

Original Article

Outcome of neoadjuvant chemotherapy in locally advanced breast cancer: A tertiary care center experience

Rahman MS¹, Akhter PS², Hasanuzzaman M³, Rahman J⁴, Bhattacharjee A⁵, Russell M⁶, Hossen N⁷, Huq AU⁸

Abstract

Breast cancer is the most common cancer among 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. This prospective study was done involving 220 newly diagnosed locally advanced breast cancer (LABC) patients from January 2010 to December 2014 in the National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka to observe the clinical and pathological response of locally advanced breast cancer after four cycles of chemotherapy and surgery. Chemotherapy schedule with Cyclophosphamide 600mg/m² and Doxorubicine 60mg/m² (AC) was prescribed and carried out three weekly for four cycles. Primary tumor size and axillary nodal size was measured and compared with the previous record. After three weeks of chemotherapy the patients

undergone mastectomy and axillary dissection. Histopathology was done to see 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) were done. 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%). 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.

Introduction

Breast cancer is the number one cancer of Bangladeshi women comprising of 24% of all female cancer.¹ 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 cancers, 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) is a common clinical presentation of mammary carcinoma in developing countries (30% to 60%). In spite of systematic screening, mammography programs and extensive public education campaigns for early detection of breast cancer in the USA, the incidence of LABC is still approximately 10%-20%. LABC is a heterogeneous group of tumors of varying clinical presentations and biological behavior. The common features are the presence of a large primary tumor, and/or extensive regional lymph node involvement, and the absence of any evidence of distant metastases. Some patients have a rapid neoplastic evolution, whereas others present with a long history of tumor growth.

Locally advanced breast cancer (LABC) refers to large breast tumors (>5 cm) associated with either skin or chest wall

1. Dr Md Setabur Rahman, Resident Surgeon & Assistant Professor, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka.
2. Professor Dr Parveen Shahida Akhter, Professor & Head, Department of Medical Oncology, NICRH, Mohakhali, Dhaka.
3. Dr Md Hasanuzzaman, Assistant Professor, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka.
4. Dr Jillur Rahman, Junior Consultant, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka.
5. Dr Avisak Bhattacharjee, Assistant Registrar, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka.
6. Dr Md Russell, Department of Surgical Oncology, BSMMU, Dhaka.
7. Dr Nabir Hossen, Department of Surgical Oncology, NICRH, Mohakhali, Dhaka.
8. Dr Ashraf Ul Huq, Associate Professor, Department of Surgery, Kushtia Medical College, Kushtia.

*For correspondence

involvement or with fixed axillary lymph nodes or with involvement of the ipsilateral internal mammary or supraclavicular nodes.⁵ However, most experts consider patients with stage IIB–IIIA (T_3N_0 , T_3N_1) as 'large operable' breast cancers, in contrast to truly inoperable cases with inflammatory and/or extensive skin involvement, fixed or very bulky axillary nodal disease and/or supraclavicular or internal mammary nodal involvement.

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 decades.⁶⁻¹⁰ 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 patients.¹¹

Primary neoadjuvant chemotherapy followed by surgery and radiotherapy, and postoperative systemic chemotherapy is now an accepted strategy. More than 70% of patients achieve an objective response (including pathological complete remission in 10%-25% of cases), and many patients experience down staging through primary chemotherapy. Breast conservation is possible in 10%-40% of patients with locally advanced breast cancer; almost all patients initially are rendered disease-free, and long-term local control is achieved in over 70% of these patients.¹²

The use of neoadjuvant chemotherapy thus replaces mastectomy by breast conservative surgery. The Milan Group achieved an 80% response rate with 15% of patients attaining complete clinical response using a combination of doxorubicin and vincristine.¹² Tumor shrinkage by the neoadjuvant chemotherapy can be easily monitored clinically both by physicians and patients. For physicians, continuation of treatment is reasonably determined based on efficacy. For patients, compliance with the scheduled courses of chemotherapy is increased because they, themselves, experience the efficacy, which helps them mentally to overcome the unpleasant adverse effects.¹³ The pathological response to the neoadjuvant chemotherapy provides reliable prognostic information.^{13,14}

The first prospective study for neoadjuvant chemotherapy in locally advanced, inoperable breast cancer is dated in 1973, by the European institute of Oncology and the primary purpose was to downstage the primary tumor in order to achieve surgical resection.¹⁵ Many other trials followed in the past two decades studying the role of induction chemotherapy. Currently NACT followed by surgery, is the treatment of choice for patients with IBC or LABC.^{15,16,17}

Methods

This prospective study was done involving 220 newly diagnosed locally advanced breast cancer (LABC) patients from January 2010 to December 2014 in the National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka to observe the clinical and pathological response of locally advanced breast cancer after four cycles of chemotherapy and surgery. In the TNM staging classification, LABC is represented by stage IIIA (T_0N_2 , T_1N_2 , T_2N_2 , T_3N_1 , T_3N_2), stage IIIB (T_4N_0 , T_4N_1 , T_4N_2) and stage IIIC disease (any T, N_3). Old age (>70 years), distant metastasis, vital functions severely compromised (ASA grade III & IV) & patients who did not receive NACT as per schedule were excluded.

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 4 cycle Paclitaxel after completion of AC schedule. The dosages of Doxorubicin was 60 mg/m² iv in day₁ and Cyclophosphamide 600 mg/m² iv in day₁. Then Paclitaxel 175 mg/m² iv (3 h infusion) in day 1. Before going to neoadjuvant chemotherapy each patient was evaluated clinically, radiologically; by routine blood test, 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 and progesterone receptor (PR) status. Clinical response was assessed after first two cycle of chemotherapy and after completion of four cycles. Surgery was done 4-6 weeks after last cycle of chemotherapy.

Responses were recorded according to Union for International Cancer control (UICC) criteria. A complete clinical response (cCR) was considered if original mass became impalpable, partial response (cPR) if there was 50% or greater reduction in bi-dimensional tumor measurements and progressive disease (cPD) if bi-dimensional measurements increased by 20% or more. Pathological response was assessed at definitive surgery on completion of neoadjuvant chemotherapy. A pathological complete response (pCR) was considered if there was no evidence of residual tumor on histological examination of the surgical specimen. The pCR rate was compared by response category after four cycles of chemotherapy. The observations and results were stated with 95% confidence interval. An appropriate method for small samples was applied to the

percentages and p values were determined by chi square test using SPSS version 16.1. Informed written consent was obtained from each patient.

Results

The results were prepared on two hundred and twenty patients. 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. In terms of menopausal status, 152 (69.09%) patients were pre-menopausal while 68 (30.91%) were post-menopausal.

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).

Twenty nine patients (13.18%) had a clinical complete response (cCR), 165 had a partial response (75%), 14 had stable disease (6.36%) and 12 had progressive disease (5.45%). (Table-I)

Table II shows that clinical examination of the axilla revealed a complete response in 50 (22.73%) and an incomplete or no response in 159 (72.27%) and rest 11 patients (5%) were graded before as N0. (Table-II)

Basic correlation between histological type of tumors and clinical response showed that 173 (78.63%) ductal carcinoma patients showed good response to therapy whereas all progression of tumor observed in total 12(5.45%) patients were lobular type of carcinoma. (Table-IV)

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

		Clinical response				Total
		Complete	Partial	Stable disease	Progressive disease	
Histological type	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	

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%)

Table- II: Clinical Response of Axillary Lymph nodes to NACT (N=220).

Complete response	50 (22.73%)
Incomplete or no response	159(72.27%)

Table III shows that the patients 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 III: Pathological Response of Tumor to NACT (N=208).

Complete pathological response	22(10.58%)
Partial response	125(60.09%)
Stable disease	61(29.32%)

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. (Table-V)

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

Parameter	Total population N (%)	Responders after four cycles N (%) (CR+PR)	Non-responders after Four cycles N (%) (SD+PD)	P value
		<u>Age</u>		
Median	36	38	45	
		<u>Tumor stage</u>		
III a	35(15.91%)	30 (85.72%)	5(14.28%)	<0.00001 ^S
III b	176 (80%)	160 (90.91 %)	16 (9.09%)	
III c	9 (4.09 %)	3 (33.33%)	6(66.67 %)	
		<u>Nodal stage</u>		
N ₀	11(5%)	11 (100%)	0	<0.00001 ^S
N ₁	49(22.27%)	45 (91.83%)	4 (8.17%)	
N ₂	143 (65%)	136 (95.10%)	7 (4.89%)	
N ₃	17 (7.73%)	1 (5.88%)	16 (94.12%)	
		<u>Tumor grade</u>		
G1	9 (4.09%)	9 (100%)	0	0.114 ^{NS}
G2	44 (20%)	35 (79.55%)	9 (20.45%)	
G3	167 (75.91%)	149 (89.22%)	18 (10.79%)	
		<u>Estrogen Receptor Status</u>		
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%)	

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 patients.¹⁸

There still might be residual tumor histologically in patients who achieved complete clinical response¹⁹⁻²⁰. 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 surgery.¹⁷ 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.¹³ Whether Magnetic Resonance Imaging (MRI) can provide a better correlation with the pathological size remains uncertain, but early results appear promising.^{21,22} 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 examination.²³ But none of our patients underwent MRI for this assessment after NACT as the imaging technique is expensive in our perspective.

Breast sparing radiotherapy for patients who achieved complete clinical response has been proposed by several groups.²⁴ Accurate estimation of the tumor size after neoadjuvant chemotherapy is crucial for deciding the type and extent of operation to be performed.^{24,25,26}

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 grade.²⁷⁻²⁹

One fifty two patients (69.09%) were found estrogen receptor positive tumor which are very near to results reported by Raina et al. that was approximately 50.5% and studied upon the Indian patients.²⁶

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.²⁷

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 chemotherapy.³⁰ Brifford et al reported a highly significant clinical response in patients with invasive ductal carcinoma (IDC).²⁷ Mathieu et al. and Newman et al. reported that invasive lobular carcinoma (ILC) is an independent predictor of ineligibility for BCS after neoadjuvant chemotherapy compared with IDC.³¹ Although all these studies show that ILC patients are less likely to achieve BCS after neoadjuvant chemotherapy, they do not address whether the use of neoadjuvant chemotherapy improves the baseline BCS rates for ILC patients.³² In our study, one hundred and seventy three patients out of 177 patients diagnosed as invasive ductal carcinoma achieved clinical response (complete or partial) to NACT. A complete clinical response was seen in only one patient with ILC (3.3%), which is also consistent with other

ILC series in the literature.³² No lobular carcinomas had a complete pathological response to NACT in this study. These findings suggest that histological type in breast carcinoma may play an important role in predicting the degree of tissue response and pathologic response to NACT.

The patients of 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 specially the AC regimen is effective in our perspective.

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