



Original Article

OUTCOME OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER: A TERTIARY CARE CENTER EXPERIENCE.

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Abstract

Background: Breast cancer is the most common cancer of Bangladeshi women. Almost all present with palpable lump and 40% of them are with locally advanced breast cancer. Neoadjuvant chemotherapy is the standard choice of treatment for the patients.

Objective: To observe the clinical and pathological response of locally advanced breast cancer after four cycles of chemotherapy and surgery.

Methods: This prospective study was carried over the newly diagnosed locally advanced breast cancer (LABC) patients from January 2010 to December 2014. Before going to neoadjuvant chemotherapy each patient was evaluated clinically, radiologically and with other relevant investigations. The size of primary tumor and axillary node was measured and recorded. Chemotherapy schedule with Cyclophosphamide 600mg/m² and Doxorubicin 60mg/m² (AC) and compared with the previous record. After 3-4 weeks of completion of chemotherapy, the patients was prescribed and carried out three weekly for four cycles.

Primary tumor size and axillary nodal size was measured who were undergone mastectomy and axillary dissection. Histopathology was done to see then the pathological response of primary tumor and axillary node. Other biological marker such as estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth receptor (HER-2) was done. After completion of study the data was compiled and analyzed.

Results: Total 220 cases of LABC were enrolled in this study. After four cycles of chemotherapy with AC, 194 patients (88%) responded clinically, 29 patients (13%) showed complete clinical response (cCr) and 165 patients (75%) partial response (pCr). Surgical specimen showed complete pathological response (cPr) in 22 patients (10%).

Conclusion: Neoadjuvant chemotherapy with AC is the standard chemotherapy schedule for locally advanced breast cancer and radical surgery was possible in 75% of the patients.

Keywords: Breast cancer, Clinical response, Neoadjuvant chemotherapy.

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Introduction

Breast cancer is the number one cancer of Bangladeshi women comprising of 24% of all female cancer¹. Forty percent of them present with locally advanced breast cancer (LABC)². According to the cancer incidence statistics of Bangladesh 14,836 cases are diagnosed as breast cancer every year.³

Among the breast cancer, LABC constitutes a major clinical challenge, because the vast majority of patients with LABC experience disease relapse and eventually die, despite aggressive multimodality treatment.⁴

Locally advanced breast cancer (LABC) refers to large breast tumors (> 5 cm) associated with either skin or chest wall involvement or with fixed axillary lymph nodes or with involvement of the ipsilateral internal mammary or supraclavicular nodes.⁵

In the TNM staging classification, LABC is represented by stage IIIA (T0N2, T1N2, T2N2, T3N1, T3N2), stage IIIB (T4N0, T4N1, T4N2) and stage IIIC disease (any T, N3).

Historically, patients with LABC were treated with radical surgery and/or radiation therapy (RT). However the management of LABC was dramatically transformed over the past two decades⁶. Primary chemotherapy (CT) became an integral part of the multidisciplinary management of LABC, probably prolonging the disease-free survival (DFS) and overall survival (OS), and making breast conserving surgery a possibility for these patients⁷.

This study observes the clinicopathological response pattern to neoadjuvant chemotherapy in patients with locally advanced breast cancer.

Materials and Methods

This study was conducted in National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka from January 2010 to December 2014. A total of two hundred forty five patients with locally advanced breast cancer (Stage IIIA, IIIB, and IIIC) were initially enrolled as study population. The patients were treated with four cycle of neoadjuvant chemotherapy. Twenty five patients were excluded since they were at the stage of metastatic disease at the time of diagnosis or failed to receive four cycle of chemotherapy. Therefore, 220 patients were finally eligible for this study. Patients more than 70 years, patients with distant metastasis, vital functions severely compromised (ASA grade III & IV) and patient who were did not receive NACT as per schedule were excluded from the study.

The neoadjuvant chemotherapy schedules were 4 cycles which was repeated 3 weekly. The drugs usually used in our center as neoadjuvant for LABC are 4 cycle AC (Adriamycin, Cyclophosphamide) with 3 weekly interval followed by Surgery, then 4 cycle Paclitaxel as adjuvant therapy. The dosages of Doxorubicin was 60 mg/m²IV in day¹ and Cyclophosphamide 600 mg/m²IV in day¹. Then Paclitaxel 175 mg/m²IV (3 h infusion) in day¹.

Before going to neoadjuvant chemotherapy each patient was evaluated clinically, radiologically; routine blood, biochemical test for liver function, kidney function and cardiac function test by ECG and Echocardiogram. Diagnosis was confirmed by FNAC and Core cut biopsy.

Baseline patient and tumor characteristics were recorded including age, tumor size, nodal stage, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status and Her² status. Clinical response was assessed after first two cycle of chemotherapy and after completion of four cycles. Surgery was done 3- 4 weeks after last cycle of chemotherapy.

Responses were recorded according to Union for International Cancer control (UICC) criteria.

A complete clinical response (cCR): original mass became impalpable.

A partial response (cPR): represented a 50% or greater reduction in bi-dimensional tumor measurements.

Progressive disease (cPD): was recorded if bi-dimensional measurements increased by 20% or more.

Stable disease (cSD): rest of the tumors belong to this group.

Pathological response was assessed at definitive surgery on completion of neoadjuvant chemotherapy.

A pathological complete response (pCR): there was no evidence of residual tumor on histological examination of the surgical specimen.

Results

The median age of the patients at the time of diagnosis was 36(± 5.9) years (range: 25–70). About 55.91% of the patients (n=123) were living in rural areas while 44.09% (n=97) came from urban areas. 152 (69.09%) patients were pre-menopausal while 68 (30.91%) were post-menopausal. The mean tumor diameter measured clinically before neoadjuvant chemotherapy was 7.9 (±1.3) cm (range 4–18 cm). Axillary nodal status was N0 in 11 patients (5%),

N1 in 49 patients (22.27%), N2 in 143 patients (65%) and N3 in 17 patients (7.73%). Thirty five patients (15.91%) had Stage IIIa disease, 176 patients (80%) had Stage IIIb disease and 9 patients (4.09%) had Stage IIIc disease. According to histological classification 177 patients (80.45%) were classified as invasive ductal carcinoma (IDC), 30 as invasive lobular carcinoma (ILC) (13.64%) and 13 as other types (5.91%), including mixed invasive patterns. Malignancy grading was also done: 9 (4.09%) were grade I, 44 (20%) were grade II and 167 (75.91%) were grade III.

Estrogen receptors showed positivity in 152 patients (69.09%), and progesterone receptors in 148 patients (58.18%). Among them her2 receptors were found overexpressed in 132 cases (67.27%) The mean tumor diameter measured in the surgical sample after neoadjuvant chemotherapy was 2.8 cm (range 0–12 cm). Receiving neoadjuvant chemotherapy, only 208 patients underwent modified radical mastectomy. Twenty two patients (10.58%) attained complete pathological response (pCR), 125 patients (60.09%) demonstrated partial response, while the rest 61 patients (29.32%) showed pathological stable disease. There was no significant difference in the response rates based on the stage of the disease (p=

>0.05)

Table-II: Baseline patient and tumour characteristics and the distribution of the characteristics by clinical response after four cycles of chemotherapy, 2014 (N= 220).

Table-I
Neoadjuvant chemotherapy response

Clinical Response of	Tumor to NACT (N=220)
Complete response	29 (13.18%)
Partial Response	165 (75%)
Stable diseases	14(6.36%)
Progressive diseases	12 (5.45%)
Clinical Response of Axillary Lymph nodes to NACT (N=220)	
Complete response	50 (22.73%)
Incomplete or no response	159(72.27%)
Pathological Response of Tumor to NACT (N=208)	
Complete pathological response	22(10.58%)
Partial response	125(60.09%)
Stable disease	61(29.32%)

Table-II

Parameter	Total population N (%)	Responders after Four cycles N (%) (CR+PR)	Non - responders after Four cycles N (%) (SD+PD)	
Age				
Median	36	38	45	
Tumor stage				
III a	35(15.91%)	30 (85.72%)	5(14.28%)	
III b	176 (80%)	160 (90.91 %)	16 (9.09%)	<0.00001 ^S
III c	9 (4.09 %)	3 (33.33%)	6(66.67 %)	
Nodal stage				
N0	11(5%)	11 (100%)	0	
N1	49(22.27%)	45 (91.83%)	4 (8.17%)	<0.00001 ^S
N2	143 (65%)	136 (95.10%)	7 (4.89%)	
N3	17 (7.73%)	1 (5.88%)	16 (94.12%)	
Tumor grade				
G1	9 (4.09%)	9 (100%)	0	
G2	44 (20%)	35 (79.55%)	9 (20.45%)	0.114 ^{NS}
G3	167 (75.91%)	149 (89.22%)	18 (10.79%)	
Estrogen Receptor Status				
ER+ve	152(69.09%)	140 (92.10 %)	12 (7.89%)	0.851 ^{NS}
ER -ve	68 (30.90%)	62(91.17%)	6 (8.82%)	

Table-III:
Showing correlation between the histological type of tumors and clinical response (N= 220).

	Histological type	Clinical response				Total
		complete	Partial	Stable disease	progressive disease	
	Ductal	28	145	4	0	177
	Lobular	1	7	10	12	30
	Medullary	0	9	0	0	9
	Tubular	0	4	0	0	4
	Total	29	165	14	12	220

p value was found <0.00001 which was statistically significant.
Chi-square analysis was done

Discussion

Neoadjuvant chemotherapy in case of locally advanced breast cancer has been found effective in our study. The clinical response of LABC after using NACT was grossly seen in 194 patients which were 88.18%. Our results were consistent with the National Surgical Adjuvant Breast and Bowel Project B-18, where objective response was seen in 80% of 747 patients⁸.

There still might be residual tumor histologically in patients who achieved complete clinical response⁹. In our study, 29 patients (13.18%) showed complete clinical response, 22 of them showed complete pathological response, and the other 7 had residual disease histologically.

Proper assessment of the tumor to see the response after NACT is very helpful for subsequent planning of surgery¹⁰. Measurement of tumor in its maximum diameter, mammography or ultrasonography depending upon the age of the patients; may provide further information regarding tumor size after NACT. Whether Magnetic Resonance Imaging (MRI) can provide a better correlation with the pathological size remains uncertain, but early results appear promising. Clouth et al. have shown that the reduction in tumor enhancement on an MRI scan correlates with the extent of the disease as seen at the pathological examination¹¹. But none of our patients underwent MRI for this assessment after NACT as the imaging technique is expensive in our perspective. Accurate estimation of the tumor size after neoadjuvant chemotherapy is crucial for deciding the type and extent of operation to be performed.

One sixty seven (75.91%) of patients who developed clinical response had Grade 3 at the time of diagnosis which are matched with some studies where it was found that the better responses could be achieved in rapidly proliferating tumors with a higher grade¹².

Redkar et al. reported 43.9% estrogen receptor positivity in 1992. Western studies reported ER

positivity in 60 – 80% of the patients. The differences in ER status in Indian and Caucasian patients could be due to lower average age at presentation or racial differences.¹³

In concordance with previous studies, we have observed the NACT responders were mostly estrogen receptors positive group. So, it was observed in this study that a higher objective response rate (cCR+ pCR) in patients who are ER-positive as compared with ER-negative patients (p=0.886). But interestingly, the results were not found statistically significant. All the patients who attained pCR are ER-positive. This finding seems to contradict the finding from Danishad et al. who identified that ER negative tumors respond better for chemotherapy¹⁴.

Conclusion: Patients with LABC admitted into our center underwent treatment with NACT have shown excellent response through downgrading the tumor size, axillary lymph nodes and pathological response. So, we may conclude here that the conventional neoadjuvant chemotherapy especially the AC regimen is effective in our perspective.

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