Original Article

Effects of Neo-adjuvant Chemotherapy on Locally Advanced Breast Cancer (LABC) and Its Correlation with Hormone Profile

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Neo-Adjuvant Chemotherapy (NACT) has been the mainstay in the treatment of Locally Advanced Breast Cancer (LABC). The clinico-radiological response of LABC to NACT is dependent on various variables, including the hormonal profile.

This observational study was aimed to study the response of LABC to NACT and its correlation with the hormonal profile of the patient.

Thirty patients with LABC were included in the study and were assessed clinically and radiologically after pre-determined intervals. Each case was classified according to the RECIST 1.1 criteria for the response to NACT. Eventually, 24 patients showed a satisfactory partial response to NACT and underwent curative surgical treatment Modified Radical Mastectomy (MRM). While the remaining six patients were found to have stable disease and continued receiving further cycles of Chemotherapy.

The Triple-negative tumours (ER/PR/Herceptin negative) showed an excellent response to NACT and all of them eventually underwent MRM. The Lumina B tumours exhibited the worst response to Chemotherapy.

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Key words **: LABC, NACT, Response Evaluation.**

Carcinoma breast is the most common malignancy in women[1]. It is the second most common malignancy after cervical cancer in India. Around 90,000 new cases of breast cancer are diagnosed every year in India. Locally Advanced Breast Cancer (LABC) accounts for 10-20% of newly diagnosed cases of breast cancers[2].

LABC includes operable disease (Stage T3 N1), inoperable disease (Stage T4 N2-3) and Inflammatory Breast Cancer (IBC) which is the clinical stage (T4d N0-3, also inoperable). This includes patients with

- T3 (>5cm) or T4 tumours (chest wall fixation or skin ulceration and/ or satellite nodules)
- N2 & N3 disease (matted axillary and/ or internal mammary metastasis).
- Supraclavicular nodes in the absence of any evidence of distant metastases[3].

Subdividing patients into these 3 broad group facilitates clinical management.

Locoregional control following the Breast Conservation Surgery (BCS) approach appears to be excellent except in patients with one or more of the features including clinical N2-3 disease, lymphovascular invasion, residual primary pathological size >2 cm and multifocal disease. Patients presenting with IBC cannot be taken for BCS even after complete resolution and is an absolute contraindication for BCS[4].

Editor's Comment :

- Neo-adjuvant Chemotherapy should be used upfront before surgery in the management of LABC.
- The hormonal profile and the concurrent chemotherapy has given results as effective as PCR, leading to probable BCS.

Neo-adjuvant Chemotherapy (NACT) has been the mainstay in the management of LABC. The main aim of NACT is to downstage and prevent early systemic micrometastasis. The effectiveness of NACT depends on the combination of used drugs[5]. Studies show that pathologic complete response is a crucial factor in long term survival[6]. Factors which affects the Pathological Complete Response (PCR) to NACT are age, size of the tumour, pre/peri/post-menopausal status, chemotherapy regimen given, number of chemotherapy cycles, IHC status, lymphovascular and perineural invasion[7]. A lot of trials have been done reporting the effectiveness of anthracycline-based chemotherapy regimens over conventional regimens[6]. In one of the clinical study conducted in India for evaluation of the efficacy of NACT for LABC it was revealed that taxane-based Chemotherapy was more effective as compared to Anthracycline-based Chemotherapy[8]. Taxanes (docetaxel or paclitaxel) have been added in the Chemotherapy regimen to get a better pathological response since then[9-11].

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Patients who achieve a pathologic Complete Response (pCR) following NACT have shown improved survival compared to patients who do not achieve pCR[12-14]. Several quantitative and categorical methods have been developed to characterise the pathological response to NACT, including Residual Cancer Burden Index (RCBI)[15] the Chevallier score[16], and the Miller-Payne score[17]. Radiologic assessment of tumour size changes based on the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines issued by the World Health Organisation (WHO)[18] correlates radiological and pathologic response of solid tumours to NACT[19,20]. Good local response of the primary tumour to NACT correlates well with improved survival[19, 21].

The determination of Estrogen (Er), Progesterone receptor (Pr) and Herceptin (Hr) content is routine in the management of Carcinoma of the Breast. Such data are commonly used to predict responses to endocrine therapy. However, little attention has been focused upon the effect of NACT on hormonal receptor expression.

This is an observational retrospective and prospective analysis to see the outcome of NACT in LABC patients and to correlate the hormonal receptor status to the response of LABC to NACT.

Materials and Methods

This was a retrospective and prospective observational study done at a Tertiary Care Centre. The study aimed to study the clinico-radiological response of LABC tumours to NACT and to correlate the hormonal profile of the patients to the clinico-radiological response. Institutional Ethics Committee approval was obtained with a waiver of consent.

All-female patients above the age of 18 with LABC who were subjected to NACT, were included in the study over five years from June, 2014 to June, 2019. Total of 30 patients were included in the study.

Their details such as age, co-morbidities, clinical size and stage of the tumour before and after NACT, details of the NACT regimen and hormonal profile (Er, Pr, Hr) of the patient were recorded.

According to the Institutional Protocol for the treatment of LABC, each patient received three cycles of CEF (Cyclophosphamide + Epirubicin or Adriamycin + 5 Fluorouracil) regimen of NACT. This protocol mandated the patient to be seen by a clinician for response assessment after the initial three cycles. Response assessment included clinical examination and USG mammography or X-ray mammography. Clinical evaluation included the comparison of clinical notes for the size of the tumour before the inception of Chemotherapy. Percentage reduction in the size of the tumour was calculated by comparing the breast to tumour ratio pre and postchemotherapy. Mean reduction in tumour size was calculated by the combination of clinical and radiological assessment.

These patients were then categorised according to the RECIST 1.1 criteria[22] into the following categories.

- **Complete Response (CR) :** Disappearance of all target lesions.
- **Partial Response (PR) :** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD) :** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.
- **Stable Disease (SD) :** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on the study[22].

There were three instances at which response assessment was done in this study.

The first response assessment was done after three cycles of NACT. Patients with CR or satisfactory PR underwent surgery. Those patients who underwent surgery were excluded from the follow-up. Those patients who did not have a satisfactory response to chemotherapy ie, unsatisfactory PR or SD were subjected to one more cycle of the same initial Chemotherapy Regimen (CEF). Second response assessment was done after the fourth cycle. Those with satisfactory response underwent surgery and the rest of the patients received four cycles of Taxens (a combination of drugs with Taxanes- docetaxel or paclitaxel) regimen. After completion of the second regimen, third response assessment was done. Those with satisfactory response underwent surgery and those with SD or PD received further cycles of Chemotherapy and radiation.

Statistical Analysis :

Qualitative data was represented in form of frequency and percentage. Association between qualitative variables was assessed by the Chi-Square test with continuity correction for all 2 X 2 tables and by fisher's exact test for all 2 X 2 tables, where the Chi-Square test not valid due to small counts. Percentage reduction in the size of the tumour was calculated by comparing the breast to tumour ratio pre and postchemotherapy. Mean reduction in tumour size was calculated by the combination of clinical and radiological assessment.

Mean reduction in tumour size was obtained by taking an arithmetic mean of the clinical and radiological response. Tumour reduction in centimetres

on clinical response was obtained by comparison of clinical notes before and after NACT. The radiological response was obtained by taking into account the reduction in tumour size on Sonomammography or X-ray mammography.

Results

The follow-up module and the study design is mentioned in figure 1.1. At the first response assessment after three cycles of NACT, out of 30, ten patients were found to have a mean reduction of 85.39% in the size of the tumour. Satisfactory Partial Response (PR) and then were selected for surgical management. These ten patients were offered a choice of surgical treatment of either undergoing BCS or Modified Radical Mastectomy (MRM). All of the patients chose to undergo MRM.

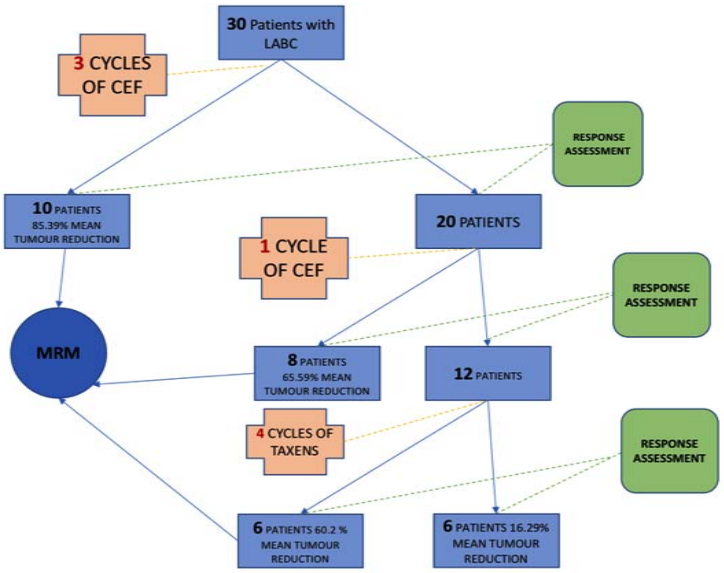

Fig 1 — A schematic diagram depicting the observations made as per the study design

The remaining 20 patients received one additional cycle of CEF Chemotherapy and were assessed after the fourth cycle. Amongst these 20 patients, eight patients were found to have had satisfactory Partial Response in terms of tumour reduction. Mean reduction was found to be 65.59%. These patients then underwent MRM. The rest of the 12 patients had mean reduction in the size of 38.24% after four cycles of CEF. These patients were then given four cycles of taxen chemotherapy regimen. After these four cycles, out of 12, six patients showed a mean reduction in the tumour size of 60.20% (Satisfactory PR) and then they underwent MRM.

The remaining six patients had a mean reduction in tumour size of 16.29% (Stable disease). They underwent further cycles of Chemotherapy (Fig 1).

Most of the patients were more than 40 years of age. (73.3%)(Table 1).

Table 1 — *Age distribution amongst the study participants*

Age (Years)	No	Percentage
30 to 39	8	26.7%
40 to 49	11	36.7%
50 to 59	6	20.0%
>60 years	5	16.7%
Total	30	100%

Twenty-four out of the 30 patients taking part in the study exhibited a partial response after various number of cycles of NACT (Table 2).

On comparison of the correlation between the hormonal profile and the Mean reduction in tumour size, the triple-negative (ER -ve/ PR -ve/ Hr – negative) patients had the best response to NACT. There were 15 patients with triple-negative hormone profile in the study. All of them eventually had a satisfactory partial response to NACT and all were subjected to MRM. On the comparison between the mean reduction in tumour size exhibited by triple-negative patients to other hormone profiles, there was a statistically significantly superior response to NACT. (P-value 0.003 chi-square test with Bonferroni correction)

LUMINAL B (ER +PR+/- Hr positive) exhibited the worst response and none of the 4 patients were subjected to MRM (Table 3).

On follow up of the patients who underwent MRM and adjuvant chemo radiation, 3cases showed distant recurrence at 1 year follow-up, The subtype we observed 2 cases were TNBC and 1 case was HR+ HER. On 6 months, there was no recurrence on PET scan.

A study done by Harris, *et al*[29] showed that TNBC

Table 2 — *Mean Reduction in tumour reduction at each response assessment step*

	MRM after 3 cycles of CEF Regimen	MRM after 4 cycles of CEF Regimen	MRM after 4 Additional cycles of PACLITAXEL Regimen	Prolonged chemo-therapy cycles	Total
Number of patients	10	8	6	6	30
Response to chemotherapy according to RECIST 1.1	Partial response	Partial response	Partial response	Stable disease	
Mean reduction in tumour size	85.39%	65.59%	60.20%	16.39%	

has absolute15-20% of cases who will benefit from chemotherap and for HR+ HER2- it was 2-3%. This study also showed distant recurrence risk in TNBC was 50-60%, and for HR+ HER2- it was10-15%.

Different subtype of breast cancer have different risk of recurrence. This findings was also observed in our study on 1 year follow up of breast cancer cases (Table 4).

Table 3 — *Hormonal Profile and Mean Reduction in tumour size*

Hormonal Profile	MRM after 3 cycles of CEF Regimen	MRM after 4 cycles of CEF Regimen	MRM after 4 Additional cycles of PACLITAXEL Regimen	Prolonged chemo-therapy cycles	Total
Number of patients	10	8	6	6	30
LUMINAL A (ER +/PR +/- HERCEPTIN -ve)	2	2	1	2	7
LUMINAL B (ER +/PR +/- HERCEPTIN +)	0	0	0	4	4
Herceptin Positive (ER -/PR - HERCEPTIN +)	1	2	1	0	4
Triple Negative (ER -PR - HERCEPTIN -)	7	4	4	0	15
Mean reduction in tumour size	85.39%	65.59%	60.20%	16.39%	

Table 4 — *Different subtype on follow up distant recurrence rate*

Subtype	Distant recurrence	Chemotherapy benefit
TNBC	2(6.66%)	Yes
HR+HER2-	1(3.33%)	Delayed Response

Discussion

WHO Response guidelines were updated in 2009 in the European Journal of Cancer (RECIST 1.1)[22]. The revised guidelines incorporated major changes to the original RECIST criteria, including a reduction in the number of lesions to be assessed, a new measurement method to classify lymph nodes as pathologic or normal, the clarification of the requirement to confirm a Complete Response (CR) or Partial Response (PR) and new recommendations for the assessment of disease progression. NACT is currently established as a standard therapeutic approach for patients with large (>2 cm) and locally advanced breast cancer. However, standard guidelines for pathologic evaluation of breast specimens after NAT have not been established. Assessment of the therapeutic response and measurement of residual disease in the breast and/or axillary lymph node is important because it may predict survival and provide guidelines for further therapy[22].

In this study, amongst the six patients with stable disease, four patients were found to have Luminal B hormone profile and two were Luminal A. Those who had a satisfactory partial response early in the chemotherapy regimen 61% of them were Triple-Negative Breast Cancer (TNBC).

Luminal B patients had the worst response to NACT while those with TNBC had the best response to chemotherapy. All of the TNBC patients in the study eventually showed a satisfactory partial response in tumour reduction. All of these patients underwent MRM.

Although TNBCs carry higher mortality as compared with luminal-type breast cancers NACTis more likely to result in a pathologic complete response (pCR) in patients with TNBC primary tumours than in those with luminal tumours[23].

Patients with TNBC were more likely to get PCR[26].

Rodenhuis, *et al* studied the neoadjuvant response in 267 patients: 55 patients (21%) had a pathological complete response in both breast and axilla. Pathological complete responses were more frequently seen in patients with triple negative tumor[27].

Elghazaly, *et al* studied 125 patients with stage-II and stage-III non-inflammatory breast cancer treated with six cycles chemotherapy. Among them 20% of patients achieved PCR[28].

In our study 14 (14%) of patients had pathological complete response following NACT. The majority (57%) of these had triple negative hormone receptor status.

PCR is an important endpoint because patients who attain this status after surgery have improved survival and this improved prognosis is greatest in the more aggressive subtypes of TNBC and HER2-positive-only tumours[24,25].

On follow up of the patients who underwent MRM and adjuvant chemo radiation, 3 cases showed distant recurrence at 1 year follow up, The subtype we observed 2 cases were TNBC and 1 case was HR+ HER. On 6 months, there was no recurrence on PET scan.

A study done by Harris, *et al*[29] showed that TNBC has absolute 15-20% of cases who will benefit from Chemotherapy and for HR+ HER2- it was 2-3%. This study also showed distant recurrence risk in TNBC was 50-60% and for HR+ HER2- it was 10-15%.

Different subtype of breast cancer have different risk of recurrence. This findings was also observed in our study on 1 year follow up of breast cancer cases.

Conclusions

- Hormonal profile is an important variable in the determination of the response of LABC to NACT
- Poor response should be expected in triple-positive cases.
- Overall response with Triple negative cases was found to be excellent.
- Different subtype of breast cancer have different risk of recurrence.

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