Neoadjuvant Chemotherapy with Anthracyclines and Taxanes in Locally Advanced Breast Cancer: Clinical Response Analysis from Sumatra, Indonesia

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Abstract

Introduction: This study evaluates the clinical response to NAC in LABC patients treated at RSUP H. Adam Malik Medan between 2020 and 2022.
Methods: This cross-sectional observational study at RSUP Haji Adam Malik Medan retrospectively analyzed breast cancer patients (2020–2022) undergoing neoadjuvant chemotherapy. Data on demographics, clinical variables, and treatment responses were extracted from medical records. Ethical approval was obtained, sample size calculated for adequate power, and statistical analyses performed using SPSS to evaluate chemotherapy efficacy.
Results: This study included 50 breast cancer patients, predominantly females over 40 years (90%), with an average age of 49.8 years. The main histopathological type was Invasive Ductal Carcinoma (70%), and Luminal A was the most common molecular subtype (40%). Most patients were diagnosed at stage IIIB (84%) and had Grade 2 tumors (60%). Among 19 patients receiving chemotherapy, the Doxorubicin-Paclitaxel regimen was most common, with all showing partial response, indicating effective treatment outcomes. There is a significant difference in response distributions across the regimens ($P<0.05$).
Conclusion: The findings suggests a significant partial clinical response following neoadjuvant chemotherapy with anthracyclines and taxane.

Keywords: Neoadjuvant Chemotherapy (NAC), Locally Advanced Breast Cancer (LABC), Clinical Response

1. INTRODUCTION

Breast cancer is still the most commonly diagnosed cancer globally (16.6%), followed by cervical, lung, and liver cancers. Lung cancer predominates in men; breast cancer leads in women.[1, 2] Breast cancer accounts for 22.4% of female malignancies in Asia, with 911,014 new cases, including 137,514 in Southeast Asia. Incidence rises rapidly in developing countries, often diagnosed late. In Indonesia, it is the most common cancer (18.6%). Effective management includes prevention, early detection, treatment, and rehabilitation).[3]

Neoadjuvant chemotherapy (NAC) is one of the therapies given to patients with Locally Advanced Breast Cancer (LABC) which aims to reduce tumor size from “inoperable” to “operable” so that surgery can be performed. Based on previous research, it was found that of the 49 patients who received neoadjuvant chemotherapy, around 87.5% of the total patients gave a response assessed based on RECIST criteria: 5

patients (9%) received a complete response, 44 patients (78.5%) received a partial response, 6 patients (10.7%) obtained stable disease and 1 patient (1.8%) received progressive disease and while when compared to other studies regarding the use of NAC in LABC patients, it was found that 37 out of 43 patients with "inoperable" after being given neoadjuvant chemotherapy about 28 out of 37 patients (75.6%) turned into "operable".[4]

Anthracyclines, such as doxorubicin and epirubicin, taxanes, including paclitaxel and docetaxel, and fluorouracil and cyclophosphamide are the current first-line therapies for combined adjuvant treatment of breast cancer. Paclitaxel (PTX), a diterpene alkaloid, is commonly used to treat breast cancer. Microtubules are the cellular target of PTX. The main actions of PTX are arrest of induced mitosis through polymerization and stabilization of microtubules and induction of cell death by apoptosis. Doxorubicin (DOX) is an anthracycline drug commonly used to treat breast cancer.[5]

However, There is a conspicuous absence of published data concerning the clinical response to neoadjuvant chemotherapy regimens comprising doxorubicin and paclitaxel in patients diagnosed with locally advanced breast cancer (LABC), especially in RSUP H. Adam Malik, Medan, Indonesia.

Therefore, the study aims to evaluate the clinical response to neoadjuvant chemotherapy using anthracyclines and taxane in patients with locally advanced breast cancer treated at RSUP H. Adam Malik Medan between 2020 and 2022.

2. METHODS

2.1. Population

This descriptive observational study with a cross-sectional design was conducted at RSUP Haji Adam Malik Central General Hospital in Medan, Indonesia. Data collection and research activities took place from July 2024 to September 2024, followed by data processing and analysis. The study population consisted of patients diagnosed with breast cancer between 2020 and 2022 who sought treatment at the hospital. A consecutive sampling method was employed to select the study sample based on specific inclusion and exclusion criteria until the minimum sample size was reached.

Inclusion criteria were patients diagnosed with Locally Advanced Breast Cancer confirmed by histopathology, possessing complete medical records, and who provided informed consent. Exclusion criteria included patients who refused to sign informed consent, those who did not complete chemotherapy, or who died before completing three cycles of chemotherapy.

Before enrollment, participants were fully informed about the study objectives and procedures and provided written informed consent. Data collection involved retrospective review of medical records to obtain demographic information such as age, sex, and comorbidities. Additionally, data on chemotherapy regimens and responses to anthracycline and taxane-based treatments at hospital admission were extracted. Clinical responses to neoadjuvant chemotherapy (NAC) with anthracyclines and taxanes, as well as treatment duration, were also documented.

The study variables were operationally defined as follows: Neoadjuvant chemotherapy (NAC) involved administration of Anthracyclines and Taxane prior to surgery in patients with large but operable locally advanced breast cancer, assessed through medical records with nominal outcomes (Yes/No). Breast cancer staging was classified according to the 2017 AJCC and IUCC TNM criteria into stages IIIA, IIIB, and IIIC, measured ordinally from medical records. Age was categorized as <40 years or >40 years based on patient records. Tumor operability status was defined nominally as operable (tumor shrinkage without chest wall metastasis or nodal enlargement allowing surgery) or non-operable (no tumor shrinkage with metastasis or nodal enlargement precluding surgery). Chemotherapy response was classified nominally as positive (patients completing 3-4 cycles and eligible for surgery) or negative (more than 4 cycles without surgery

eligibility). The RECIST criteria were used to evaluate chemotherapy effectiveness, categorizing response as complete response, partial response, progressive disease, or stable disease on an ordinal scale. Molecular subtypes of breast cancer were determined by immunohistochemistry (IHC) and categorized as Luminal A, Luminal B, Triple-negative basal, or HER2-enriched. All data were extracted from medical records to ensure consistency and reliability.

2.2. Ethical Compliance

This research already followed the ethical standard that had bee granted by each institution according to Helsinki Declaration. This study was also reviewed by Ethical Committee for Health Research Universitas Sumatera Utara as the Institutional Research.

2.3. Sample Size

The sample size for this study was calculated using the hypothesis test formula for relative risk based on the difference in proportions between two groups, with parameters P1=0.72, P2=0.47, and a pooled proportion P=0.595. Using a significance level of 0.05 and a power of 80% the required sample size was approximately 59 subjects per group to detect a minimum meaningful difference of 25% between the two proportions. This calculation ensures an adequately powered and representative sample for testing the relative risk hypothesis in categorical data.

2.4. Outcome

The primary outcomes of this study focused on evaluating the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. Outcomes were assessed based on chemotherapy response categorized as positive or negative, where a positive response indicated patients who completed 3 to 4 cycles of chemotherapy and were eligible for surgery, while a negative response referred to those requiring more than 4 cycles and deemed ineligible for surgery. Additionally, the effectiveness of chemotherapy was measured using RECIST criteria, classifying responses into complete response, partial response, progressive disease, or stable disease. These outcomes were analyzed in relation to tumor operability status, cancer stage, age, and molecular subtype to determine the impact of neoadjuvant chemotherapy on tumor reduction and surgical eligibility.

2.5. Statistical Analysis

The primary data collected were processed and analyzed using SPSS software v.25. The data handling procedure included the following steps: (1) editing to verify the accuracy and completeness of the data recorded on the observation sheets, (2) coding to assign numerical identifiers to variables, (3) data entry into the computer system, (4) data cleaning to detect and correct any input errors, and (5) saving the finalized dataset. Descriptive statistics were applied to summarize demographic data. For inferential analysis of categorical variables related to chemotherapy response across different regimens in patients with Locally Advanced Breast Cancer at RSUP H. Adam Malik Medan, Chi-square tests were primarily used. When

assumptions for Chi-square were not met, Fisher's exact test or the Kolmogorov-Smirnov test were employed as alternatives. Statistical significance was set at a p-value of less than 0.05.

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3. RESULTS

This study involved a total of 143 breast cancer patients, of whom only 50 met the inclusion criteria. The average age of the participants was 49.8 years, with a standard deviation of 8.5 years, indicating that the study population primarily consisted of individuals in their productive to older adult years. The majority of patients (90%, n=45) were aged over 40 years, while a smaller proportion (10%, n=5) were under 40 years of age (table 1).

Table 1 Demographic Characteristic

Variable	Frequency (n)	Percentage(%)
Age (Mean±SD (Min-Maks)	49,8±8.5 year (32 years – 69 Years)	
Age group		
<40 years	5	10%
≥40 years	45	90%
Sex		
Female	50	100%
Menopause		
Pre Menopause	18	36%
Peri Menopause	6	12%
Pasca Menopause	16	32%
Histopathology Type		
Non Special Type	35	70%
Invasive Lobular Carcinoma	10	20%
Subtype		
Luminal A	20	40%
Luminal B	15	30%
HER2-enriched	10	20%
Tripel Negatif	5	10%
Grading		
Grade I	8	16%
Grade II	30	60%
Grade III	12	24%

Regarding gender distribution, all 50 patients (100%) were female, which aligns with the epidemiological trend that breast cancer predominantly affects women. Nevertheless, the presence of male breast cancer cases, although rare, confirms that HER2-positive breast cancer can also occur in men, albeit with much lower prevalence (table 1).

Among the participants, 16 (32%) were postmenopausal, 18 (36%) were premenopausal, and 6 (12%) were perimenopausal. The incidence of breast cancer was slightly higher in premenopausal women compared to postmenopausal women. It is noted that late onset of menopause is associated with an increased risk of breast cancer. Generally, premenopausal women have a lower risk of developing breast cancer than postmenopausal women when matched for age and reproductive history (table 1).

The predominant histopathological type observed was Invasive Ductal Carcinoma, accounting for 70% (n=35) of cases, followed by Invasive Lobular Carcinoma at 20% (n=10), with other types comprising the

remaining 10% (n=5). The most common molecular subtype identified was Luminal A, present in 40% (n=20) of patients (table 1).

Regarding tumor grading, the majority of patients (60%, n=30) were classified as Grade 2, which was the most frequently observed category. Grade 3 tumors were found in 24% (n=12) of patients, while Grade 1 tumors were present in 16% (n=8) (table 1). The majority of patients were diagnosed with stage IIIB breast cancer, comprising 42 individuals (84%). Additionally, 7 patients (14%) were classified as having stage IIIA breast cancer, while only 1 patient (2%) presented with stage IIIC disease.

Among the 19 patients who underwent chemotherapy, There is a significant difference in response distributions across the regimens ($P<0.05$). .The most frequently administered regimen was the combination of Doxorubicin and Paclitaxel, given to 9 patients (47.4%). This was followed by the combination of Epirubicin and Paclitaxel, which was used in 5 patients (26.3%). Additionally, 3 patients (15.8%) received a combination of Paclitaxel and Cisplatin, while 2 patients (10.6%) were treated with a regimen combining Doxorubicin and Brexel. Notably, all patients treated with the Doxorubicin and Paclitaxel combination exhibited a partial response. This was similarly observed in patients receiving the Epirubicin and Paclitaxel combination, indicating a favorable therapeutic effect in these groups (table 2).

Table 2 Response to Neoadjuvant Anthracyclines and Taxane Chemotherapy. PR: Partial Response,, SD: Stable disease, PD: Progressive disease

	Chemotherapy Response			p-value
Regimen	PR	SD	PD	
Doxorubicin + Paclitaxel	9	0	0	0.001*
Epirubicin + Paclitaxel	4	0	1	
Paclitaxel + Cisplatin	3	0	0	
Doxorubicin + Brexel	1	1	0	

*Analyzed with Kolmogorov Smirnof

4. DISCUSSION

Based on the age distribution, the mean age of the patients was 49.8 years with a standard deviation of 8.5 years, indicating that the study population was predominantly composed of patients in their productive to elderly years. The majority of patients were aged over 40 years, accounting for 45 individuals (90%), while those under 40 years old numbered 5 (10%). The higher number of patients aged 40 years and above is attributed to the increased risk of breast cancer with advancing age. Breast cancer incidence accelerates notably between the ages of 40 and 49, with the risk continuing to rise until the age of 50, where the probability is approximately 1 in 50 women.[6] This finding aligns with the study by Ervina et. Al., 2011 conducted at Hasan Sadikin Hospital, which reported the highest incidence of breast cancer among women aged 40-49 years.[7] Similarly, data from Zhongshan University Cancer Hospital involving 6,263 patients showed the largest patient group was aged 45-49 years (25.52%), followed by those aged 40-44 years (15.8%), and 54-59 years (15.5%).[8]

It is estimated that 1 in 8 women will develop breast cancer during their lifetime. The greatest likelihood of disease progression occurs in women with hormonal factors unrelated to breast cancer incidence in menopausal women.[8] Consistent with the study by Sihombing et al., 2014, the percentage of breast cancer patients diagnosed under the age of 40 was lower (31.1%) compared to those diagnosed at age 40 or older (68.9%).[9] Furthermore, a study conducted in Africa by Ambrosone et al. (2015) reported that among breast cancer patients, only 6.5% (107 patients) were diagnosed under 40 years of age, whereas 93.5% (1,531

patients) were diagnosed at 40 years or older.[10] Similarly, Kang et al., 2020 found the highest incidence of breast cancer in the 40-49 year age group (33.4%), followed by the 50-59 year group (30.4%).[11]

The majority of respondents in this study were premenopausal, accounting for 18 individuals (36%), followed by postmenopausal respondents at 16 individuals (32%), and perimenopausal respondents at 6 individuals (12%). Delayed menopause in women prolongs exposure to estrogen hormones, which increases the risk of developing breast cancer. Research has shown that for every 5-year delay in menopause, the risk of breast cancer increases by 17%. After menopause, progesterone levels drop to zero and estrogen levels become very low, resulting in a significantly reduced rate of cell proliferation. Studies indicate that women who experience menopause before the age of 45 have half the risk of breast cancer compared to those who menstruate until age 50 or beyond.[12]

According to the Centers for Disease Control and Prevention (CDC), the risk of breast cancer increases with age. Breast cancer diagnosis can be categorized based on menopausal status: postmenopausal breast cancer is the most commonly observed, while premenopausal breast cancer is typically diagnosed in women aged 40 to 55 years. Breast cancer during reproductive age usually occurs in women under 40 years old.[11] Menopause generally occurs between the ages of 45 and 55, with the average age being around 50 years; menstruation typically ceases between ages 48 and 52.[13]

Previous research found a correlation between delayed menopause and the incidence of breast cancer, with hormonal factors playing a significant role. The risk of breast cancer increases by a factor of 1.050 (95% CI: 1.044–1.057; $p < 0.0001$) for each year earlier onset of menarche, and independently, by a smaller magnitude of 1.029 (95% CI: 1.025–1.032; $p < 0.0001$) for each additional year of delayed menopause.[14] Premenopausal breast cancer has been closely linked to prolonged ovarian hormone exposure.[15] Msolly et. Al. conducted a study showing a strong association between postmenopausal breast cancer and body mass index (BMI) in women over 55 years old.[16] Excessive BMI in postmenopausal women increases breast cancer risk because estrogen production in menopausal women primarily originates from adipose tissue.[17]

The risk of breast cancer increases with age, possibly due to long-term exposure to estrogen and other risk factors that require extended periods to trigger cancer development.[18] This may result from a combination of impaired DNA repair mechanisms in older age, leading to accumulated DNA damage. Over time, carcinogen exposure increases while the immune system's effectiveness declines, including reduced production of interferon-gamma (IFN-γ). Consequently, natural killer cells and cytotoxic T cells, which rely on perforin pathways, become less effective at detecting and combating cancer cells.[19]

It has been theorized that women over the age of 30 have a higher risk of being diagnosed with breast cancer, and this risk increases further around the age of 50 and after menopause.[14] The likelihood of breast cancer diagnosis tends to rise with advancing age in women. Among women under 45 years old, approximately one in eight is diagnosed with invasive breast cancer, whereas two out of three women diagnosed with invasive breast cancer are over 50 years old at the time of detection.[20]

In this study, the majority of patients were diagnosed with stage IIIB breast cancer, accounting for 42 patients (84%). Seven patients (14%) were diagnosed with stage IIIA, and one patient (2%) with stage IIIC. Based on staging, stage IIIB was the most frequently diagnosed stage in this study. These findings differ from studies conducted in the United States and Korea, where stage II was the most commonly found stage, representing 42.9% in the U.S. and 49.5% in Korea.[21] Similarly, Ceccatto et al. (2012) reported that stage II was the most prevalent stage, accounting for 35% of cases. The discrepancy in these results may be attributed to delays in seeking medical care, late diagnosis, and a lack of patient awareness regarding their health.[22]

Most breast cancer patients tend to visit hospitals at stage III.[23] This phenomenon occurs because, in the early stages of breast cancer, patients usually do not experience pain or any noticeable symptoms. When breast abnormalities do occur, women often initially disregard them until the condition becomes severe.[24] The factors contributing to the high number of breast cancer patients presenting at stage III in hospitals remain unclear. One significant issue is that breast cancer screening in Indonesia is still conducted

on an individual basis, resulting in early detection programs that are neither effective nor efficient. Limited information and education, widespread advertising of alternative treatments, insufficient diagnostic tools such as mammography and ultrasound, and a lack of medical personnel skilled in diagnosing breast malignancies contribute to patients often being diagnosed at stage III. The predominance of stage III cases indicates a very low level of awareness among respondents regarding early treatment of initial symptoms. Most respondents were unaware of breast cancer symptoms, early detection methods, treatment-seeking behavior, and preventive measures.[25]

This study's findings align with those of Eugenio et al., 2016, who reported that grade III tumors are most commonly found in women under 40 years old with breast cancer.[26] Advanced stages with high-grade tumors in younger women are associated with aggressive and invasive tumor biology and a lack of early detection, leading to most cases being diagnosed at advanced stages with high grades. Thapa et al. (2013) noted that in developed countries, the high incidence of breast cancer is partly due to limitations in the accuracy of diagnostic tools such as mammography and physical breast examinations, which complicate screening efforts[27] In developing countries, in addition to limited diagnostic equipment, low public knowledge and awareness, financial constraints, and long distances to healthcare facilities contribute to high breast cancer morbidity and mortality.

Clinical responses in this study were categorized as either good response or no response across Anthracyclines, Taxane, and combination therapy groups. Good response included Partial Response (PR) and Complete Response (CR), while no response encompassed Stable Disease (SD) and Progressive Disease (PD). In the Anthracyclines group, 13 patients (26%) showed a good response, and 4 subjects (8%) showed no response. The Taxane group had 8 patients (16%) with a good response and 3 patients (6%) with no response. The combination therapy group showed 17 patients (34%) with a good response and 2 subjects (4%) with no response. Statistical analysis using the Chi-Square test yielded a p-value > 0.05, indicating no statistically significant effect of chemotherapy type on therapy response in breast cancer patients.

Chemotherapy regimens for breast cancer are administered either as monotherapy or in combination. Several studies have reported that adding drugs to monotherapy regimens can influence treatment outcomes. These studies compared dual-agent chemotherapy to single-agent chemotherapy but did not conclusively determine whether combination or monotherapy strategies are preferable. It is important to note that both monotherapy and combination chemotherapy are often used with various therapeutic approaches.[28]

Combination chemotherapy has become the standard treatment for hormone-refractory metastatic breast cancer.[29] Its use is based on theoretical principles and practical experience.[30] According to theory, using agents that do not exhibit cross-resistance and have non-overlapping toxicities can produce therapeutic synergy and overcome drug resistance.[31] Greenspan demonstrated that combination regimens are associated with higher response rates than single-agent regimens.[32] Randomized trials from the pre-taxane era showed that combination chemotherapy was superior to single-agent therapy in metastatic settings regarding response rates and/or overall survival, findings confirmed by recent meta-analyses.[33] However, some clinical trials comparing combination therapy with sequential therapy in this context have yielded conflicting results, although these were statistically less robust.[34]

This study offers significant strengths, particularly in its focus on evaluating the clinical response to neoadjuvant chemotherapy (NAC) using anthracyclines and taxane in patients with Locally Advanced Breast Cancer (LABC). By utilizing data from RSUP H. Adam Malik Medan over a recent period (2020-2022), the research provides valuable, context-specific insights that contribute to the existing body of scientific knowledge. The methodological approach, which includes prospective data collection, enhances the reliability and validity of the findings by minimizing bias and allowing for a more accurate assessment of treatment outcomes. However, the study also has limitations. Its scope is geographically and institutionally confined, which may affect the generalizability of the results to broader populations or different healthcare settings. Additionally, This study may be influenced by selection bias due to its single-center design, information bias from incomplete records, confounding bias from unmeasured variables, and reporting bias favoring positive

outcomes. These biases could limit data accuracy, reduce representativeness, and affect the overall validity and generalizability of the findings.

The study primarily focuses on anthracyclines and taxane regimens without exploring other emerging therapies such as monoclonal antibodies or gene therapy, which limits the comprehensiveness of therapeutic evaluation. The absence of a centralized cancer registry system further restricts the ability to perform large-scale epidemiological analyses and long-term follow-up, which are crucial for understanding treatment efficacy and patient outcomes over time. Future research should involve multi-center studies, include emerging therapies like monoclonal antibodies and gene therapy, establish a centralized cancer registry, and conduct prospective longitudinal studies to improve breast cancer treatment and outcomes.

5. CONCLUSION

The study identified key demographic and clinical characteristics of patients with locally advanced breast cancer at RSUP H. Adam Malik Medan, revealing a predominance of patients aged over 40 years (mean age 49.8 ± 8.5) and stage IIIB cancer (84%). The most prevalent molecular subtype was Luminal A (40%), followed by Luminal B, HER2-Enriched, and Triple Negative Breast Cancer. The findings suggests a significant partial clinical response ($p < 0.05$) following neoadjuvant chemotherapy with anthracyclines and taxane.

Acknowledgements

I would like to express my deepest gratitude to my supervisor, Suyatno, M.D. for his invaluable guidance, insightful feedback, and unwavering support throughout the course of this research. His expertise and encouragement have been instrumental in shaping both the direction and quality of this work.

I am also sincerely thankful to the faculty and staff of the Department of Oncology, Surgical Department at Universitas Sumatera Utara for providing the resources and academic environment that made this study possible.

Finally, I would like to thank my family and friends for their patience, understanding, and constant encouragement during the ups and downs of this academic journey.

Conflict of Interest

The author hereby declares that there are no financial, personal, or professional relationships or interests that could be perceived as influencing the content, findings, or conclusions presented in this manuscript. The author confirms that no actual or potential conflicts of interest exist with respect to the subject matter of this work.

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