Original Article

Pathological Complete Response Of Neo-adjuvant Chemotherapy Doxorubicin Plus Cyclophosphamide In Patients With Locally Advanced Breast Cancerat Jinnah Hospital Lahore

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Objective: Objective of the study was to determine the frequency of pathological complete response (pCR) with neo adjuvant doxorubicin and cyclophosphamide in locally advanced breast cancer.

Material and Methods: This prospective study was conducted in 92 patients of locally advanced breast cancer. Pathological response was evaluated on Modified radical mastectomy samples that was performed after 4 cycles of neo adjuvant doxorubicin and cyclophosphamide.

Results: The mean age of the study population was 45.63 year.Among these the 49.63(38%) had stage T3 lesion , 53(57.6) had T4 and only one patient (1.1%) with T1 at presentation. 97.8 (92%) patients were with grade 2 and grade 3.Post anthracycline based NACT 8.7 %(8) had pathological complete response, 54.3 %(50) had partial response, 37%(34) had stable disease. Overall 63% (58) patients had responded to this treatment.

Conclusion: It is concluded from the this study that Anthracycline based NACT is a good option for these patients of developing countries. Though the results are not comparable with developed countries but better results can be achieved if these patients present at early stage or we should use taxanes based NACT to improve the response.

Key words: B

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in female with estimated new cases of 229, 060 in United States in 2012.[1] About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries.[2,3] Approximately one in every nine of Pakistani women will suffer from breast cancer at some point in their lives.[4] Breast cancer incidence in Pakistan is the highest reported in any South-Central Asian country. It accounts for 38.5% of all female cancers and about half (43.7%) of all breast cancers are locally advanced.[5] In women diagnosed with LABC in Pakistan, patients with lower socioeconomic status (SES) have larger, more aggressive tumors with worsened survival outcomes.[6]

Locally advanced breast cancer (LABC) includes non-metastatic tumours more than 5cm in size or involving skin/chest wall. It may be associated with fixed axillary lymph nodes, ipsilateral supraclavicular, infraclavicular or internal mammary nodal involvement.[7]

The pCR is defined as absence of the invasive carcinoma on the pathological examination of the breast tissue and axillary lymph nodes.[21] Complete response to chemotherapy is associated with longer disease-free survival (DFS), overall survival and surrogate marker of long term prognosis when compared to non-responders.[9,22,23]

The established data showsClinical Complete Response (CR) in the range of 7% to 65% and pathological CR (pCR) in 4% to 29%.[8-14]The variation in pathological response is linked with receptors status, grade, tumor characteristics.[15-20]

Material And Methods

It was descriptive case series, conducted in Department Of Oncology Jinnah Hospital Lahore. After non probability purposive sampling total 92 cases over the period of one year were enrolled in the study. The sample size was calculated with 95% confidence level, 10% margin of error and taking expected percentage of pathologic complete response i.e: 13% of neo-adjuvant chemotherapy with Doxorubicin plus Cyclophosphamide in locally advanced Breast Cancer.

Women between 20-70 years of age with locally advanced breast cancer, who were having no co morbidities or previous history of treatment were included. They were given 4 cycles of neo adjuvant

chemotherapy doxorubicin 60mg/m2 and cyclophosphosphamide 600mg/m2 q 3weekly.MRM with axillary clearance was done 6 weeks after the last cycle of chemotherapy.

Data collected on proforma was entered into the Statistical Package of Social Sciences (SPSS), version 10 software. Quantitative variables like age were presented as mean and standard deviation. Qualitative variables like gender, disease response (complete, partial, or no response) were taken as frequency and percentage. As it was a descriptive study so no test of significance was required

Results

In 8 resected specimens, no viable residual tumor cells could be identified so the tumor was staged pathologic (p) T0N0 and pathological complete response pCR was concluded as 8.7 % **(Table 4)**. The overall response was 63% (58) (complete and partial) while 37% (34) patients did not respond to treatment

Patients were categorized in pre and post menopausal groups (age <45yr and >45yr).

The overall response in pre menopausal was 40.1% (38) and in post menopausal it was 22.7% (21.Pre-treatment staging of the tumor showed that majority of the patients were having T4 lesion 57.6% (53) and N 2 52.2% (48) .

69.3% patients were receptor positive and 49.9% (46) patients showed pathological response (complete/partial).32.2%(28) patients were receptor negative.12.9% (12)patients with receptor negative status showed pathological response to treatment. Triple negative patients were 42.3% (39).22.7% (21) of them showed complete /partial pathological response while 19.5% (18) patient did not show any

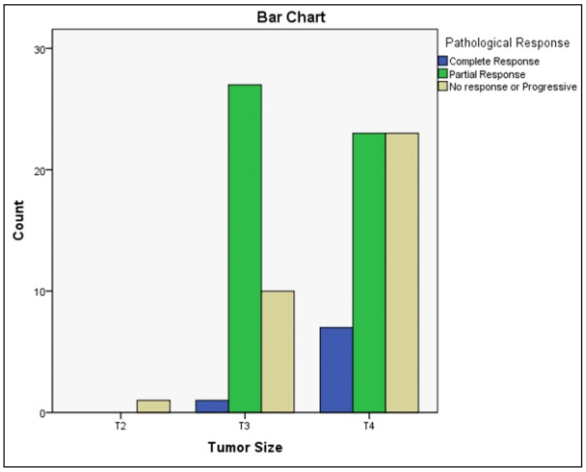

Fig-1: Pathological responses in various tumor sizes.

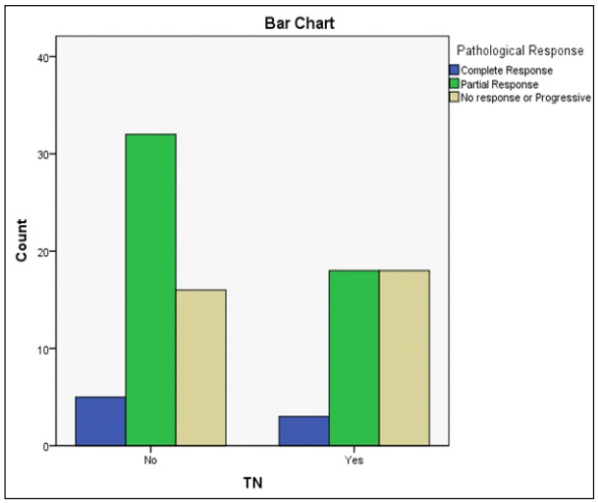

Fig-2: Pathological Response in triple negative breast cancer.

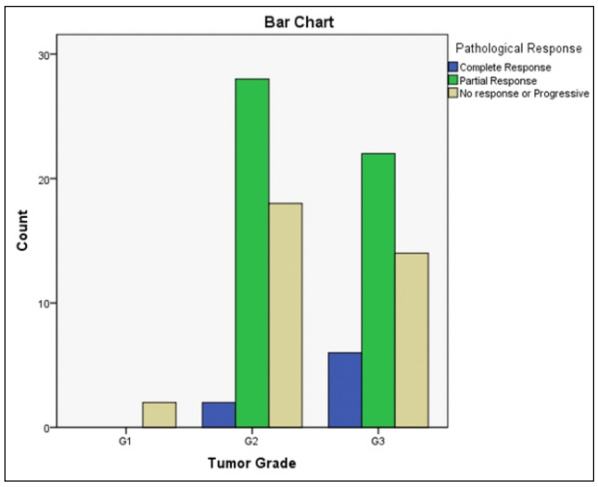

Fig-3: Pathological Responses in Various Grades.

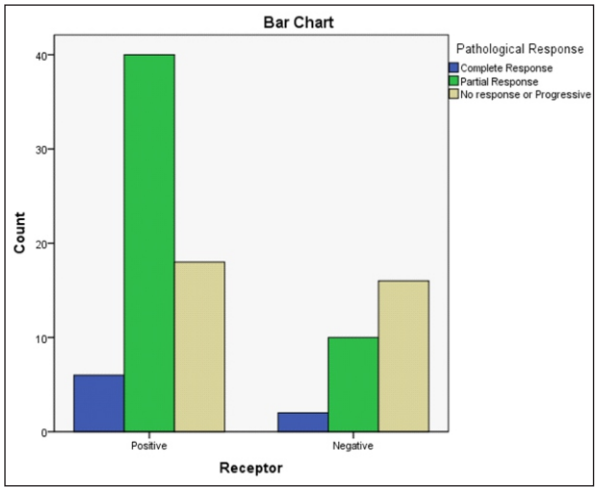

Fig-4: Pathological responses in receptor positive and negative tumors.

63% (58) patients with N2/N3 showed response(complete or partial) (p= 0.3)to the treatment. There was only one patient with N1. **(Table 1)**

Most of the patients who responded to treatment were having grade 2 and grade 3 tumor.8.6 % (8) patients showed pathological complete response to treatment were having grade 2/3 tumor.54.3% (50) patients showed partial response who were with grade 2/3 tumor.**(graph 3)**

Table-1: Response rates according to demographic and baseline tumor characteristics.

Response		pCR[a]	pCR[b]	D
Age (Median)	<45 years (n=49)	3.2% (3)	36.9% (34)	12% 12
	>45 years (n=43)	5.4% (5)	17.3% (16)	23.9% (22)
Receptor Status	Receptor status +ve	6.5% (6)	343.4% (40)	19.5% (18)
	Receptor status -ve	2.1% (2)	10.8% (10)	17.3% (16)
	TND[e] (n=39)	3.2% (3)	19.5% (18)	19.5% (18)
Tumor Size	T3 (N=38)	1.08% (1)	29.3% (27)	10.8% (10)
	T4 (N-63)	7.6% (7)	25% (23)	25% (23)
Nodal status	N0 (1)	0	0	1.08%(1)
	N1 (n=41)	3.2% (3)	28.2% (26)	44.5% (41)
	N2 (n=48)	5.4% (5)	26% (24)	52% (48)
	N3 (n=2)	0	0	2.1% (2)
Grade	G1	0	0	2.1% (2)
	G2	21.% (2)	30.4% (8)	19.5% (18)
	G3	6.5% (6)	23.9% (22)	15.2% (14)

A. PCR Pathological complete response B. PCR Pathological Partial response C. PD Progressive disease D. PS status disease E. TND stable disease

Discussion

LABC accounts for 40-60% of all breast cancers in developing countries.[4,5] Pakistan has highest prevalence of breast cancer in Asia especially in young women.[2-5] 10 years data of local cancer hospital in Karachi showed that 58 % patients present with locally advanced breast cancer.[12]

In India, between 50% and 70% of patients have locally advanced or metastatic disease at diagnosis .This proportion is high compared with developed countries, where 38% of European and 30% of US breast cancer cases were reported to be either locally advanced at diagnosis or lymph-node positive. 50% of patients with breast cancer in Egypt are reported to be diagnosed with invasive tumors that are larger than 4·5 cm. In USA 40% of invasive breast cancers are diagnosed when tumors are smaller than 1 cm.[4,5] In current study 57.6%[22] patients were with T4 and there were 41.30% with T3 lesion.

Clinical and pathological response of breast cancer to NACT is a short-term marker for a long term outcome [(15)] LABC is usually inoperable and neoadjuvant systemic therapy (NACT) generally is nearly always indicated. The goal of neoadjuvant systemic therapy is to induce tumor response and facilitate local control through surgical resection and radiation therapy[24] NACT also provides the earliest possible treatment of micro metastases and thus improves survival[25]

Nodal involvement at presentation is associated with a higher risk of a locoregional recurrence (HR 1.61, 95% CI 1.28-2.02).[14] In current study there were 44.57% patients with N1,52.2 % with N2 and 2.2% with N3 disease. In contrast to western world where they detect breast cancer early due to screening and better health facilities and in most studies more than 50% patients have no nodal involvement at presentation.[15] This high percentage of nodal involvement in current study indicates the need for screening and early detection.[4,5] ER was positive in 67.39% and PR was 52.11 % of our patients which is more or less similar to the western data available [(24)]

In current study pCR and pPR was seen in8.7 % and 54.3% patients respectively with AC regimen, but in

studies done in Western world the CR and PR rates are 13% (pCR) but 40% (pPR) with the same regimen.[13,14] This observation shows that many of our patients responded to treatment in terms of partial response The reason for high response rates in these studies was that patients were having early stage disease with N0,N1 status.

The pathological response is better when taxanes are added into it as NACT. The c PR improves to 26%.with taxanes.[13] The pCR rate with carboplatin and paclitaxel is up to31 percent in patients who were HER2-positive and 67 percent in patients who were ER-negative patients [2,3] In contrast, in patients with ER-positive, HER2-negative disease, the pCR rate was 12 percent.[2] AC regimen proved effective in this study in terms total pathological response though the cPR was inferior to the published data. For unknown reasons the response rates were high in post menopausal and receptor positive groups. Hormone receptor status seems to be predictive of relative chemoresistance; multiple trials have shown that the probability of achieving a pCR is significantly inferior in tumors expressing hormone receptors.[26] The previous available data for response in different receptor groups is controversial.[15-17] It is the level of expression of ER and progesterone receptor that might be correlated with the probability of response to neoadjuvant chemotherapy.[27] So for any receptor status response to NACT is difficult to comment on.

High-grade tumors are more responsive to chemotherapy.[18-20] Similar trends were observed in the current study.63%[18] of GradeII and Grade III tumors showed pathological response.(complete/partial) to NACT.

Conclusion

It is concluded from this study that Anthracycline based NACT is good option for these patients of developing countries. Though the results are not comparable with developed countries but better results can be achieved if these patients present at early stage. Moreover taxanescan be incorporated in NACT to improve the response. Further research with other available options is also needed. We should focus more on screening and prevention modalities so as to deal with this problem at very first step.

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