# **Original Research Article**

DOI: http://dx.doi.org/10.18203/2349-2902.isj20181999

# A study on role of neo adjuvant chemotherapy in locally advanced nonmetastatic breast cancer

# Thota Siddhartha, B. Kanchana\*

Department of General Surgery, Aarupadai Veedu Medical College and Hospital, Pondicherry, India

Received: 20 April 2018 Accepted: 28 April 2018

# \*Correspondence:

Dr. B. Kanchana,

E-mail: kanchana.balaguruswamy@avmc.edu.in

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## **ABSTRACT**

**Background:** Nearly 1.7 million new breast cancer cases were diagnosed worldwide in 2012.Breast cancer is the second most common cancer in women worldwide. Globally, breast cancer now represents one in four of all cancers in women. breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,00 women and mortality 12.7 per 100,000 women. Around 90,000 new cases of breast cancer are diagnosed every year in India and majority present as Locally Advanced Breast Cancer (LABC). Neo adjuvant chemotherapy is a commonly used modality for LABC, that gives an upfront systemic therapy in high risk patients with expected micro metastatic burden and also helps in down staging the disease and offering radical cure.

**Methods:** All Locally Advanced Non-Metastatic Breast Carcinoma (T3 N0, T3 N1, T4a, T4b, T4c, Any N2/N3, MO patients who received Neo Adjuvant Chemotherapy and underwent surgery were included. All these patients received 5-Fluorouracil, Adriamycin and Cyclophosphamide (FAC) regime, following therapy patients were offered either Modified Radical Mastectomy or Breast Conservative Surgery with axillary node dissection and Radiotherapy.

**Results:** Complete response was achieved in 20 (66.6%) patients,3 (10%) of the patients had partial response and 7 (23.3%) progressed clinically.

**Conclusions:** Neo adjuvant chemotherapy helped to study response of tumour size to NAC, down stage disease and to convert inoperable cases to resectability.

Keywords: FAC regime, Locally advanced non-metastatic breast cancer, Neo adjuvant chemotherapy

# **INTRODUCTION**

Breast cancer is the most common cancer affecting females worldwide and accounts for roughly 25% of all cancers in women. Survival rates for women with breast cancer are improving; but are still poorest for patients who present with late stage disease, patient cannot be offered radical cure and it also increases the cost of treatment and causes both physical and psychological trauma to the patient. Consequently, there is great interest in providing improved care to patients with advanced breast cancer. Locally Advanced Breast Cancer is a heterogenous clinical entity that includes patients with

large tumour >5cm primary breast tumors or T4 tumours with chest wall involvement, peau d' orange appearance or ulceration of the skin,or inflammatory cancer and /or extensive clinical lymph node involvement as defined by the N2 and N3 categories from the American Joint Committee on Cancer TNM classification system.¹ Locally Advanced Breast Cancer comprises a diverse array of clinic-pathologic features. Down-staging by neoadjuvant chemotherapy allows breast surgery to be undertaken in some patients considered inoperable prior to treatment and even permits breast conservative surgery.² The Pathological Complete Response (PCR) is considered as biological marker for survival outcomes.

The PCR is considered when there is complete eradication of locoregional disease.<sup>3,4</sup> Knowledge of a patient's response to neoadjuvant therapy is essential and has important consequences for optimal and cost-effective management. Accurate response assessment also aids eventual surgical planning, facilitating the correct surgical procedure to be undertaken, whether this is breast conserving surgery or mastectomy.

The objective of this study was to assess the response to Neo Adjuvant Chemotherapy in LABC in terms of pathological response, overall survival, feasibility of breast conservative surgery and convert inoperable cases to resectability.

#### **METHODS**

A retrospective review of 30 patients of LABC who received both neoadjuvant chemotherapy and underwent surgery at Aarupadai Veedu Medical College and Hospital (AVMC&H), Pondicherry between August 2015 and August 2017 were made. A formal approval was taken from the Institutional Ethical Committee of AVMC&H prior to data collection. Patients who were diagnosed with Early breast cancer and Inflammatory breast cancer, metastatic breast cancer, breast cancers during pregnancy and malignant phyllodes tumor were excluded from the study.

The patients were staged as per TNM staging system proposed by American Joint Committee on Cancer. All stage IIB (T3NO), III (T4a, T4b, T4c; Any N2/N3) disease. All the patients were assessed by triple assessment. Bilateral Mammography and ultrasound breast were performed in all 30 patients.

Core needle biopsy was done to arrive Histopathological diagnosis, in both pre and post-menopausal women Estrogen and Progesterone receptors and Her2 status was determined on pre-treatment biopsy by Immunohistochemistry (IHC).

The chemotherapeutic regime used was 5-Fluorouracil, Adriamycin and Cyclophosphamide (FAC). All patients received 4 cycles (q21days) i.e.,5-Fluorouracil 600mg/m² Body Surface Area (BSA) administered 4hrs Intra Venous (IV), Adriamycin 60mg/m² BSA IV over 4hours and Cyclophosphamide 600mg/m² BSA IV over 4 hours given.

To evaluate the tumor response to neoadjuvant chemotherapy, Response Evaluation Criteria in Solid tumors published in February 2000 by European Organization for Research and Treatment of Cancer was used and was documented as follows<sup>5</sup>:

Clinical Complete Response (cCR): Complete disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10mm.

Clinical Partial Response (cPR): Defined as 30% reduction in larger diameter of the tumour size.

Progressive Disease (PD): Defined as atleast 20% increase in the tumor size or appearance of new metastasis (according to RECIST criteria).

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for Progressive disease (PD).

All patients eventually underwent either Modified Radical Mastectomy (MRM) or Breast Conserving Surgery (BCS) with axillary lymphnode dissection. The surgical procedure under taken was based upon patient's choice, tumor-to-breast size and clinical response to Neoadjuvant Chemotherapy. Contraindications to breast conservative surgery included multifocal disease, previous irradiation to the breast, patient refusal and positive surgical margins.

The size of the invasive component, histological type of the tumour, grade of the tumour and number of positive of lymph nodes were all recorded, the median dissected lymph node was 13. Adjuvant systemic therapy of 2 cycles of FAC regime given as needed. Radiotherapy was given to all patients who had BCS and MRM. Hormone therapy was given to patients with positive hormone receptors. Patients were then followed to exclude local or distant metastasis. Free Survival was defined as being free of cancer relapse. Frequency and percentage were calculated for categorical variables while mean and standard deviation were calculated for numerical variables. Stastical Package for Social Sciences version 16.0 was used for stastical analysis.

Patients underwent surgery, RT or CT in the department of surgery, G.R. Medical College and J.A. Group of Hospital Gwalior and Cancer Hospital and Research Institute Gwalior, (CHRJ, Gwalior) during the year Jan.2001 to 2006. The patients were investigated and treated according to the protocols.

# **RESULTS**

A total of 30 patients were included in the study. The median age of the patients at the time of diagnosis was 47 years (range: 36-65 years ). Twelve patients (40 %) were older than 45 years. Twenty patients (66.66 %) were premenopausal at the time of diagnosis.

Invasive ductal carcinoma accounted for 28 (93.33%) cases, while 2 (6.66 %) patients were diagnosed with lobular carcinoma. Lympho-vascular invasion were present in 26 cases (86.66%). ER/PR receptor positive in 18 patients (60 %). While 2 (6.66%) patients were ER positive/PR negative. 10 (33.33%) patients were ER-ve and PR negative. While 16 (53.35 %) patients were triple positive i.e., ER positive, PR positive and Her 2 positive.

The tumor size (T) st presentation was T2 = 14 (46.66 %)cases, T3=10 (33.33%) cases, T4=6 (20%) cases respectively. The nodal status being N0=4 (13.33%), N1=20 (66.66 %), N2=6 (20%) respectively. Accordingly, 6 (20%) patients had stage IIB disease,18 (60%) patients had stage IIIA disease and 6 (20%) had stage IIIB disease respectively.

While 20 patients (66.66%) had Complete Response (CR),3 (3%) of the patients had partial response to neoadjuvant chemotherapy. While 7 (23.33%) patients had progressive disease. There was no severe cardiac toxicity or any other serious adverse events (Figure 1).

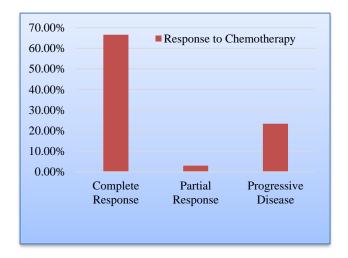


Figure 1: Response to neo adjuvant chemotherapy.

Surgery was performed in all these patients after Neoadjuvant chemotherapy; 25 (83.33%) patients underwent Modified Radical Mastectomy (MRM),5 (16.66%) had Breast Conservation Surgery (BCS); all had Axillary lymph node dissection and followed by adjuvant chemotherapy. All patients undergoing breast conservation surgery were given adjuvant radiotherapy. All the patients with receptor positive cancer were given hormone therapy (Figure 2).

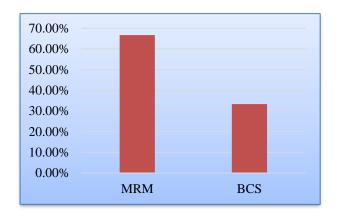


Figure 2: Type of surgery post neo adjuvant chemotherapy.

The mean follow-up period was 15 months (range: 3-26 months) in the patients undergoing Breast Conservative Surgery and 16.1 months (range: 4-51 months) for the patients having modified radical mastectomy respectively. No patient in either groups had local or distant metastasis.

The most common toxicity criteria following neoadjuvant chemotherapy we encountered was grade 2 alopecia (25 patients; 83.33%), followed by fatigue (20 patients; 66.66%) Arthralgia and myalgia were developed in 5 patients (16.66%) whereas febrile neutropenia occurred in only 3 patients (10 %). All patients completed the treatment protocol without interruption of treatment.

### **DISCUSSION**

Locally advanced breast carcinoma encompasses a heterogenous collection of breast neoplasia with widely different clinical and biological characterstics. Neoadjuvant chemotherapy for locally advanced advanced breast carcinoma patients has significantly changed management options over the last 4 decades. It provides appropriate local control, the possibility of breast conserving surgery and increased survival rate in LABC.

The overall response to neoadjuvant chemotherapy in this study was 76.66 %, partial= 3 (3%) and complete response = 20 (66.66%). Several other studies have shown a similar overall objective response of the primary tumor in patients with locally advanced breast cancer ranging from 71 to 87 %.<sup>7,8,9</sup> On the other hand, the present results are much higher than that reported by Yadav et al who found that only 23 % showed response to neoadjuvant chemotherapy.<sup>10</sup> Another study by Tamer et al. in 2010 also showed much lesser overall response rates to neoadjuvant chemotherapy 54.5 %(CR 3% and PR 51.5%) and Kim et al also reported that the overall response rate to neoadjuvant chemotherapy is 60 %(CR 4% and PR 56%) respectively.<sup>11,12</sup>

Several studies have documented the feasibility and safety of breast conservation for locally advanced breast after pre-operative chemotherapy. conservation is possible in 27-90% of patients after preoperative chemotherapy. 13,14 In this study,5 patients (16.66 %) underwent Breast conservative surgery after neoadjuvant chemotherapy. Similar results were reported by other authors. Danforth et al conducted their study on 126 patients with locally advanced breast cancer who received neoadjuvant chemotherapy. They found that 42 (33%) of them were downstaged to the extent that breast conservation surgery became a feasible technique for them.<sup>15</sup> In other study, Yadav et al reported that 23% of patients with locally advanced breast cancer are good candidates for breast conservation surgery after neoadjuvant chemotherapy provided that they are carefully selected.

## **CONCLUSION**

LABC is a common presentation of carcinoma breast in India.Neo adjuvant chemotherapy offers downstaging of disease in Locally Advanced Non metastatic Breast Carcinoma patients making more conservative surgery feasible.It also increases chance of curative resection in patients with LABC with large tumor mass.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

#### REFERENCES

- 1. Naji S,Alexander E, Robert W. Locally advanced breast cancer. Treatment guideline implementation with particular attention to low and middle income countries. Cancer 2008;113:2315-24.
- Kuerer HM, Singletary SE, Buzdar AU, Ames FC, Valero V, Buchholz TA et al. "Surgical conservation planning after neoadjuvant chemotherapy for stage II and operable stage III breast carcinoma" Am J Surg. 2003;182:601-8
- 3. Iqbal J, Kausar B, Saeed A, Akram M, Zeba A. Survival of women with locally advanced breast cancer at a teaching hospital in Lahore. J Pak Med Assoc. 2010;60:721-5.
- Buzdar AU. Pre-operative chemotherapy treatment of breast cancer; a areview. Cancer. 2007;110:2394-407
- 5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours:Revised RECIST guideline. Eur J Cancer 2009;45:228-47.
- 6. Vicente V, Aman UB, Gabriel NH. Locally advanced breast cancer. Oncologist. 1996;1:8-17.
- 7. El-Sayed MI, Maximous DW, Aboziada MA, Abdel-Wanis ME, Mikhail NN. Feasibility of breast conservation after neoadjuvant taxene based chemotherapy in locally advanced breast cancer: a prospective phase-I trial. ANN Surg Innov Res. 2010;4:5.

- Machiavelli MR, Romero AO, Perez JE, Lacava JA, Dominguez ME, Rodriguez R, et al. Prognostic significance of pathological response of primary tumor and metastatic axillary lymphnodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am. 1998;4:125-31.
- Viswambharam JK, Kadambari D, Iyengar KR, Srinivasan K. Feasibility of breast conservation surgery in locally advanced breast cancer downstaged by neoadjuvant chemotherapy: a study in mastectomy specimens using simulation lumpectomy. Indian J Cancer. 2005;42:30-4
- Yadav BS, Sharma SC, Singh R, Singh G. Pateerns of relapse in locally advanced breast cancer treated with neoadjuvant chemotherapy followed by surgery and radiotherapy. J Cancer Res Ther 2007;3:75-80.
- 11. ElBakary TA, ElGohary SE, Elgendy MM, Barakat AF, Younes SG. Conservative breast surgery in early and locally advanced breast cancer. J Am Sci 2010;6:713-20.
- 12. Kim R, Osaki A, Tanabe K, Toge T. Neo adjuvant chemotherapy for locally advanced breast cancer with stage III-B. Oncol Rep. 2004;11:1265-72.
- 13. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M et al Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990;82:1539-45.
- 14. Fisher B, Bryant J, Wolmark N. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
- 15. Danforth DN Jr, Zujewski J, O'Shaughnessy J, Riseberg D, Steinberg SM, McAtee N, et al. Selection Of local therapy after neoadjuvant chemotherapy in patients with stage III-A, B breast cancer. Ann Surg Oncol.1998;5,2:150-8.

Cite this article as: Siddhartha T, Kanchana B. A study on role of neo adjuvant chemotherapy in locally advanced non-metastatic breast cancer. Int Surg J 2018;5:2110-3.