016/j.ejca.2021.07.033, PMID 34450552.
11. Pusztai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM. Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100000 women from 86 randomised trials. Ann Oncol of F J Eur Soc Med Oncol. 2022;32(5):1277-92.
12. Amayo AA, Kuria JG. Clinical application of tumour markers: a review. East Afr Med J. 2009;86(12)Suppl:S76-83. doi: 10.4314/eamj.v86i12.62909, PMID 21591514.
13. Kabel AM. Tumor markers of breast cancer: new prospectives. J Oncol Sci. 2017;3(1):5-11. doi: 10.1016/j.jons.2017.01.001.
14. Sehgal C, Seema KM, Kaur M, Kumar A. Comparison of post-operative value with preoperative value of Ca 15-3 and its prognostic value. Asian J Pharm Clin Res. 2021;14(11):88-9. doi: 10.22159/ajpcr.2021.v14i11.43078.
15. Thompson JA, Grunert F, Zimmermann W. Carcinoembryonic antigen gene family: molecular biology and clinical perspectives. J Clin Lab Anal. 1991;5(5):344-66. doi: 10.1002/jcla.1860050510, PMID 1941355.
16. Zhao S, Mei Y, Wang J, Zhang K, Ma R. Different levels of CEA, CA153 and CA125 in milk and benign and malignant nipple discharge. PLOS One. 2016;11(6):e0157639. doi: 10.1371/journal.pone.0157639, PMID 27327081.
17. Hahn EE, Hays RD, Kahn KL, Litwin MS, Ganz PA. Use of imaging and biomarker tests for posttreatment care of early-stage breast cancer survivors. Cancer. 2013;119(24):4316-24. doi: 10.1002/cncr.28363, PMID 24105101.
18. Jager W, Eibner K, Loffler B, Gleixner S, Kramer S. Serial CEA and CA 15-3 measurements during follow-up of breast cancer patients. Anticancer Res. 2000;20(6D):5179-82. PMID 11326691.
19. Molina R, Barak V, Van Dalen A, Duffy MJ, Einarsson R, Gion M. Tumor markers in breast cancer-European group on tumor markers recommendations. Tumour Biol. 2005;26(6):281-93. doi: 10.1159/000089260, PMID 16254457.
20. Bast RC, Ravdin P, Hayes DF, Bates S, Fritsche H, Jessup JM. 2000 Update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19(6):1865-78. doi: 10.1200/JCO.2001.19.6.1865, PMID 11251019.
21. Kurebayashi J. Biomarkers in breast cancer. Gan To Kagaku Ryoho. 2004;31(7):1021-6. PMID 15272579.
22. Ryu JM, Kang D, Cho J, Lee JE, Kim SW, Nam SJ. Prognostic impact of elevation of cancer antigen. Patients Early Breast Cancer Norm Serum. 2023;26(2):126–35.
23. Karthikhaeyan TR, Periasamy AK, Sharma A. Correlation of CA 15.3 levels with Metastasis in Breast Cancer. Asian J Pharm Clin Res. 2023;16(9):42-4. doi: 10.22159/ajpcr.2023v16i9.49016.
24. Kementerian Kesehatan RI, Payudara BPK; 2016. Available from: http://www.depkes.go.id/resources/download/pusdatin/infodatin/InfoDatinBulanPeduliKankerPayudara_2016.pdf. [Last accessed on 21 Nov 2023].
25. Gupta SK, Kumar V, Anees A, Goel A. The study of prognostic significance of CA 15-3 in breast cancer. Int Surg J. 2018;5(2):580. doi: 10.18203/2349-2902.isj20180356.
26. Mahmoud Z, Abd Elwahed S, El Badry D, Mohammed A. Association of CA 15-3 and CEA with clinicopathological parameters in patients with metastatic breast cancer. Sohag Medical Journal. 2018;22(1):173-8. doi: 10.21608/smj.2017.40972.
27. Park BW, Oh JW, Kim JH, Park SH, Kim KS, Kim JH. Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. Ann Oncol. 2008;19(4):675-81. doi: 10.1093/annonc/mdm538, PMID 18037623.
28. Hasan D. Diagnostic impact of CEA and CA 15-3 on chemotherapy monitoring of breast cancer patients. J Circ Biomark. 2022;11:57-63. doi: 10.33393/jcb.2022.2446, PMID 36381348.
29. da Yu K, Huang S, xin ZJ. Liu G yu, Shao Z ming. Association between delayed initiation of adjuvant CMF or anthracycline-based chemotherapy and survival in breast cancer: a systematic review and meta-analysis. BMC Cancer. 2013;240(13):1-10.
30. Chavez MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol. 2016;2(3):322-9. doi: 10.1001/jamaoncol.2015.3856, PMID 26659132.
31. Abdel Razeq H, Mansour A, Edaily S, Dayyat A. Delays in initiating anti-cancer therapy for early-stage breast cancer-how slow can we go? J Clin Med. 2023;12(13):4502. doi: 10.3390/jcm12134502, PMID 37445537.
32. Forster M, Deal AM, Page A, Vohra S, Wardell AC, Pak J. Dose delay, dose reduction, and early treatment discontinuation in Black and White women receiving chemotherapy1. Oncologist. 2024;29(10):11–7.
33. Mcclenaghan E. Mann-Whitney U test: assumptions and example. Technol Netw; 2022.
34. Webb LR. Mostly harmless statistics. Libretexts; 2021. p. 239. Available from: https://stats.libretexts.org/Bookshelves/Introductory_Statistics/Mostly_Harmless_Statistics. [Last accessed on 10 Jan 2025].
35. Mcclenaghan E. Post-hoc tests in statistical analysis. Technol Netw. 2023.
36. Al-Azawi D, Kelly G, Myers E, McDermott EW, Hill AD, Duffy MJ. CA 15-3 is predictive of response and disease recurrence following treatment in locally advanced breast cancer. BMC Cancer. 2006;6:220. doi: 10.1186/1471-2407-6-220, PMID 16953875.
37. Bartsch R, Wenzel C, Pluschnig U, Hussian D, Sevelda U, Altorjai G. Prognostic value of monitoring tumour markers CA 15-3 and CEA during fulvestrant treatment. BMC Cancer. 2006;6:81. doi: 10.1186/1471-2407-6-81, PMID 16563172.
38. Mudduwa LK, Wijayaratne GB, Peiris HH, Gunasekera SN, Abeysiriwardhana D, Liyanage N. Elevated pre-surgical CA15-3: does it predict the short-term disease-free survival of breast cancer patients without distant metastasis? Int J Womens Health. 2018;10:329-35. doi: 10.2147/IJWH.S162867, PMID 29983596.

39. Okines AF, Kipps E, Irfan T, Coakley M, Angelis V, Asare B. Impact of timing of adjuvant chemothapy for early breast cancer: the Royal Marsden Hospital experience. Br J Cancer. 2021;125(2):299-304. doi: 10.1038/s41416-021-01428-4, PMID 34017085.
40. Kallioniemil OP, Oksa H, Aaran RK, Hietanen T, Lehtinen M, Koivula T. Serum CA 15-3 assay in the diagnosis and follow-up of breast cancer. Br J Cancer. 1988;58.
41. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Med. 2015;13(1):195. doi: 10.1186/s12916-015-0439-8, PMID 26278220.
42. Duffy MJ, Duggan C, Keane R, Hill AD, McDermott E, Crown J. High preoperative CA 15-3 concentrations predict adverse outcome in node-negative and node-positive breast cancer: study of 600 patients with histologically confirmed breast cancer. Clin Chem. 2004;50(3):559-63. doi: 10.1373/clinchem.2003.025288, PMID 14726467.
43. Perrier A, Boelle PY, Chretien Y, Gligorov J, Lotz JP, Brault D. An updated evaluation of serum sHER2, CA15.3, and CEA levels as biomarkers for the response of patients with metastatic breast cancer to trastuzumab-based therapies. PLOS One. 2020;15(1):e0227356. doi: 10.1371/journal.pone.0227356, PMID 31910438.
44. Clatot F, Perdrix A, Beaussire L, Lequesne J, Levy C, Emile G. Risk of early progression according to circulating ESR1 mutation, CA-15.3 and cfDNA increases under first-line anti-aromatase treatment in metastatic breast cancer. Breast Cancer Res. 2020;22(1):56. doi: 10.1186/s13058-020-01290-x, PMID 32466779.
45. Bhosale RR, Janugade BU, Chavan DD, Thorat VM. Current perspectives on applications of nanoparticles for cancer management. Int J Pharm Pharm Sci. 2023;15(11):1-10. doi: 10.22159/ijpps.2023v15i11.49319.