

Doxorubicin, Cyclophosphamide Followed by Paclitaxel Vs 5-Fluorouracil, Doxorubicin, Cyclophosphamide in Locally Advanced Breast Cancer

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Abstract

Background: Breast cancer is the most common female malignancy in Bangladesh and the second most common cancer overall. Many patients with locally advanced disease (LABC) require multimodality therapy, including chemotherapy, surgery, and radiotherapy. Neoadjuvant chemotherapy serves as the essential initial treatment strategy for these patients.

Objective: To compare the treatment response and acute toxicities of Doxorubicin, Cyclophosphamide, followed by Paclitaxel (AC→P), with 5-Fluorouracil, Doxorubicin, and Cyclophosphamide (FAC) in the treatment of LABC.

Methods: This quasi-experimental study was conducted at two cancer centers in Dhaka from January 2017 to June 2018. Using convenience sampling, 120 biopsy-proven LABC patients were enrolled and alternately allocated to two groups: Group A received 3 neoadjuvant FAC cycles; Group B received 4 neoadjuvant AC cycles. Both underwent surgery and then received 3 adjuvant FAC cycles (Group A) or 4 adjuvant paclitaxel cycles (Group B). Clinical response was assessed preoperatively; pathological response from surgical specimens. Follow-up occurred at 2, 4, and 6 months post-treatment.

Result: Mean age was 43.9±10.2 years; groups were comparable in ECOG performance status, tumor stage, and nodal involvement ($p>0.05$). Clinical complete response favored AC→P (16.7% vs 5.0%; $p=0.068$); pathological complete response occurred only in AC→P (10.0%; $p=0.027$). Anemia (88.3% vs 70.0%; $p=0.023$) and taxane-related toxicities predominated in AC→P. Mucositis (58.3% vs 6.6%; $p<0.05$) and hyperpigmentation characterized FAC. Six-month recurrence was similar (6.7% vs 5.0%; $p=1$).

Conclusion: AC→P achieved significantly higher pathological complete response than FAC, particularly in triple-negative disease, despite increased hematologic and taxane-related toxicities. Both regimens demonstrated comparable short-term disease control. AC→P appears more effective for the neoadjuvant treatment of LABC.

Keywords: Locally advanced breast cancer, Neoadjuvant chemotherapy, AC→P regimen, FAC regimen, Pathological complete response.

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Introduction

Breast cancer has been recognized for millennia, with some of the earliest descriptions traced to ancient Egypt more than 3,500 years ago.¹ A later-discovered surgical record, the Edwin Smith Papyrus, described multiple cases of

breast carcinoma and reflected the therapeutic limitations of that era, noting that widely spread, cool, bulging breast tumors had no effective treatment.^{2,3} Explanatory frameworks continued to evolve across centuries, from ancient theories such as the “wandering womb”

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to a more medicalized understanding that accelerated in the nineteenth century, when improvements in sanitation and infectious disease control extended female life expectancy and made cancers, including breast cancer, more visible as a major clinical problem requiring structured treatment.⁴ Today, carcinoma of the breast remains a leading global public health challenge.⁵ It is widely recognized as the most common cancer among women and a major cause of cancer-related mortality.⁶ Global estimates from GLOBOCAN 2018 reported approximately 2.08 million new breast cancer cases, comprising 11.6% of all cancers, with about 626,000 deaths, or 6.6% of all cancer deaths.⁷ Incidence varies substantially by region, ranging from below 25.9 per 100,000 in South-Central Asia to above 90 per 100,000 in Australia and New Zealand, with a corresponding global mortality rate of about 13 per 100,000.⁷ Projections suggest further escalation: by 2040, global incident cases may rise to about 3.06 million, with deaths approaching 991,000 annually.⁷ Bangladesh mirrors this growing burden. In 2018, an estimated 12,764 new cases were recorded. Breast cancer ranked as the most common malignancy among Bangladeshi women, and annual deaths were estimated at 6,846; by 2040, incidence and mortality are projected to increase markedly.⁷ From an anatomical standpoint, the breast is positioned in the superficial fascia of the anterior chest wall, extending roughly from the sternal edge to near the mid-axillary line, and from the second to the sixth ribs, with the axillary tail representing an important superolateral extension. Lymphatic drainage is clinically central because malignant obstruction redirects flow through minor pathways, influencing nodal spread patterns that commonly involve axillary, parasternal, and sometimes supraclavicular nodes.⁸ Risk for breast cancer is multifactorial, yet approximately half of affected women may have no identifiable risk factor beyond increasing age and female sex.⁹ Risk determinants are often grouped into modifiable and non-modifiable categories, and include hereditary susceptibility such as BRCA1 or BRCA2 mutations, reproductive factors, and

exogenous hormonal exposures, among others.^{5,10,11} Invasive ductal carcinoma is the most frequent histologic subtype, accounting for the majority of invasive cases.⁵ A clinically critical subgroup is locally advanced breast cancer (LABC), a heterogeneous category that includes bulky tumors with possible skin or chest wall involvement and significant nodal disease; it encompasses operable presentations such as T3N1, inoperable presentations such as T4 and/or N2-3, and inflammatory breast cancer.^{5,12} Management typically requires multimodality therapy, with neoadjuvant chemotherapy increasingly used to downstage disease, facilitate definitive surgery, and provide an early indicator of regimen effectiveness.^{13,14} Pathological complete response after neoadjuvant therapy is strongly associated with improved survival outcomes, reinforcing the importance of optimizing neoadjuvant strategies in settings where FAC and AC followed by paclitaxel are commonly used.¹⁵ The aim of the study is to compare the treatment response and acute toxicities of Doxorubicin, Cyclophosphamide, followed by Paclitaxel (AC→P), with 5-Fluorouracil, Doxorubicin, and Cyclophosphamide (FAC) in the treatment of LABC.

Methodology & Materials

This quasi-experimental multicenter study was conducted from January 2017 to June 2018 at the Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh. Using convenience sampling, 120 biopsy-proven locally advanced breast cancer (LABC) patients were enrolled. Written informed consent was obtained from all participants, and ethical approval was secured from both institutional ethics committees.

Inclusion criteria

Eligible participants were women aged 18-70 years with non-metastatic (M0) LABC, including T3N1, T4, and/or N2-3, or inflammatory breast cancer (T4dN0-3). All patients had invasive ductal carcinoma confirmed on diagnostic biopsy.

Exclusion criteria

Patients were excluded if they were pregnant or lactating, male, had metastatic disease, double primaries, ECOG performance status >2, or had undergone definitive surgery of the primary site except a diagnostic biopsy. Those with severe concomitant medical illnesses—including significant heart disease, uncontrolled diabetes mellitus, or hypertension, were also excluded.

Study procedure

Following baseline evaluation, patients were alternately allocated to two groups. Group A (n=60) received three neoadjuvant FAC cycles (5-Fluorouracil 500 mg/m², Doxorubicin 50 mg/m², Cyclophosphamide 500 mg/m² IV on day 1 every 21 days)¹⁶, followed by surgery and three adjuvant FAC cycles. Group B (n=60) received four neoadjuvant AC cycles (Doxorubicin 60 mg/m², Cyclophosphamide 600 mg/m² IV on day 1 every 21 days)¹⁷, followed by surgery and four adjuvant Paclitaxel cycles (175 mg/m² IV on day 1 every 21 days). Modified radical mastectomy with level I/II axillary dissection was performed approximately three weeks post-neoadjuvant chemotherapy.

Postoperative radiotherapy (40 Gy in 15 fractions over 3 weeks) was delivered to the chest wall and supraclavicular fossa using a conventional 2D technique. Furthermore, tamoxifen 20 mg daily was prescribed for hormone-receptor-positive disease. Tumor response was assessed using RECIST 1.1 criteria¹⁸ at baseline, before each cycle, and preoperatively. Pathological complete response was determined from surgical specimens. Follow-up assessment occurred at 2, 4, and 6 months post-treatment.

Statistical analysis

Data were compiled in Microsoft Excel and analyzed using SPSS version 24.0. Categorical variables were compared using Chi-square or Fisher's exact tests, as appropriate. A p-value <0.05 was considered statistically significant.

Results

This quasi-experimental study enrolled 120 biopsy-proven LABC patients via convenience sampling at two Dhaka cancer centers (January 2017–June 2018). Patients were alternately allocated: Group A received three neoadjuvant FAC cycles; Group B received four neoadjuvant AC cycles.

Table I

Baseline age distribution and ECOG performance status by treatment group

Variable	Category	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)	p-value
Age group (years)				
	20–29	2 (3.33)	4 (6.67)	0.401
	30–39	15 (25.00)	17 (28.33)	
	40–49	20 (33.33)	21 (35.00)	
	50–59	16 (26.67)	14 (23.33)	
	60–69	2 (3.33)	4 (6.67)	
	70–79	1 (1.67)	0 (0.00)	
	Mean ± SD	44.73 ± 10.86	43.15 ± 9.69	
ECOG				
	0	24 (40.0)	28 (46.7)	0.796
	1	30 (50.0)	27 (45.0)	
	2	6 (10.0)	5 (8.3)	

Chi-square tests were used.

The two treatment groups were well-balanced at baseline, as shown in Table 1. No significant differences were observed in age distribution (p=0.401) or ECOG performance status (p=0.796), confirming comparability.

Table II
Socioeconomic and educational characteristics of participants by treatment group

Variables	Category	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)
Monthly income (Taka)	<12,260	42 (70.0)	33 (55.0)
	12,260–31,640	14 (23.3)	20 (33.3)
	>31,640	4 (6.7)	7 (11.7)
Occupational status	Student	1 (1.7)	1 (1.7)
	Job holder	3 (5.0)	7 (11.7)
	Housewife	56 (93.3)	50 (83.3)
	Businessman	0 (0.0)	2 (3.3)
Educational status	No formal education	31 (51.7)	21 (35.0)
	Up to primary	21 (35.0)	22 (36.7)
	Up to SSC	5 (8.3)	11 (18.3)
	Up to HSC	3 (5.0)	3 (5.0)
	Above HSC	0 (0.0)	3 (5.0)

Chi-square tests were used.

Socioeconomic and educational characteristics are presented in Table 2. Although some numerical differences existed in income, occupation, and education, the groups remained broadly comparable.

Menopausal status distribution of the study population is illustrated in Figure 1. Premenopausal women constituted the largest proportion (58.5%).

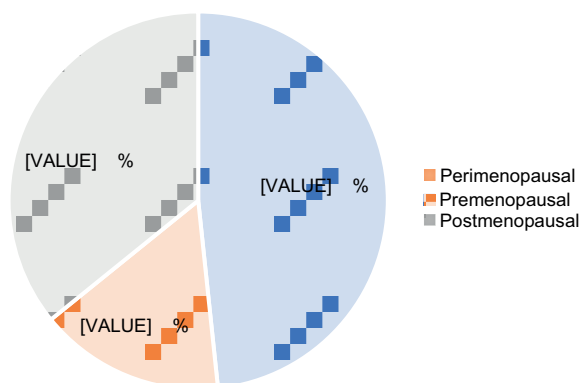


Figure 1: Menopausal status distribution among the study population (n=120)

Table III
Baseline tumor characteristics and clinical stage distribution by treatment group

Variables	Category	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)	p-value
Tumor size	T2	6 (10.0)	6 (10.0)	0.962
	T3	35 (58.3)	33 (55.0)	
	T4	19 (31.7)	21 (35.0)	
Nodal status	N0	2 (3.3)	3 (5.0)	0.953
	N1	30 (50.0)	30 (50.0)	
	N2	23 (38.4)	21 (35.0)	
	N3	5 (8.3)	6 (10.0)	
Laterality	Left	31 (51.7)	25 (41.7)	0.36
	Right	29 (48.3)	35 (58.3)	
Stage	IIIA	34 (56.7)	35 (58.3)	0.74
	IIIB	21 (35.0)	18 (30.0)	
	IIIC	5 (8.3)	7 (11.7)	

Chi-square tests were used.

Baseline tumor characteristics were comparable between groups, as detailed in Table 3. No significant differences were found in tumor size ($p=0.962$), nodal status ($p=0.953$), laterality ($p=0.36$), or disease stage ($p=0.74$).

Clinical response patterns are summarized in Table 4. Although complete response was higher in the AC→P (16.7% vs 5.0%), the overall RECIST response distribution did not reach statistical significance ($p=0.068$). However, pathological complete response significantly favored the AC→P (10.0% vs 0%; $p=0.027$).

Hematologic toxicities are presented in Table 5. Anemia was significantly more frequent in AC→P (88.3% vs 70.0%; $p=0.023$). Other

hematologic toxicities showed no significant between-group differences: neutropenia ($p=0.084$), thrombocytopenia ($p=0.743$), febrile neutropenia ($p=0.272$), and cardiotoxicity ($p=1$).

Non-hematologic toxicities showed distinct regimen-specific patterns (Table VI). FAC was associated with significantly higher oral mucositis and hyperpigmentation ($p<0.05$). The AC→P demonstrated significantly higher rates of taxane-related toxicities: myalgia, arthralgia, and peripheral sensory neuropathy ($p<0.05$). Nausea ($p=0.614$), vomiting ($p=0.404$), and hypersensitivity ($p=0.242$) were similar between groups, while diarrhea showed borderline significance ($p=0.051$). Alopecia was universal (100% both groups).

Table IV

Clinical response to neoadjuvant chemotherapy (RECIST 1.1) and pathological complete response by treatment group

Outcome	Category	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)	p- value
Clinical response (RECIST)	Partial response (PR)	45 (75.0)	45 (75.0)	0.068
	Complete response (CR)	3 (5.0)	10 (16.7)	
	Stable disease (SD)	10 (16.7)	4 (6.7)	
	Progressive disease (PD)	2 (3.3)	1 (1.7)	
Pathological response	pCR (Yes)	0 (0.0)	6 (10.0)	0.027
	pCR (No)	60 (100.0)	54 (90.0)	

Chi-square test; Fisher's exact test for pCR

Table V

Hematologic toxicities by treatment arm, overall incidence, and higher-grade events

Toxicity	Group A, FAC n (%)	Group B, AC→P n (%)	p-value	Grade 3-4 events, n (%)
Anemia	42 (70.0)	53 (88.3)	0.023	2 (3.3) vs 5 (8.3)
Neutropenia	42 (70.0)	50 (83.3)	0.084	2 (3.3) vs 7 (11.7)
Thrombocytopenia	6 (10.0)	4 (6.7)	0.743	0 (0.0) vs 0 (0.0)
Febrile neutropenia	2 (3.3)	6 (10.0)	0.272	2 (3.3) vs 6 (10.0)
Ejection fraction decrease	1 (1.7)	0 (0.0)	1	1 (1.7) vs 0 (0.0)

Chi-square test; Fisher's exact test where appropriate. Note: Toxicities graded per CTCAE criteria. Grade 3 = severe; Grade 4 = life-threatening

Table VI
Non-hematologic toxicities by treatment arm during treatment course

Toxicity	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)	p-value
Alopecia	60 (100)	60 (100)	0.439*
Oral mucositis	35 (58.3)	4 (6.6)	<0.05
Hyperpigmentation	49 (81.6)	3 (5.0)	<0.05
Myalgia	4 (6.6)	55 (91.6)	<0.05
Arthralgia	3 (5.0)	43 (71.6)	<0.05
Peripheral sensory neuropathy	5 (8.3)	43 (71.6)	<0.05
Nausea	44 (73.3)	49 (81.6)	0.614
Vomiting	24 (40.0)	33 (55.0)	0.404
Diarrhea	10 (16.6)	2 (3.3)	0.051
Hypersensitivity	2 (3.3)	5 (8.3)	0.242

Chi-square tests were used.

Table VII
Six-month disease progression or recurrence following completion of therapy by treatment group

Outcome	Group A, FAC (n=60) n (%)	Group B, AC→P (n=60) n (%)	p-value
Local and or distant progression	4 (6.7)	3 (5.0)	1.00

Fisher's exact test was done.

Six-month disease progression or recurrence rates were comparable between groups (FAC 6.7% vs AC→P 5.0%; $p=1$), as shown in Table VII.

Discussion

Neoadjuvant chemotherapy (NACT) is central to contemporary management of locally advanced breast cancer (LABC), because it can downstage the primary tumor, increase operability, and provide an in vivo assessment of chemosensitivity. In Bangladesh, however, comparative evidence on commonly used anthracycline-based regimens remains limited. In this quasi-experimental multicenter study (n=120), baseline profiles were broadly comparable between the two treatment groups, with a similar age distribution (mean of about mid-40s years), ECOG performance status predominated by ECOG 0–1, and comparable clinical stage composition dominated by stage III disease. The cohort also reflected typical regional patterns, including a substantial

premenopausal proportion and a hormone receptor positive fraction close to one half, aligning with reports that South Asian and Middle Eastern populations often present younger and with a high burden of advanced stage disease.^{19,20} Clinically, both regimens produced substantial tumor regression. Partial response was identical in both groups (75%), while clinical complete response was numerically higher with AC→P (16.7% vs 5.0%); however, the overall distribution per RECIST (Response Evaluation Criteria in Solid Tumors) did not reach statistical significance ($p=0.068$). This pattern aligns with the known efficacy of anthracycline-based regimens in locally advanced breast cancer (LABC) and with institutional series reporting overall response rates of 50–80%.^{19,21} The key discriminator was pathological complete response (pCR)—absence of invasive cancer in resected breast and lymph nodes—observed only in the AC→P group (10.0%; $p=0.027$). This finding is clinically important

because pCR correlates with improved long-term outcomes in pooled analyses, particularly in biologically aggressive subtypes.²² The observed pCR rate also sits within the range reported across neoadjuvant series, and it mirrors regional experience with AC-based neoadjuvant treatment, where pCR approximated 10%.^{21,23} Mechanistically and historically, the advantage of incorporating a taxane after an anthracycline is supported by major cooperative group evidence showing that sequential taxane administration increases both clinical and pathological response rates compared with anthracycline alone.²³ Subgroup patterns in this study reinforce that biology drives depth of response. In triple-negative breast cancer (TNBC), the distribution of response differed significantly between groups ($p=0.028$), with the AC→P group showing a higher complete response signal while the FAC group had no complete responders in this subtype. This aligns with the established observation that basal-like and TNBC phenotypes are often more chemosensitive to anthracycline-based regimens, and that achieving pCR in these subtypes carries a particularly favorable prognostic implication relative to residual disease.^{22,24} In practical terms, the TNBC signal in this cohort supports prioritizing regimens that maximize the probability of pCR where feasible, while still recognizing that the study design, sample size, and short follow-up constrain definitive comparative effectiveness conclusions. Toxicity patterns were mixed and predictable based on regimen composition. Hematologic toxicity was common in both groups, with anemia significantly more frequent in the AC→P group (88.3% vs 70.0%, $p=0.023$) and a higher-grade signal (grade 3 anemia 8.3% vs 3.3%). Neutropenia and febrile neutropenia were numerically higher with AC→P, though not statistically significant here, and clinically meaningful cardiotoxicity was rare in both groups. These findings are directionally consistent with broader clinical experience that chemotherapy-induced anemia is frequent, varies by regimen intensity, and is often underaddressed in routine practice.²⁵ Non-hematologic toxicity showed a clear trade-off:

FAC was associated with substantially higher oral mucositis and hyperpigmentation, whereas AC!P was strongly associated with taxane-linked musculoskeletal symptoms (myalgia, arthralgia) and peripheral sensory neuropathy, with statistically significant between-group differences for these endpoints. This toxicity partition closely matches comparative evidence from prospective observational work evaluating FAC versus AC followed by paclitaxel, where mucositis and hyperpigmentation clustered with FAC, and neuropathy plus myalgia clustered with the taxane-containing approach.²⁶ From an implementation standpoint, these results argue for regimen selection that balances the clinical objective of deeper response, particularly pCR in higher risk biology, against the expected toxicity spectrum, supportive care capacity, and patient preferences. Finally, short-term disease progression or recurrence at 6 months was low and similar between groups (6.7% vs 5.0%, $p=1$). Given the limited follow-up window, this should be interpreted cautiously and not as evidence of equivalent disease control. Longer follow-up is necessary to assess disease-free and overall survival, and future work in Bangladesh would benefit from more robust allocation methods, standardized supportive care protocols, and the incorporation of contemporary HER2 targeted strategies where indicated, because these factors can materially affect both response depth and longer-term outcomes. Overall, within the constraints of this study, AC→P demonstrated a clinically relevant advantage in pCR, particularly with a notable signal in TNBC, at the cost of greater taxane-associated neuropathy and musculoskeletal toxicity, while FAC showed more mucosal and pigmentary toxicity and no pCR in this cohort.^{22,23,26}

Limitations of the study:

This study had several limitations. A randomized controlled trial was not conducted. The six-month follow-up was insufficient for long-term outcomes. The modest sample size ($n=120$) reduced statistical power. The quasi-experimental design with alternate allocation introduced potential selection bias. Financial constraints limited comprehensive biomarker testing.

Conclusion

In this multicenter quasi-experimental study of 120 women with locally advanced breast cancer, both regimens produced substantial clinical tumor regression, with identical partial response rates. However, the Doxorubicin, Cyclo-phosphamide followed by Paclitaxel schedule is more effective than 5-Fluorouracil, Doxorubicin, and Cyclophosphamide in terms of pathological complete response (PCR). The pCR advantage, together with the more favorable response pattern in triple-negative disease, supports AC→P as the more effective option for deeper neoadjuvant response in this cohort. Toxicity profiles differed by regimen. FAC was associated with higher mucositis and hyperpigmentation, whereas AC→P resulted in more taxane-related myalgia, arthralgia, peripheral neuropathy, and higher rates of anemia, with most events remaining manageable. Short-term recurrence or progression at 6 months was low and comparable between groups, indicating acceptable early disease control with either approach.

Recommendations

Further multicenter research with randomized allocation and a larger sample is recommended to strengthen comparative effectiveness estimates. In addition, extended follow-up is needed to evaluate 5-10-year survival outcomes, including disease-free and progression-free survival, and to document late and long-term toxicities.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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