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Original Research Article

A clinical study of outcome of neoadjuvant chemotherapy in 30 cases of locally advanced breast carcinoma

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ABSTRACT

Background: Locally advanced breast cancer presents with a difficult management problem. It remains a challenge to achieve local and distant control of locally advanced breast cancer. Over the last decade preoperative/ neoadjuvant chemotherapy has emerged as the standard of care for these patients. Successful reduction in the size of the tumor is associated with increased rate of operability. The objective of this study is to observe the response of neoadjuvant chemotherapy in locally advanced breast carcinoma in form of outcome and complications. The outcome is measured as down staging or downgrading of tumor, results of surgery and its complications, disease free survival and recurrence.
Methods: This is the observational prospective study of consecutive 30 cases of locally advanced breast cancer admitted in department of general surgery during a period from May 2017 to August 2018 at new civil hospital, Surat. Neo adjuvant chemotherapy were given every three weekly and the response of therapy calculated in form of reduction in the size of tumor or getting the margin free from skin or pectoral muscles or reduction in the axillary lymph node mass.
Results: In this study about 93% of cases responded to neoadjuvant chemotherapy with 10% of cases shows complete clinical response where tumor becomes completely free from skin or pectoral muscles or negative axillary lymph nodes.
Conclusions: With the evidence from the literature and study conducted earlier, our observations of clinical response of neoadjuvant chemotherapy in patients with locally advanced breast cancer had corroborative evidence.

Keywords: Locally advanced breast cancer, Neoadjuvant chemotherapy, Breast conserving surgery

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women worldwide with over 1.3 million new cases year. There is a wide variation in the geographical burden of the disease with the highest incidences seen in the more developed regions of the world and the lowest incidences observed to be increasing in the least developed regions.

Locally advanced breast cancer

Locally advanced breast cancer (LABC) is defined by presence of a large primary tumor (>5 cm or T3), associated with or without skin or chest-wall involvement (T4) or with fixed (matted) axillary lymph nodes or with disease spread to ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases.[1] LABC accounts for 10-20% in the

West, while in India, it accounts for 30-35% of all cases.[1] The treatment of LABC has changed dramatically over last few decades. The introduction of neoadjuvant chemotherapy (NACT) in LABC offered us advantages like initiation of early systemic therapy, down-staging of tumors, which makes inoperable tumors operable and renders tumors suitable for breast conserving surgery (BCS). Neoadjuvant chemotherapy (NACT) is increasingly used to treat patients with locally advanced breast cancer (LABC).[2]

Role of systemic and local treatment

The mainstay of local treatment has been radiotherapy. This is because surgery, generally mastectomy, results in high rates of local recurrence. In contrast, radiotherapy alone can produce high rates of local remission in both the breast and axilla, but radiotherapy alone only 30% of the patients remain free of loco regional disease at death. A combination of appropriate systemic treatment and radiotherapy can increase the initial rate of local response to over 80%.

Objectives

The objective of this study is to observe the response of neoadjuvant chemotherapy in locally advanced breast carcinoma in form of outcome and complications. The outcome is measured as down staging or downgrading of tumor, disease free survival and local recurrence.

METHODS

This is the observational prospective study of consecutive 30 cases of locally advanced breast cancer admitted in department of surgery during a period from May 2017 to August 2018 at new civil hospital and government medical college Surat, Gujarat. After getting permission from ethical committee and written informed consent of patients, the study was conducted with inclusion and exclusion criterion mentioned below. The data from case records, follow up visits at outpatient department was recorded and analysed.

Inclusion criteria

All breast carcinoma indoor patients presenting at our hospital, of any age with large primary tumour (>5 cm, T3); chest wall extension (T4a); skin ulceration, peu'd orange and satellite nodules (T4b); inflammatory carcinoma (T4d); fixed axillary lymph nodes (N2a); clinically apparent internal mammary nodes (N2b); periclavicular nodes (N3).

Such cases span Stage IIB, Stage IIIA and Stage IIIB of AJCC classification of breast carcinoma.

Exclusion criteria

Exclusion criteria were patients with carcinoma breast with primary tumor <5 cm (T0, T1, T2) with N0 and primary tumor <2 cm with N1 i.e. stage I and stage IIA; patients clinically diagnosed as locally advanced breast carcinoma, on investigation found to be having distant metastases; local recurrence and development of subsequent systemic metastases would be taken as the parameters to assess the outcome.

On admission after thorough clinical examination, radiological investigation in the form of mammography or sonography, patients were subjected to core cut tissue biopsy. Upon confirmation of the tissue diagnosis with ER (estrogen receptors), PR (progesterone receptors) and HER-2-neu receptor status patients were advised for neoadjuvant chemotherapy. Whenever possible 2D echo, Ultrasonography of abdomen and bone scan were done to rule out any possible distant metastasis prior to starting to neoadjuvant chemotherapy.

After complete clinical examination of 30 cases about the size of tumor, infiltration to skin or muscles & the status of axillary lymph nodes; patients were given systemic chemotherapy. Diagnosis was confirmed by FNAC or biopsy. Under the guidance of the oncosurgeon proper combination chemotherapy were decided and dose calculated according to body surface area. Chemotherapy were given every three weekly and the response of therapy calculated in form of reduction in the size of tumor or getting the margin free from skin or pectoral muscles or reduction in the axillary lymph node mass. Response was graded as complete response (CR), partial response (PR) or no response (NR) after each cycle of chemotherapy.

RESULTS

In this study maximum number of cases with locally advanced breast carcinoma belongs to age group between 35-54 years; At first visit 11 (36.6%) cases were premenopausal while 19 (63.6%) were postmenopausal; maximum cases belong to T3 (17, 56.6%) while T2 and T4 were (8, 26.6%) and (5,16.6%) respectively (Table 1); 36.6% patients were found out to be ER, PR positive while 36.6% were ER,PR negative and in 23% patients ER,PR status was not known (Table 2).

Table 1: Distribution of LABC cases (n=30).

Types of LABC	%	No. of patients
T2	26.6	8
T3	56.6	17
T4	16.6	5
N0	6.6	2
N1	63.3	19
N2	30	9

In present study about 93% of cases responded to neoadjuvant chemotherapy with 10% of cases shows complete clinical response where tumor becomes completely free from skin or pectoral muscles or negative

axillary lymph nodes (Table 3). While partial response (PR) was seen in 83.3% and no response in 6.6%.

Table 2: Distribution of LABC on the basis of receptor study (n=30).

Receptor study	%	No. of patients
ER, PR +ve	36.6	11
ER, PR -ve	36.6	11
Not known	26.8	8

Table 3: Response to NACT (n=30).

Response	%	No. of patients
CR	10	3
PR	83.3	25
NR	6.6	2

After completion of neoadjuvant chemotherapy cases responded to therapy with free margins were subjected to modified radical mastectomy. Postoperative radiotherapy was given to the local area after complete healing of the scar.

Cases were followed up during post therapy period every month. The aim of follow up to detect any local recurrence or systemic spread of disease. In each follow up clinical examination done for local area to detect recurrence, per abdominal examination for metastasis, examination of chest and spine for distant spread. Necessary investigation like chest X ray, sonography of abdomen, MRI or bone scan were done for metastasis. The median follow up time was 3 months.

DISCUSSION

Management of Locally advanced breast carcinoma remains a clinical challenge as the majority of patients with this diagnosis develop distant metastases despite appropriate therapy. The prognosis of women with locally advanced breast tumors are also heterogeneous and depend on tumor size, extent of lymph node involvement, and the presence or absence of inflammatory carcinoma. Women with locally advanced disease require multimodal therapy, and coordinated treatment planning among the medical oncologist, surgical oncologist and radiation oncologist.[3]

Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, which indicate that 7% of patients have stage III disease at diagnosis in United States. In populations that receive regular screening mammography, the percentage of patients with locally advanced disease is less than 5%. According to SEER data, the 3 and 5 year relative survival rates for women with stage III breast cancer are 70% and 55% respectively. Median survival for women with Stage III disease is 4.9 years.

Diagnosis and pretreatment evaluation of LABC

If breast cancer is suspected, a tissue biopsy is necessary to confirm the diagnosis. Estrogen receptor (ER) and progesterone receptor (PR) status, HER-2/neu status, p53 status, and nuclear grade can all be determined from core needle biopsy.

The National Comprehensive Cancer Network has published guidelines for women with stage III disease, the recommended evaluation includes:

- History and physical examination;
- Laboratory evaluation with CBC, platelets and liver enzymes;
- Bilateral mammogram and ultrasound and chest X-ray;
- Pathology review, determination of ER, PR and HER-2 status;
- Breast magnetic resonance imaging (MRI), bone scan; and abdominal computerized tomography (CT) scan (optional).

Prognostic factors

The prognostic factors for locally advanced tumors are similar to the prognostic factors for earlier stage breast cancer, with lymph node status and tumor size having the strongest effects on survival. Most patients with locally advanced disease have axillary lymph nodes involved with their tumors, but a subset of patients has large primary tumors without lymph node involvement.

The prognosis for patients without lymph node metastases is better than for those with lymph node involvement. For patients with lymph node metastases, a greater number of lymph nodes involved and higher nodal stage predict poorer survival.

The size of primary tumor is also associated with survival; patients with larger cancers have poorer survival rates. Valagussa et al. 1983 found that 5-year survival rates were 65%, 36% and 16% for breast tumors measuring <5 cm, 5-10 cm, and >10 cm respectively.

Hormone receptor positivity is associated with a longer survival time. Estrogen receptor positivity predicted a significantly longer disease free interval and overall survival, but only in the subset of patients with operable breast cancer. In patients with locally advanced breast tumors found that ER and PR negativity was associated with shorter overall survival times in univariate analyses.

Other variables that have been investigated as possible prognostic markers in locally advanced breast cancer include measures of proliferation, p53, HER-2 and nuclear grade. The thymidine labeling index (TLI) was an independent prognostic factor, with a high TLI predicting poorer survival. P53 positivity was associated with a shorter overall survival time.

Therapy

The treatment of locally advanced breast cancer requires a combination of systemic chemotherapy, surgery and radiotherapy to optimize the chance of cure. The earliest therapy for locally advanced breast cancer was radical mastectomy. However, patients with supraclavicular involvement, edema of the arm, satellite skin nodules and extensive breast edema were considered markers of inoperable disease. Patients who were treated with primary radiotherapy also had a high risk for disease recurrence and death, as well as the complications of chest wall fibrosis, lymphedema, skin ulceration and skin necrosis.

Chemotherapy before surgery

Successful neoadjuvant chemotherapy will shrink the tumor before surgery, making it easier to remove. This treatment will also decrease the chances of recurrence. For a small number of women, having neoadjuvant chemotherapy may allow them to have breast conserving surgery, such as lumpectomy, rather than a mastectomy.

The first reports of the use of induction chemotherapy (neoadjuvant chemotherapy) for locally advanced disease were published in the 1970's. Since then, the use of systemic chemotherapy has become standard and has substantially improved the prognosis of locally advanced breast cancer.

Bonadonna et al.in 1995 demonstrated a survival benefit for women with node positive breast cancer treated with CMF chemotherapy.[4] The early breast trialists' collaborative group published a meta-analysis of all known randomized trials of adjuvant chemotherapy and demonstrated a significantly lower mortality rate for women treated with chemotherapy in 1998. The benefit was independent of tumor size or nodal status, indicating that women with locally advanced disease are likely to receive the same proportional reduction in risk of recurrence as women with early breast cancer. The data in aggregate clearly support the use of systemic chemotherapy for women with locally advanced breast cancer.

The survival rates of women treated with adjuvant or neoadjuvant chemotherapy are equivalent, making either approach reasonable for a woman with operable breast cancer. For inoperable disease, the initial approach should be chemotherapy with the goal of achieving resectability.

Many standard chemotherapy regimens exist for the adjuvant and neoadjuvant treatments of breast cancer. The early breast cancer trialists' group (EBCTG) established the superiority of anthracycline-based chemotherapy regimens. For patients with node positive breast cancer (LABC), the addition of a taxane to an anthracycline-based regimen improves overall survival. The anthracycline and taxane can be given in sequence or in combination. Using doxorubicin and docetaxel in combination produces a higher rate of febrile neutropenia than when these drugs are given in sequence. However, in patients with metastatic disease, the response rates are higher from combination therapy than from sequential treatment, although survival rates are similar.

For the treatment of locally advanced disease, particularly in the setting of inoperable disease, using a regimen with the highest likelihood of shrinking the tumor should improve the chances of converting the disease to operable breast cancer. A phase II trial has evaluated the combination of docetaxel and epirubicin in patients with locally advanced breast cancer and found a response rate of 77%, showing that combination therapy is effective in patients with locally advanced disease.

The role of dose dense therapy has also recently been explored for patients with node positive and locally advanced breast cancer. Citron et al. reported a higher survival rate in node positive patients who were treated with dose dense chemotherapy in that trial, women who were treated with chemotherapy every 2 weeks with filgrastin support had better disease free and overall survival rates than women treated with a conventional 3 week regimen.[5] It remains unclear whether the survival benefit seen in that trial revelas a general principle of dose dense chemotherapy scheduling or reflects the known schedule dependent effects of the drug paclitaxel. A trial from M.D Anderson Cancer Centre previously demonstrated a doubling of pathologic response rates when paclitaxel was administered on a weekly versus 3-weekly schedule. Two trials have evaluated dose dense chemotherapy in patients with locally advanced breast cancer, and neither found a significant difference in response rate or survival between the dose dense and standard arms.

Despite the difficulty in accurately assessing response, patients who have complete clinical or pathologic responses to neoadjuvant chemotherapy have better outcomes. Kuerer et al, reported a series of 372 patients with locally advanced breast cancer who were all treated with neoadjuvant anthracycline-based chemotherapy.[6] A total of 43 (12%) patients achieved a pathologic CR, and those patients had a significantly better survival rate. Although the survival time of responders was better than that of non-responders, 13% of the complete responders had relapsed or died by 5 years.

In present study, the tumor response rate was found to be similar to that reported in literate with Complete pathological response were seen in 13.3%, CR in 10% and PR in 83.3% (Table 4).[8-10]

After patients complete neoadjuvant chemotherapy. They should proceed with definitive local therapy. The traditional approach has been to treat women with locally advanced tumors with modified radical mastectomy.

Table 4: Comparison of response to NACT.

Study	cCR (%)	cPR (%)	pCR (%)
Hortobagyi et al[8]	17	71	8
Van der hage et al[9]	6.6	42.3	3.7
Raina et al[10]	13.3	71.1	7.8
My study	10	83.3	13.3

However, after induction chemotherapy, many of these women become candidates for breast conserving therapy. Singletary et al. reviewed a series of 143 patients treated at the M.D Anderson cancer Centre for locally advanced disease to determine whether breast conservation was a feasible option after chemotherapy.[7] Strict criteria were applied to determine which patients would theoretically be good candidates for breast conservation. All patients were treated with a standard approach of mastectomy and axillary lymph node dissection. Of the 33 patients who would have been candidates for breast conservation, 42% were found to have a pathologic CR to chemotherapy, and none had multi-centric disease, which suggested that breast conservation would have been a safe approach.

An alternate approach to breast conservation has been the use of primary radiation therapy in place of surgery, as most studies that have compared primary radiation therapy with primary surgical therapy have shown equivalent outcomes in patients of locally advanced breast cancer receiving neoadjuvant chemotherapy.

CONCLUSION

With the evidence from the literature and study conducted earlier, our observations of clinical response of neoadjuvant chemotherapy in patients with locally advanced breast cancer had corroborative evidence. Definitely, neoadjuvant chemotherapy to be given to all patients of locally advanced breast cancer.

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REFERENCES

1. Valero VV, Buzdar AU, Hortobagyi GN. Locally Advanced Breast Cancer. Oncologist. 1996;1:8-17.
2. Mougalian SS, Soulos PR, Killelea BK, Lannin DR, Abu-Khalaf MM, DiGiovanna MP, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer. 2015;121(15):2544-52.
3. Arimappamagan A, Kadambari D, Srinivasan K, Krishnan R, Elangovan S, Reddy KSN. Complete axillary conversion after neoadjuvant chemotherapy in locally advanced breast cancer: a step towards conserving axilla?. Indian J Cancer. 2004;1(41):13-7.
4. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Eng J Med. 1995;14:901-6.
5. Kümmel S, Krocker J, Kohls A, Breitbach GP, Morack G, Budner M, et al. Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer. Br J Cancer. 2006;94:1237-44.
6. Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol. 1999;17:460-9.
7. Singletary SE, McNeese MD, Hortobagyi GN. Feasibility of breast-conservation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer. 1992;69:2849-52.
8. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 1988;62:2507-16.
9. VanderHage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: Results from the European organization for research and treatment of cancer trial 10902. J Clin Oncol. 2001;19:4224-37.
10. Raina V, Kunjahari M, Shukla NK, Deo SV, Sharma A, Mohanti BK, et al. Outcome of combined modality treatment including neoadjuvant chemotherapy of 128 cases of locally advanced breast cancer: Data from a tertiary cancer center in Northern India. Indian J Cancer. 2011;48:80-5.

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