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Research Article

# Response of Neoadjuvant Chemotherapy with Adriamycin and Cyclophosphamide versus Adriamycin and Docetaxel in Patient with Locally Advanced Breast Cancer

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- Adriamycin
- Cyclophosphamide
- Docetaxel

## Abstract

**Background:** Neoadjuvant chemotherapy is an innovative approach that has got significant attention for treating breast cancer. Optimal management of locally advanced breast cancer (LSBC), generally includes a combination of neoadjuvant chemotherapy followed by surgery, local radiotherapy and adjuvant chemotherapy with or without hormone therapy.

**Methodology:** Our study was carried out on histopathologically confirmed 60 locally advanced breast cancer patient [tumor > 5cm in diameter (T3), with mobile or fixed nodes (N1-2), OR associated with involvement of skin or chest wall (T4), OR with fixed axillary nodes or ipsilateral Supraclavicular nodes] were enlisted and were divided into two study groups. Arm-A consisting of 30 patients were treated with Adriamycin 60 mg/m2 and Cyclophosphamide 600 mg/m2 (AC), & Arm-B consisting of 30 patients were treated with Adriamycin 50 mg/m2 and Docetaxel 75 mg/m2 (AD), 4 cycle 3 weeks interval.

**Results:** The study was designed to compare the response of neoadjuvant chemotherapy with Adriamycin and Cyclophosphamide versus Adriamycin and Docetaxel in locally advanced breast cancer. As the result of the study, baseline characteristics were almost similar between the two arms. In Arm-A clinical complete response (CR), was achieved in 05 patients (16.7%), and clinical partial response (PR), was 18 patients (60%). In Arm-B clinical complete response (CR), was achieved in 08 patients (26.7%), and clinical partial response (PR), was 19 patients (63.3%). Overall clinical response (complete & partial), in Arm-A & Arm-B was 76.7% versus 90%. After 4 cycle chemotherapy, 23 patients in Arm-A and 27 patients in Arm-B underwent a modified radical mastectomy. Among them, pathological complete response (CR), was found in 02 patients (8.7%), in Arm-A and 04 patients (14.9%), in Arm-B. Hematological toxicities especially grade-3 anemia & neutropenia were more in Arm-B than Arm-A, but no patient develop grade-3 thrombocytopenia. Among non-hematologic toxicities, grade-3 nausea vomiting was more in Arm-A but alopecia and neuropathy were more in Arm-B. All these toxicities were managed by symptomatic management.

**Conclusion:** The overall clinical and pathological response was found greater in Arm-B but not statistically significant. Both hematologic and non-hematological toxicities were a little bit more in Arm-B specifically grade-3 neutropenia, except the incidence of nausea and vomiting was more in Arm-A but those were acceptable and manageable.

## INTRODUCTION

Being a major public health problem, breast cancer is the most common and second most common cause of death among women. Only in 2008, almost 184,450 new cases were raised and caused 40,930 deaths in USA. Though the etiology in most of the cases remain unknown, numerous risk factors play a vital role behind this disease such as patient's age, family history of breast cancer at a young age, early menarche, late menopause, older age at first five childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irritation, benign proliferative breast disease and genetic mutation [1,2].

Locally advanced breast cancer (LABC), is a term that refers to a heterogeneous group of diseases, a subset of stage IIB (T3N0M0), stage III disease including inflammatory breast cancer (IBC), are included in this group [3-5]. Approximately 7% of breast cancer patients have the stage-III disease at diagnosis with a median survival time of 4.9 years, while the 5-year relative survival rate for this group of women is 55% when treated with multimodality treatment not including biologics according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), program analysis [6-8]. However, tumor size, lymph node involvement, and the presence of inflammatory carcinoma are the main prognostic factors, while the prognostic

value of tumor grade, ER/PR and HER-2/neu status is not fully clarified [9-11].

Over and above, pathologic complete response (pCR), has emerged as the most commonly used surrogate endpoint and seems to be associated with a favorable prognosis [12,13]. Improving overall survival (OS), and disease-free survival (DFS), are major goals in our selected group of patients. The conversion of initially inoperable breast cancer to an operable only or even more to conservatively operable is also of crucial importance. Nevertheless, both the locoregional and systemic control represents major clinical problems in LABC. The risk of recurrence and death is extremely high, particularly in poorly responding to induction chemotherapy patients. The risk of recurrence and death is extremely high, particularly in poorly responding to induction chemotherapy patients [2,14].

Neoadjuvant chemotherapy is the standard treatment for the patient with locally advanced breast cancer. Contrariwise, neoadjuvant chemotherapy got some drawbacks such as initial tumor size and the number of involved nodes that could not be accurately assessed; much greater disease burden to treat; uncertainty that neoadjuvant treatment will be beneficial with consequences of delay in curative local therapy; suspicion that it could promote drug resistance and increased risks for surgical complications [15-19].

Selecting the optimal chemotherapy regimen and the duration of treatment have been extensively assessed in induction systemic chemotherapy but no consensus has been developed so far. Beyond the pivotal data from an early anthracycline, cyclophosphamide, methotrexate, and fluorouracil containing studies of neoadjuvant chemotherapy, more recent randomized trials in LABC focus on the addition of newer agents. All these trials are based on well-established regimens used in the adjuvant setting research. A phase-III randomized trial in LABC patients confirmed the superiority of the sequential neoadjuvant approach of 4 cycles of anthracycline regimen followed by 4 cycles of the docetaxel-based regimen. This regimen was compared to 8 cycles of an anthracycline regimen alone [20]. A high number of relative trials evaluated the role of different combinations of anthracyclines and taxanes. In sequential administration of an anthracycline and taxane, in the neoadjuvant setting overall response rate was 85 to 95%. In concomitant administration of anthracycline and taxane, the overall response rate was 68 to 93% (17). The results from this trial suggest that docetaxel containing regimen can be considered as a standard in the neoadjuvant chemotherapy setting. Although several clinical trials have been performed. However, more research is needed to determine the superiority of the regimen in the neoadjuvant setting.

## METHODOLOGY

A yearlong Quasi-experimental investigation was carried out with the involvement of the patients suffering from breast cancer attending the Department of Radiotherapy, Rajshahi Medical College Hospital, Bangladesh. All the patients were closely examined and interviewed accordingly with the fulfillment of the inclusion and exclusion criteria included in the study maintain systemic random sampling procedure.

### Selection Criteria

**Inclusion Criteria:**

a) Patients with histopathologically confirmed locally advanced breast cancer.

b) Patients within age 18-70 years.

c) Patients having ECOG performance status score up to grade 2.

d) Minimum laboratories criteria are:

- Hemoglobin level should be more than 10 gm/dl or > 60%.
- Total WBC count more than or equal to 4000 cells/cmm.
- Platelet count more than or equal to 100000 cells/cmm.
- S. bilirubin level should be equal to or less than 1.5 mg/d.
- SGOT (Serum Glutamic Oxaloacetic Transaminase) level not more than 4 times of the upper limit.
- Creatinine clearance should be more than or equal to 60 ml/min.
- Blood urea level less than 50mg/d.

**Exclusion Criteria:**

- Patients with other than histopathologically confirmed LABC.
- Patients with prior treatment by radiotherapy or chemotherapy.
- Patients with initial surgery (lumpectomy) of the primary site.
- Patients having performance status > grade 2.
- Patients with distant metastasis
- Patients dropped out or lost to follow up before completion of the study.
- Patients with double primaries
- Patients with uncontrolled infection and severe concomitant systemic disease.
- Pregnant or lactating mother.
- Prisoner.

**Risk Factors Observation:**

- Menopausal Status
- History of oral contraceptive pill intake
- Parity (Nullipara / Multipara)
- Habit: Smoking/alcohol
- History of malignancy
- History of prior radiation exposure
- Family history of malignancy

### Sample Collection Procedure

A total number of 60 patients with histopathologically confirmed locally advanced breast cancer were selected for the study and divided equally into two groups containing 30 patients in each group (Arm-A and Arm-B). Every individual had to go through some pretreatment evaluations such as complete physical history, general screening, laboratory studies (total blood count, liver function test, renal function test) and some imaging studies (Urine Specific Gravity; USG of breast and axilla, mammography of the breast).

SAMPLE SIZE IS CALCULATED BY USING THE FOLLOWING FORMULA:

$$n = \frac{z^2(p \times q)}{d^2}$$

N = REQUIRED SAMPLE SIZE.

p = prevalence rate 4.6 % = 0.046 [21]

Q = 1-P = 1-0.046 = 0.954.

z = 1.96 (confidence limit)

d = 0.05(degree of freedom)

$$n = \frac{1.96^2(0.046 \times 0.954)}{(0.05)^2} = 66.$$

(Considering drop out during treatment, a total of 60 patients was selected as sample 30 in each arm).

### Assessment of Treatment Response

The total treatment response assessment process was undergone after four-cycle neoadjuvant chemotherapy according to RECIST (Response Evaluation Criteria in Solid Tumor) criteria. (Schwartz et al., 2016)

Toxicities were observed via Common Terminology Criteria for Adverse Events, v.4.03 [22,23]. Response assessment was done clinically & radiological investigation (USG of breast and axilla, mammography, MRI of the breast), was used wherever appropriate. Each specimen was sent to the pathologist to confirm a pathological complete response. Pathological complete response was defined as the absence of disease from breast and axilla on histopathology report.

### Experimental Distribution

**Arm-A:** 30 patients were treated with Inj. Adriamycin 60 mg/m2 plus Inj. Cyclophosphamide 600 mg/m2 day 1 Iv (3 weekly) 4 cycle .

**Arm-B:** 30 patients were treated with Inj. Adriamycin 50 mg/m2 plus Inj. Docetaxel 75 mg/m2 IV day 1 ( 3 weekly ), 4 cycle.

### Experimental Data Analysis

Data analysis was done according to the objectives of the study by using SPSS (Statistical Package for Social Science) software program. Data were checked for validity and consistency. Then data were analyzed by applying relevant statistical tests (both parametric and non –parametric) with appropriate probability level (p=0.05).

### Ethical Clearances

Permissions were taken from the community medicine department of Rajshahi medical college hospital. All the patients with locally advanced breast cancer (fulfilling the inclusion criteria) were counseled about the study, the procedure of treatment, expenditure, side effects of chemotherapy and radiotherapy and expected to result of treatment among both groups. They were also informed that there was no guarantee about disease cure. They also permit me to preserve all documents and records related to the disease for the study. Informed written consent was taken from each patient before enrolling in the study.

### List of variables

1. Age
2. Sex
3. Religion
4. Occupation
5. Economic condition
6. Educational status
7. Residence
8. Menstrual and obstetric history,
9. History of the oral contraceptive pill,
10. History of radiation exposure,
11. Family history, personal history, and history of illness.
12. Primary tumor size
13. Axillary and cervical lymph node size
14. Histopathological differentiation of tumor
15. TNM Staging of the disease at diagnosis
16. Performance status
17. Treatment response
18. Toxicity /toxicities

## RESULTS

### Evaluation of Baseline Characteristics

**Age:** A total number of 60 patients were enlisted in the study and divided equally in to two groups (Arm-A and Arm-B). The age distribution of the patients of both arms are mentioned in Table 1 below. The median age was 46.5 years (range: 30-65 years) in Arm-A and 46.5 years (range: 36-68 years) in Arm-B (P value= 0.292) Figure 1.

- **Age of menarche:** The age of menarche was less than 12 years for 01 patient (3.3%), in Arm-A and 02 patients (6.7%), in Arm-B. In opposite, 29 patients (96.7%), in Arm-A and 28 patients (93.3%), in Arm-B had their menarche stage after or at 12 years of age (P= 0.554), mentioned below in Table 2 and Figure 2.

**Table 1:** Age distribution of patients in two groups; Arm-A and Arm-B.

| Age Groups | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|
| | N=30 | % | N=30 | % | |
| **30-39** | 07 | 23.3 | 03 | 10.0 | 0.292 |
| **40-49** | 09 | 30.0 | 14 | 46.7 | |
| **50-59** | 11 | 36.7 | 12 | 40.0 | |
| **60-69** | 03 | 10.0 | 01 | 3.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

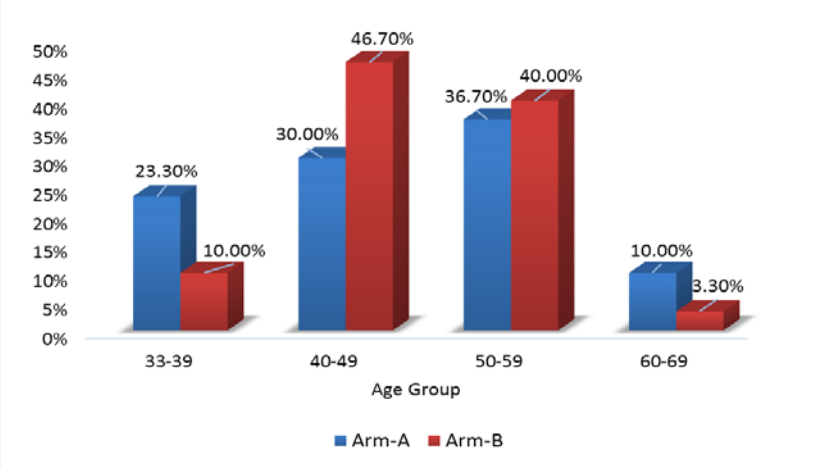


**Figure 1** Age distribution of patients in two groups; Arm-A and Arm-B.

**Table 2:** Age at menarche of patients in two groups; Arm-A and Arm-B.

| Age of menarche | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **< 12 years** | 03 | 5.0 | 01 | 3.30 | 02 | 6.70 | 0.554 |
| **≥ 12 years** | 57 | 95.0 | 29 | 96.7 | 28 | 93.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

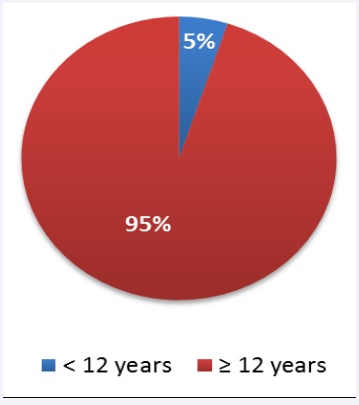


**Figure 2** Age at menarche of patients in two groups; Arm-A and Arm-B

- **Age at menopause:** The age of menopause was <55 years for 18 patients (60%), in Arm-A and 18 patients (60%) in Arm-B and ≥55 years was for 01 patient (3.3%) in Arm-A. There was no patient in Arm-B with menopause ≥55 years. There were 11 patients (36.7%), in Arm-A and 12 patients (40%), in Arm-B was on reproductive period (P= 0.593) (Table 3 and Figure 3).

**Menopausal status:** Total 26 patients (43.3%), were pre-menopausal and 34 patients (56.7%), were post-menopausal. Among them 12 patients (40%), in Arm-A and 14 patients (46.7%), in Arm-B was pre-menopausal and 18 patients (60%) in Arm-A and 16 patients (53.3%), in Arm-B was post-menopausal (P= 0.602) (Table 4 and Figure 4).

**Parity:** A total number of 04 patients (06.7%), were nulliparous and 56 patients (93.3%), were multiparous. Among them 03 patients (10%) in Arm-A and 01 patients (3.3%) in Arm-B was nulliparous and 27 patients (90%) in Arm-A and 29 patients (96.7%) in Arm-B was multiparous (P= 0.301) (Table 5 and Figure 5).

**History of lactation:** Among 60 patients 48 (80%), patients used to breastfeed their children and remaining 12 (20%), patients did not.

**History of OCP (Oral Contraceptive Pill) intake:** Among 60 patients 53 (88.3%), patients were used to take oral contraceptive as their contraception 07 (11.7%), patients took

**Table 3:** Age at menopause of patients in two groups; Arm-A and Arm-B.

| Age of menopause | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **< 55 years** | 36 | 60.0 | 18 | 60.0 | 18 | 60.0 | 0.593 |
| **≥ 55 years** | 01 | 1.70 | 01 | 3.30 | 00 | 0.00 | |
| **On reproductive period** | 23 | 38.30 | 11 | 36.70 | 12 | 40.00 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

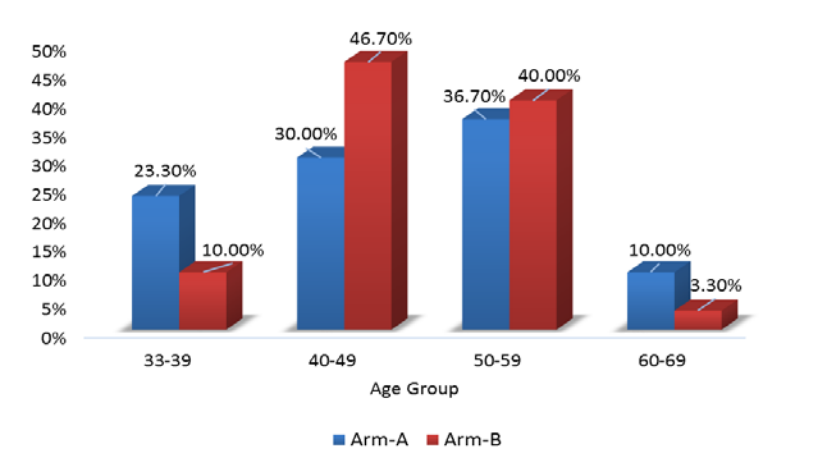


**Figure 3** Age at menopause of patients in two groups; Arm-A and Arm-B.

**Table 4:** Menopausal status of patients in two groups; Arm-A and Arm-B.

| Menopausal status | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Pre- Menopausal** | 26 | 43.30 | 12 | 40.0 | 14 | 46.70 | 0.602 |
| **Post- Menopausal** | 34 | 56.70 | 18 | 60.0 | 16 | 53.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

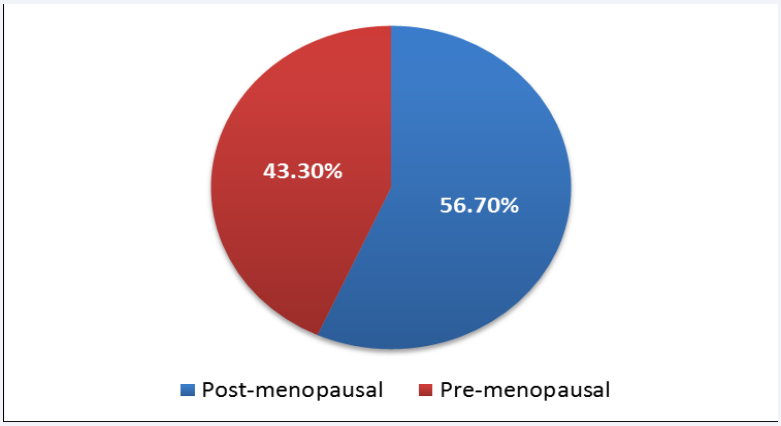


**Figure 4** Menopausal status of patients in two groups; Arm-A and Arm-B.

other contraception method not Oral contraceptive. The use of contraceptives between Arm-A & Arm-B was 86.7% vs. 90% (P=0.688), (Table 6 and Figure 6).

**Obesity:** Among 60 patients only 06 (10 %), patients were found obese and rest of the patients 54 (90%) were normal according to their BMI (Figure 7 and Figure 8).

**Family history of malignancy:** Family history of malignancy was positive for 04 patients (06.7%), and negative for 56 patients (93.3%). Among them 03 patients (10%), in Arm-A and 01 patient (3.3%), in Arm-B had family history positive and 27 patients

**Table 5:** Parity of patients in two groups; Arm-A and Arm-B.

| Parity | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Nulliparous** | 04 | 6.70 | 03 | 10.0 | 01 | 3.30 | 0.301 |
| **Multiparaous** | 56 | 93.30 | 27 | 90.0 | 29 | 96.70 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

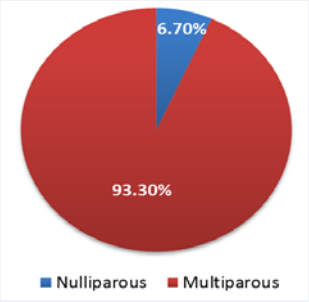


**Figure 5** Parity of patients in two groups; Arm-A and Arm-B.

**Table 6:** History of OCP intake among two groups; Arm-A and Arm-B.

| OCP | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Yes** | 53 | 88.30 | 26 | 86.70 | 27 | 90.0 | 0.688 |
| **No** | 07 | 11.70 | 04 | 13.30 | 03 | 10.0 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

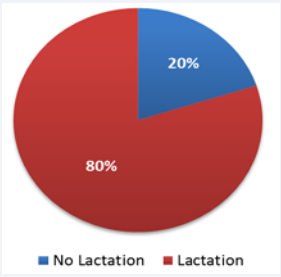


**Figure 6** History of lactation among the study group; Arm-A and Arm-B.

**Table 7:** Family history of malignancy in two groups; Arm-A and Arm-B.

| Malignancy | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Yes** | 04 | 6.70 | 03 | 10.0 | 01 | 3.30 | 0.301 |
| **No** | 56 | 93.30 | 27 | 90.0 | 29 | 86.70 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

(90%) in Arm-A and 29 patients (96.7%) in Arm-B had negative family history (P= 0.301) (Table 7 and Figure 9).

**History of radiation exposure:** Among 60 patient 57 (95%), patients did not experience any radiation therapy in their lifetime and 03 (05%), patients had the history of getting radiation therapy in their early age for any kind of cancers or other diseases (Figure 10).

**Site of tumor:** Total 41 (68.3%), patients had left sided breast tumor and 19 (31.7%), had right sided breast tumor. Left breast tumor between two arms was 60% vs. 76.7% and right sided tumor between two arms was 40 % vs. 23.3% (P= 0.165) (Table 8 and Figure 11).

**Location of tumor in breast:** Among 60 patients 37 (61.7%) patients had Upper-outer quadrant, 02 (03.3%), patients Lower-outer, 01 (1.7%), patient Lower-inner, 07 (11.7%), patients Upper-inner and 13 (21.7), patients had central breast tumor (Table 9 and Figure 12).

**AJCC staging (American Joint Committee on Cancer:** Majority of the patients in both arms had stage IIIB disease (Arm-A 16 patient 53.3% vs. Arm-B 16 patients 53.3%; P= 0.733). Stage IIIA was the next most common in both arms (Table 10 and Figure 13).

**Histopathology:** Invasive duct cell carcinoma was 95.0% and Invasive lobular cell carcinoma was 05.0% among study group. Invasive duct cell carcinoma between two arms was 93.3% vs. 96.7% and Invasive lobular cell carcinoma was 6.7% vs. 3.3% (P= 0.554) (Table 11 and Figure 14).

**ECOG performance status:** 60% patients in Arm-A and 86.7% patients in Arm-B had ECOG performance status 0. 36.7% patients in Arm-A and 13.3% patients in Arm-B had

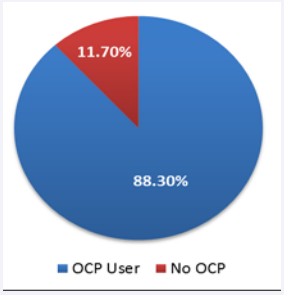


**Figure 7** History of OCP intake among two groups; Arm-A and Arm-B.

**Table 8:** Site of tumor of patients in two groups; Arm-A and Arm-B.

| Site of tumor | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Right Breast** | 19 | 31.70 | 12 | 40.0 | 07 | 23.30 | 0.165 |
| **Left Breast** | 41 | 68.30 | 18 | 60.0 | 23 | 76.70 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

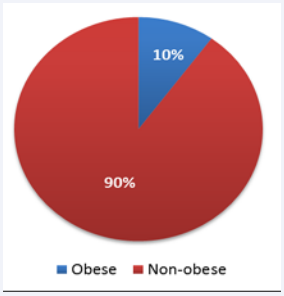


**Figure 8** Obesity among two groups; Arm-A and Arm-B.

**Table 9:** Location of tumor in breast of patients in two groups; Arm-A and Arm-B.

| Location of tumor | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Upper-outer** | 37 | 61.70 | 17 | 56.70 | 20 | 66.70 | 0.833 |
| **Lower-outer** | 02 | 3.30 | 01 | 3.30 | 01 | 3.30 | |
| **Lower-inner** | 01 | 1.70 | 01 | 3.30 | 00 | 0.00 | |
| **Upper-inner** | 07 | 11.70 | 04 | 13.30 | 03 | 10.0 | |
| **Central** | 13 | 21.70 | 07 | 23.30 | 06 | 20.0 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 10:** AJCC staging of patients in two groups; Arm-A and Arm-B.

| AJCC Stages | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **IIIA** | 18 | 30.00 | 08 | 26.70 | 10 | 33.40 | 0.733 |
| **IIIB** | 32 | 53.30 | 16 | 53.30 | 16 | 53.30 | |
| **IIIV** | 10 | 16.70 | 06 | 20.00 | 04 | 13.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 11:** Histopathology of patients in two groups; Arm-A and Arm-B.

| Histopathology | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **Invasive ductal cell carcinoma** | 57 | 95.00 | 28 | 93.30 | 29 | 96.70 | 0.554 |
| **Invasive lobular cell carcinoma** | 03 | 5.00 | 02 | 6.70 | 01 | 3.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 12:** ECOG performance status of patients in two groups; Arm-A and Arm-B.

| Performance Status | In Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|
| | N=60 | % | N=30 | % | N=30 | % | |
| **0** | 44 | 73.30 | 18 | 60.00 | 26 | 86.70 | 0.057 |
| **1** | 15 | 25.00 | 11 | 36.70 | 04 | 13.30 | |
| **2** | 01 | 1.70 | 01 | 3.30 | 00 | 0.00 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

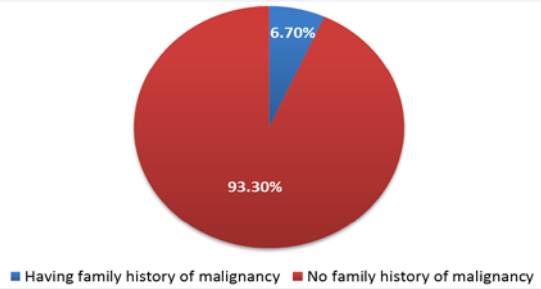


**Figure 9** Family history of malignancy in two groups; Arm-A and Arm-B.

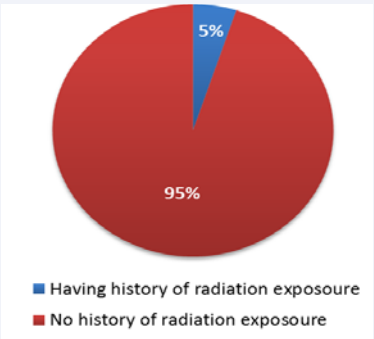


**Figure 10** Family history of malignancy in two groups; Arm-A and Arm-B.

ECOG performance status 1. In Arm-A 3.3% patients had ECOG performance status 2 (Table 12, 13 and Figure 15).

## ASSESSMENT OF TREATMENT RESPONSE

### Clinical response

After 4 cycle of neoadjuvant chemotherapy 05 patients (16.7%), in Arm-A and 08 patients (26.7%), in Arm-B had achieved clinical complete response. 18 patients (60%), in Arm-A and 19 patients (63.3%), in Arm-B had achieved clinical partial response. 04 patients (13.3%), in Arm-A and 02 patients (6.7%), in Arm-B had achieved progressive disease. 03 patients (10%), in Arm-A and 1 patient (3.3%), in Arm-B had achieved stable disease (p=0.496). Overall clinical response (CR+PR) between

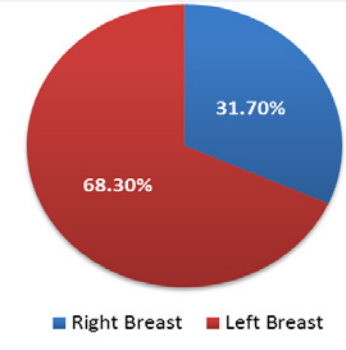


**Figure 11** Tumor distribution according to the site of breast in the study group.

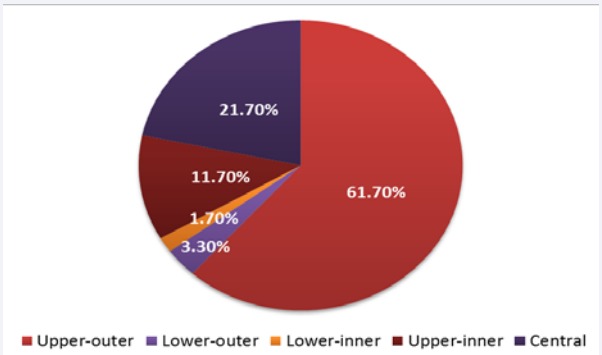


**Figure 12** Tumor distribution according to quadrant of breast in the study group.

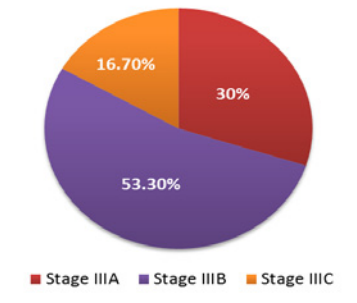


**Figure 13** AJCC staging of patients in the study group.

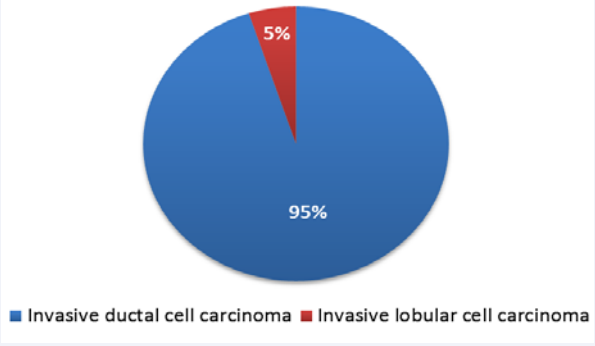


**Figure 14** Histopathology of patients in the study group.

Arm-A & Arm-B was 76.7% versus 90% (P= 0.526) (Table 14 and Figure 16).

## Pathological response after MRM

Among 30 patients in each group 07 patients in Arm-A and 03 patients in Arm-B did not undergo surgery after neoadjuvant chemotherapy owing to progressive disease stable disease and or inoperability. Modified radical mastectomy was done 23 patients in Arm A and 27 patients in Arm B. Each specimen was sent to pathologist to confirm pathological complete response. Pathological complete response was defined as absence of disease from breast and axilla on histopathology report. After neoadjuvant chemotherapy 02 (8.7 %), patients in Arm-A and 04 (14.9%) patients in Arm-B had achieved pathological complete response (p=0.506) (Table 15 and Figure 17).

## Clinical Response evaluation in different stages

After 4 cycle of chemotherapy complete response was achieved in 26.7% and partial response 33.3% for stage IIIA disease , complete response was 16.7% and partial response 70%.for stage IIIB disease and complete response was 0.0% and partial response 20% for stage IIIC disease (Table 16 and Figure 18).

## Assessment of toxicity

04 (13.3%), patients in Arm-A and 05 (16.6%), patients in Arm-B develop grade 1, 2 anemia and 01 (3.3%), patient in Arm-A and 02 (6.7%), patients develop grade 3 anemia (P=0.768). 04 (13.3%), patients in Arm-A & 09 (30%), patients in Arm-B develop grade 1, 2 neutropenia and 01 (3.3%), patient in Arm-A & 05 (16.7%), patients develop grade 3 neutropenia (0.037). 03 (10%) patients in Arm-A & 04 (13.3%), patients in Arm-B develop grade 1, 2 thrombocytopenia but no patient develop grade 3 thrombocytopenia (P=0.688). Incidence of nausea and vomiting was more in Arm-A and grade 3 nausea and vomiting was 6.7% Vs 0.0% in arm A and Arm-B (P= .255). 3.3% patients in Arm-A and 16.7% patients in Arm-B develop grade 1, 2 neuropathy but no patient in both arm develop grade 3 neuropathy (P=0.085). Total 20 (66.7%) patients in Arm-A & 25 (83.3%), patient in Arm-B develop alopecia. Among them grade 2 alopecia was 16.7% Vs 33.3% between Arm-A & Arm-B (0.189) [24] (Table 17 and Figure 19).

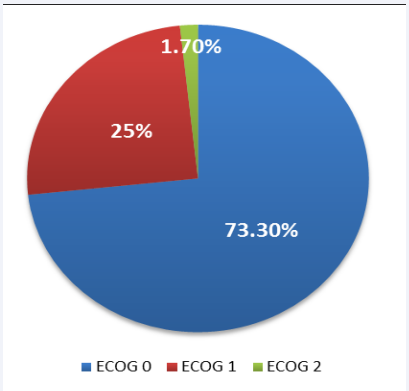


**Figure 15** ECOG performance status of patients in the study group.

**Table 13:** Baseline characteristics of the patients in two groups; Arm-A and Arm-B.

| Baseline Characteristics | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|
| | | N=30 | % | N=30 | % | |
| **Age (Years)** | Mean ± SD | 46.13 ± 8.74 | | 47.53 ± 7.26 | | 0.605 |
| | Median | 46.5 | | 46.5 | | |
| | Range | 30-65 | | 36-68 | | |
| **Religion** | Muslim | 28 | 93.3 | 30 | 100.0 | 0.150 |
| | Hindu | 02 | 6.70 | 00 | 00.0 | |
| **Residence** | Urban | 09 | 30.0 | 06 | 20.0 | 0.371 |
| | Rural | 21 | 70.0 | 24 | 80.0 | |
| **Education** | Illiterate | 18 | 60.0 | 24 | 80.0 | 0.145 |
| | Primary | 07 | 23.3 | 05 | 16.7 | |
| | Secondary | 05 | 16.7 | 01 | 3.30 | |
| **Socio-economic status** | Poor | 08 | 26.7 | 04 | 13.3 | 0.416 |
| | Lower-middle | 17 | 56.7 | 21 | 70.0 | |
| | Middle | 05 | 16.7 | 05 | 16.7 | |
| **Age of menarche** | < 12 years | 01 | 3.30 | 02 | 6.70 | 0.554 |
| | ≥ 12 years | 29 | 96.7 | 28 | 93.3 | |
| **Age of menopause** | < 55 years | 18 | 60.0 | 18 | 60.0 | 0.602 |
| | ≥ 55 years | 01 | 3.30 | 00 | 00.0 | |
| | Reproductive | 11 | 36.7 | 12 | 40.0 | |
| **Menopausal Status** | Pre-menopausal | 12 | 40.0 | 14 | 46.7 | 0.602 |
| | Post-menopausal | 18 | 60.0 | 16 | 53.3 | |
| **Parity** | Nullipara | 03 | 10.0 | 01 | 3.30 | 0.301 |
| | Multipara | 27 | 90.0 | 29 | 96.7 | |
| **History of lactation** | Yes | 22 | 73.3 | 26 | 86.7 | 0.196 |
| | No | 08 | 26.7 | 04 | 13.3 | |
| **Family history of malignancy** | Yes | 03 | 10.0 | 01 | 3.30 | 0.301 |
| | No | 27 | 90.0 | 29 | 96.7 | |
| **History of Radiotherapy exposure** | Yes | 01 | 3.30 | 02 | 6.70 | 0.553 |
| | No | 29 | 96.7 | 28 | 93.3 | |
| **Oral contraceptive pill** | Yes | 26 | 86.7 | 27 | 90.0 | 0.688 |
| | No | 04 | 13.3 | 03 | 10.0 | |
| **Obesity** | Obese | 02 | 6.70 | 04 | 13.3 | 0.389 |
| | Non-obese | 28 | 93.3 | 26 | 86.7 | |
| **Site of tumor** | Right breast | 12 | 40.0 | 07 | 23.3 | 0.165 |
| | Left breast | 18 | 60.0 | 23 | 76.7 | |
| **Location of tumor** | Upper-outer | 17 | 56.7 | 20 | 66.7 | 0.833 |
| | Lower-outer | 01 | 3.30 | 01 | 3.30 | |
| | Lower-inner | 01 | 3.30 | 00 | 0.00 | |
| | Upper-inner | 04 | 13.3 | 03 | 10.0 | |
| | Central | 07 | 23.3 | 06 | 20.0 | |
| **ECOG performance status** | 0 | 18 | 60.0 | 26 | 86.7 | 0.057 |
| | 1 | 11 | 36.7 | 04 | 13.3 | |
| | 2 | 01 | 3.30 | 00 | 0.00 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 14:** Clinical responses of patients in two groups; Arm-A and Arm-B.

| Clinical Responses | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|
| | N=30 | % | N=30 | % | |
| **CR (complete response)** | 05 | 16.7 | 08 | 26.7 | 0.496 |
| **PR (partial response)** | 18 | 60.0 | 19 | 63.3 | |
| **PD (progressive disease)** | 04 | 13.3 | 02 | 6.70 | |
| **SD (stable disease)** | 03 | 10.0 | 01 | 3.30 | |
| **Overall response (CR+PR)** | 23 | 76.7 | 27 | 90.0 | 0.526 |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 15:** Pathological responses of patients in two groups; Arm-A and Arm-B.

| Pethological responses | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|
| | N=30 | % | N=30 | % | |
| **pCR (complete response)** | 02 | 8.70 | 04 | 14.9 | 0.506 |
| **pCR (partial response)** | 21 | 91.3 | 23 | 85.1 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 16:** Response evaluation in different stages.

| Response | IIIA | | IIIB | | IIIC | | P-value |
|---|---|---|---|---|---|---|---|
| | N=18 (30.0%) | % | N=32 (53.3%) | % | N=10 (16.7%) | % | |
| CR (complete response) | 08 | 27.7 | 05 | 16.7 | 00 | 0.00 | 0.022 |
| PR (partial response) | 10 | 33.3 | 21 | 70.0 | 06 | 20.0 | |
| PD (progressive disease) | 00 | 0.00 | 03 | 10.0 | 03 | 10.0 | |
| SD (stable disease) | 00 | 0.00 | 03 | 10.0 | 01 | 3.30 | |

*Arm-A: Doxorubicin + Cyclophosphamide, Arm-B: Doxorubicin + Docetaxel

**Table 17:** Toxicity assessment of patients in two arms.

| Toxicity assessment | | Total | | Arm-A | | Arm-B | | P-value |
|---|---|---|---|---|---|---|---|---|
| | | N=60 | % | N=30 | % | N=30 | % | |
| **Anemia** | No | 48 | 80.0 | 25 | 83.4 | 23 | 76.7 | 0.768 |
| | Grade 1,2 | 09 | 15.0 | 04 | 13.3 | 05 | 16.6 | |
| | Grade 3 | 03 | 05.0 | 01 | 03.3 | 02 | 06.7 | |
| **Neutropenia** | No | 41 | 68.3 | 25 | 83.3 | 16 | 53.3 | 0.037 |
| | Grade 1,2 | 13 | 21.7 | 04 | 13.3 | 09 | 30.0 | |
| | Grade 3 | 06 | 10.0 | 01 | 03.3 | 05 | 16.7 | |
| **Thrombocytopenia** | No | 53 | 88.3 | 27 | 90.0 | 26 | 86.7 | 0.688 |
| | Grade 1,2 | 07 | 11.7 | 03 | 10.0 | 04 | 13.3 | |
| | Grade 3 | 00 | 00.0 | 00 | 00.0 | 00 | 00.0 | |
| **Nausea and Vomiting** | No | 48 | 80.0 | 22 | 73.3 | 26 | 86.7 | 0.255 |
| | Grade 1,2 | 10 | 16.7 | 06 | 20.0 | 04 | 13.3 | |
| | Grade 3 | 02 | 03.3 | 02 | 06.7 | 00 | 00.0 | |
| **Neuropathy** | No | 54 | 90.0 | 29 | 96.7 | 25 | 83.3 | 0.085 |
| | Grade 1,2 | 06 | 10.0 | 01 | 03.3 | 05 | 16.7 | |
| | Grade 3 | 00 | 00.0 | 00 | 00.0 | 00 | 00.0 | |
| **Alopecia** | No | 15 | 25.0 | 10 | 33.3 | 05 | 16.7 | 0.189 |
| | Grade 1 | 30 | 50.0 | 15 | 50.0 | 15 | 50.0 | |
| | Grade 2 | 15 | 25.0 | 05 | 16.7 | 10 | 33.3 | |

## DISCUSSIONS

Neoadjuvant chemotherapy (NAC), has become the standard treatment for inoperable cases such as locally advanced and inflammatory breast cancer. In these cases, the use of NAC enables local control after the acquirement of respectability by reducing primary tumor size. Recently NAC has become frequently used in patients with operable, early breast cancer. NAC increases the probability of breast-conserving surgery (BCS), inpatients requiring mastectomy at initial presentation. Furthermore, it permits the rapid assessment of tumor response to a particular chemotherapy regimen. This assessment sometimes provides an opportunity for additional chemotherapy with non-cross resistant drugs in patients who fail the first-line regimen [25].

Several prospective clinical trials have been conducted to demonstrate the benefit of NAC compared to adjuvant chemotherapy. Although no survival advantage of NAC over the adjuvant chemotherapy was apparent, NAC was associated with a higher rate of BCS, which was directly beneficial to patients because of reduced surgical morbidity and improve body image [26-28]. Arm-A consisting 30 patients treated by Adriamycin 60 mg/m$^2$ and Cyclophosphamide 600 mg/m$^2$ & Arm- B were treated with Adriamycin 50 mg/m$^2$ and Docetaxel 75 mg/m$^2$ (AD) 4 cycle 3 weeks interval. The patients who fulfill the inclusion and exclusion criteria were selected.

This study aimed to evaluate the response of neoadjuvant chemotherapy with Adriamycin and Cyclophosphamide versus Adriamycin and Docetaxel inpatient with locally advanced breast cancer. Data collection was done by history taking, clinical examination and from relevant investigations during admission and hospital stay. Findings were recorded in a data collection sheet. Data was presented in graphs or tabulated form. Every ethical issue was discussed with the patient regarding the study and informed written consent was obtained. They were also be informed of their right to refuse or withdraw from the study at any time and all data was handled confidentially. Result of the study, baseline characteristics were well balanced between the two arms mentioned in Table 17. The median age was 46.5 years (range: 30-65 years) in Arm-A and 46.5 years (range: 36-68 years), in Arm-B (P = 0.292) (Table 13).

In this study, after completing 4 cycles of neoadjuvant chemotherapy, 05 patients (16.7%) from Arm-A and 08 patients (26.7%). from Arm-B had achieved a clinical complete response. 18 patients (60%), in Arm-A and 19 patients (63.3%). in Arm-B had achieved a clinical partial response. 04 patients (13.3%), in Arm-A and 02 patients (6.7%). in Arm-B had achieved progressive disease. 03 patients (10%). in Arm-A and 1 patient (3.3%). in Arm-B had achieved stable disease (p=0.496). Overall clinical response between Arm-A & Arm-B was 76.7% versus 90% (P= 0.526), mentioned in Table 14 and Figure 16. Pathological complete response (CR), was found in 02 patients (8.7%), in Arm-A and 04 patients (14.9%), in Arm-B (P=0.506) [Table 15, Figure 17].

A study conducted by Amat et al. inoperable stage II–III breast cancer patients showed an overall clinical response rate was 68% and a pathological complete response rate was 19.8%. Six cycles of docetaxel were administered at 100 mg/m2 every 3 weeks before surgery and radiotherapy to 88 patients (50). In my study overall clinical response was 90% pathological complete response 14.9% in docetaxel containing Arm (Arm-B). This observation may be due to the combined use of docetaxel and doxorubicin in my study.

Evans et al compared six cycles of neoadjuvant AC (docetaxel plus doxorubicin) to AT (doxorubicin plus docetaxel), in women with locally advanced, inoperable, inflammatory, or large, operable primary breast cancer. Both the overall response rate was 88% versus 78% and the pathological response rate was 8% versus 12% were comparable for AT and AC, respectively (26). In my study overall clinical response of Arm-A (AC), and Arm-B (AT) was 76.7% versus 90% (P= 0.526). Pathological complete response (CR), was 8.7% in Arm-A (AC), and 14.9% in Arm-B (AT) (P=0.506). This finding is almost similar to the study of Evans et al. The response of my study was a little bit better than a study conducted by Gradishar WJ (1997), evaluate the response of 4 cycle docetaxel 3 weekly followed by surgery. Preliminary

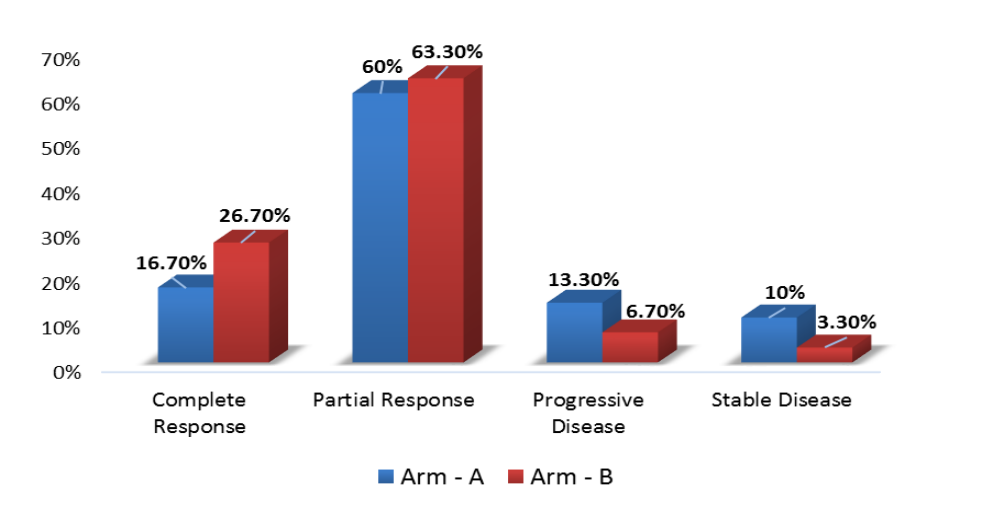


**Figure 16** Clinical responses in two groups; Arm-A and Arm-B

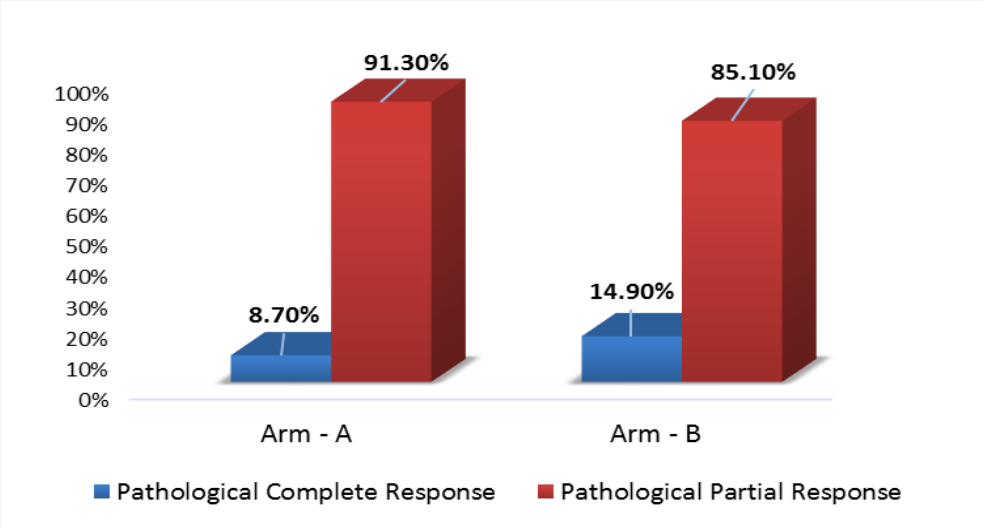


**Figure 17** Pathological responses in two groups; Arm-A and Arm-B.

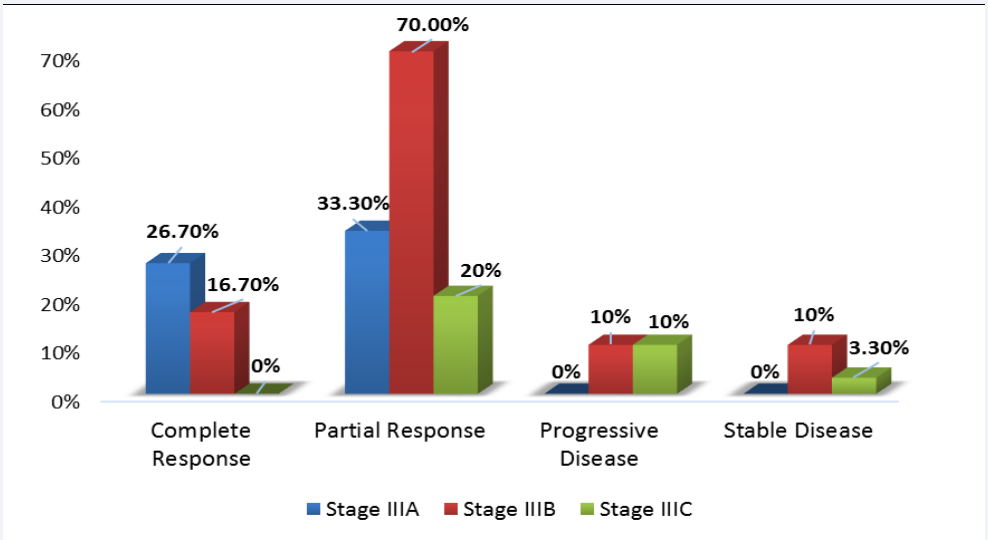


**Figure 18** Response evaluation in different stages.

result from 33 patients- complete responses were achieved in 6 patients (18%), partial response was achieved in 22 patients (67%), with the complete pathological response in one patient (24%). This result was may be due to the use of doxorubicin with docetaxel and in my study. Pathological complete response (CR), was found in 02 patients (8.7%), in Arm-A and 04 patients (14.9%), in Arm-B (P=0.506). This response was similar to a study by Nakatsukasa K et al., (2017). Fifty-two patients were enrolled in this study and 4 cycle chemotherapy with docetaxel 75 mg /m2 and cyclophosphamide 600 mg/m2 was given in every 3 weeks out of these 94.2% completed 4 cycles of TC. The overall pathological complete response rate was 16.3% [29].

In another phase-II study by von Minckwitz G et al., 42 patients with histologically confirmed primary breast cancer received doxorubicin 50 mg/m2 over 15 min and docetaxel 75 mg/m2 over 1 h every 2 weeks (24 patients) or every 3 weeks (18 patients) for four cycles. The overall response rate (ORR), as assessed by physical examination, was 93%, the remission rate as assessed by sonographic measurement was 67%. Of note, two patients (5%), had histologically confirmed complete response. The clinical response rate of my study is almost similar to this study [30].

Major toxicities (Table 17, Figure 19), were found in 04 patients (13.3%). in Arm-A and 05 patients (16.6%). in Arm-B developed grade 1, 2 anemia and 01 (3.3%). patients (3.3%). in Arm-A and 02 (6.7%). patients develop grade 3 anemia (P= 0.768). 04 patients (13.3%) in Arm-A and 09 patients (30%). in Arm-B develop grade 1, 2 neutropenia and 01 patient (3.3%). in Arm-A and 05 patients (16.6%) in Arm-B develop grade 3 neutropenia (P-0.037). 03 patients (10%), in Arm-A and 04 patients (13.3%). in Arm-B develop grade 1, 2 thrombocytopenia but no patient develop grade 3 thrombocytopenia (P=0.688).

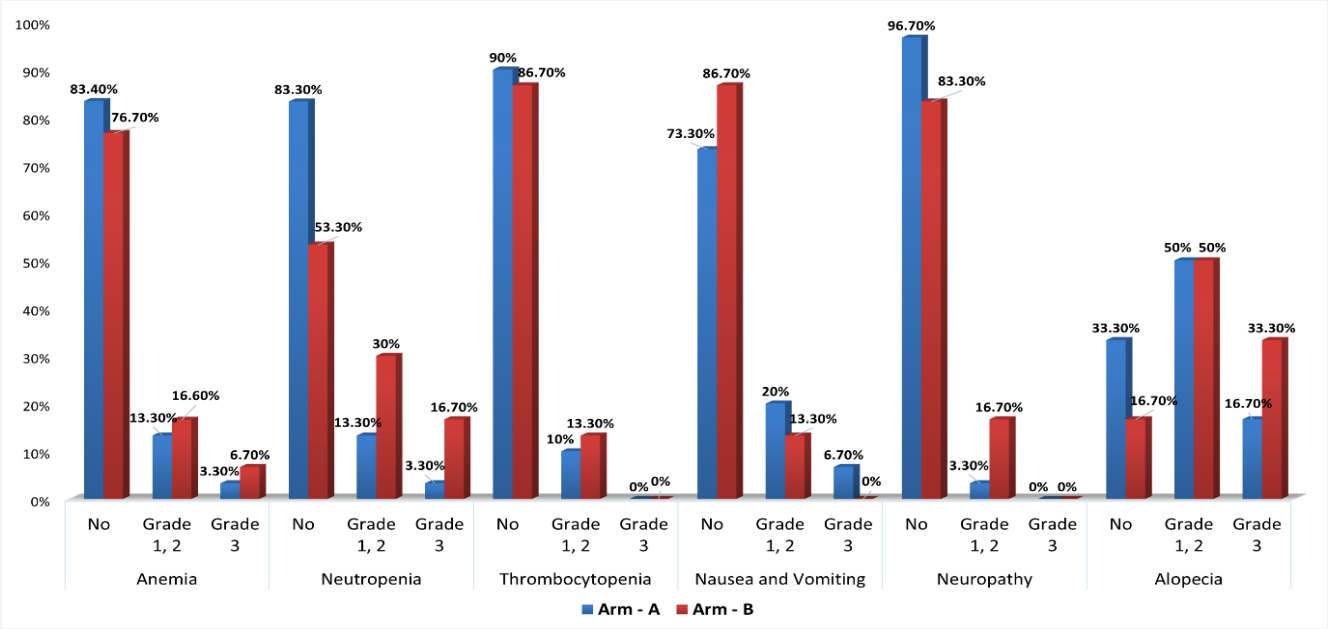


**Figure 19** Toxicity assessment of patients in two groups; Arm-A and Arm-B.

This was similar to a study conducted by Woo Sung Hong et al; that showed the response and toxicity of AD versus AC, where hematologic toxicities were more severe in the AD group. Most women in the AD group suffered from grade 3, 4 neutropenia (P<0.001) and neutropenic fever (P <0.001) [31].

Among non-hematologic toxicities, nausea and vomiting were more in Arm-A and grade 3 nausea and vomiting was 6.7% vs. 0.0% in Arm-A & Arm- B (P=0 .255). 3.3% of patients in Arm-A and 16.7% of patients in Arm-B develop grade 1, 2 neuropathy but no patient in both arms develop grade 3 neuropathy (P=0.085). Total 20 patients (66.7%) in Arm-A & 25 patients 83.3% in Arm-B develop alopecia. Among them, grade 2 alopecia was 16.7% vs. 33.3% between Arm-A & Arm-B (0.189).

From the above discussion it can be said, clinical & pathological response of neoadjuvant chemotherapy with a combination of Adriamycin and Docetaxel was better than the combination of Adriamycin and Cyclophosphamide in locally advanced Breast cancer but was not statistically significant. Though toxicities were more in Adriamycin and Docetaxel arm but managed by symptomatic treatment easily.

## LIMITATIONS OF THE STUDY

1. The period was not enough to conduct a qualitative study.
2. Sample size was a major limitation in getting accurate clinical outcomes.
3. All relevant investigations could not be done due to financial constrain.
4. The study was analyzed among the patients who attended Rajshahi medical college only. Therefore, the entire situation of the patients with locally advanced breast cancer in the country has not been provided.

## CONCLUSIONS

Neoadjuvant chemotherapy integrated into a multimodality program is the established treatment in LABC. Although efforts in this field of research are ongoing, Clinical management of LABC could be modified based on advances in our knowledge of cancer biology and genomic profiling to a highly effective individualized approach. As the result of the study, baseline characteristics were almost similar between the two arms. In Arm-A clinical complete response (CR), was achieved in 05 patients (16.7%), and clinical partial response (PR), was 18 patients (60%). In Arm-B clinical complete response (CR) was achieved in 08 patients (26.7%), and clinical partial response (PR), was 19 patients (63.3%). Overall clinical response (complete & partial) in Arm-A & Arm-B was 76.7% versus 90%. Pathological complete response (CR), was found in 02 patients (8.7%) in Arm-A and 04 patients (14.9%), in Arm-B. Both hematologic and especially toxicities in Arm-B were a little bit more than Arm-A specially grade 3 neutropenia, except the incidence of nausea and vomiting was more in Arm-A.

So it can be said that the overall clinical pathological response was found greater in Arm-B but was not statistically significant. Both hematologic and nonhematologic toxicities were a little bit more in Arm-B than Arm-A especially grade 3 neutropenia, except the incidence of nausea and vomiting was more in Arm-A but those were acceptable and manageable.

## RECOMMENDATIONS

Given the findings of the present study and discussion thereof, the following recommendations are laid down to reach a rational decision:

1. As the present study was done on a relatively small sample, a large-scale clinical-pathological to be conducted to make the findings of the study generalizable to the nonhematologicreference population.

2. Further studies are recommended aimed at increasing the number of pathologic complete responses in patients with LABC may require the use of docetaxel in combination with another active agent.

3. Patients should be observed for overall survival.

## ACKNOWLEDGEMENT

This prospective study was performed at the Department of Radiotherapy, Rajshahi Medical College Hospital, Rajshahi, Bangladesh.

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