

Original Research Article

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Clinical presentation and management of locally advanced breast carcinoma

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ABSTRACT

Background: Locally advanced breast cancer (LABC) encompasses a heterogeneous collection of breast neoplasia with widely different clinical and biological characteristics. Multidisciplinary therapy has become the treatment of choice for these patients. The present study was undertaken to study the clinical presentation and effects of various modes of management of LABC.

Methods: Total 45 patients presented with stage III and inflammatory carcinoma of breast were included in the study and treated with neoadjuvant chemotherapy, followed by surgery and radiotherapy. Clinical and pathological responses to different chemotherapy regimens were assessed according to World Health Organization criteria.

Results: Majority of patients were in stage IIIA (55.6%) followed by stage IIIB (37.7%). Lump was most common symptom in all the cases followed by distortion of nipple (35.5%). After neoadjuvant chemotherapy, 70% of cases had clinical partial response and 25% of cases had clinical complete response and all except one case were converted from inoperable to operable cases. Histopathology was found to be infiltrating ductal carcinoma in 91.1% of cases. Flap necrosis (27.2%) and seroma (15.9%) was major complications of surgery while alopecia (88.8%), anemia (62.2%) were major complications of chemotherapy. Follow up data suggested that 77.7% patients doing well. One patient had expired after developing distant metastasis and 20% patients were lost to follow up.

Conclusions: Treatment of LABC is multimodal and neoadjuvant chemotherapy converts inoperable cases to operable cases and improves longevity of life of the patient. The results of inflammatory carcinoma remain to be dismal in spite of multimodality treatment.

Keywords: Adjuvant therapy, Histopathology, Inflammatory carcinoma, Locally advanced breast carcinoma, Neoadjuvant chemotherapy

INTRODUCTION

Locally advanced breast cancer (LABC) is a very common clinical presentation of mammary carcinoma in developing countries, (30% to 60%). LABC accounts for 10-20% in the West while in India, it accounts for 30-35% of all cases.¹ This higher incidence of LABC in developing countries due to illiteracy, lack of active screening, early detection programs, low awareness of

breast cancer, poor access to health care due to poverty and cultural issues are the contributory factors for late presentation.

LABC is a heterogeneous group of tumors of varying clinical presentations and biological behavior whose only common bonds are the presence of a large primary tumour (>5 cm), associated with or without skin or chest-wall involvement or with matted axillary lymph nodes or

with disease spread to the ipsilateral internal mammary or supraclavicular nodes in the absence of any evidence of distant metastases.²

LABC encompasses a wide spectrum of malignant breast tumors with varying presentation and poses a significant therapeutic challenge. The treatment of LABC has changed dramatically over last few decades. Multidisciplinary therapy has become the treatment of choice for patients with LABC. It provides appropriate local control, prolonging the survival rate in patients with LABC by preventing and delaying distant metastasis and improving quality of life.¹ The most common approach for treating LABC in developed countries consists of neoadjuvant chemotherapy with anthracyclines and taxanes followed by surgery and radiation therapy; while hormonal treatment is added for receptor-positive disease, and patients with Her2neu-positive disease receive trastuzumab therapy. Most patients have good clinical responses to induction chemotherapy in both the primary tumor and regional lymph nodes. The present study was undertaken to evaluate the epidemiologic characteristics like age distribution, clinical presentation, stage at presentation and various modalities of treatment in our institute.

METHODS

After obtaining Institutional Ethical Committee approval, this prospective study was conducted in 45 patients with stage III and inflammatory breast cancer at tertiary care centre from December 2014 to May 2016. The presence of distant metastasis proved on investigations was excluded from the study.

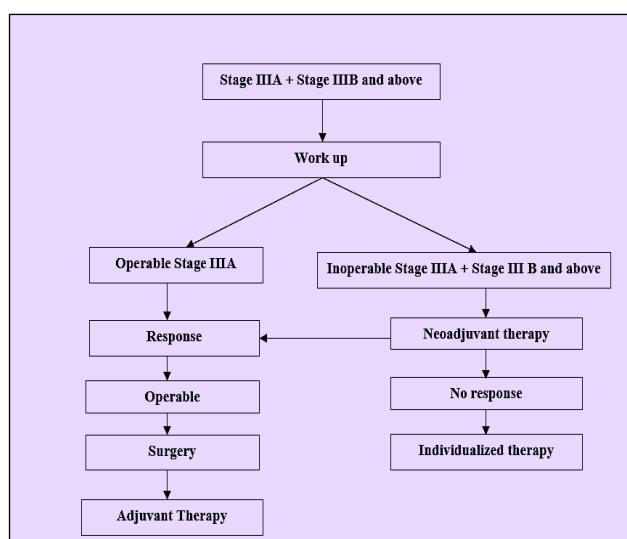


Figure 1: Flow chart of procedure.

The pathologic diagnosis was confirmed by fine needle aspiration cytology and TRU-CUT biopsy for receptor studies. Routine hematological investigations and complete metastatic workup with chest X-ray, ultrasound

abdomen, and bone scan of each patient was done. ECG and 2D ECHO were done prior to start neoadjuvant chemotherapy. Chemotherapy regimens used were CAF: Cyclophosphamide 500 mg/m², Adriamycin (Doxorubicin) 60 mg/m² I.V, 5-Fluorouracil 500 mg/m².

Adjuvant therapy

Measure of response to neoadjuvant (induction) chemotherapy was assessed as

- Clinical complete response (cCR): No palpable tumour in the breast and axilla,
- Clinical Partial response (cPR): >50% reduction in the size of tumour and
- Stable disease (cSD): <50% reduction in the size of tumour.

RESULTS

Total 120 patients with breast carcinoma admitted during the study period among them 45 (37.5%) patients were identified as patients of LABC. The mean age of patients was 42.4 years, ranged from 27 to 65 years. The maximum number of patients were in age group of 41-50 years 18 (40%) followed by 31-40 years 15 (33.3%). 51.1% of the patients was educated up to school only and majority of the spouses of patients (55.5%) were educated up to graduation. Most of the patients had duration of symptoms from 3 to 6 months (42.2%) with a mean of 7.71 months (Table 1).

Table 1: Presentation to the hospital with complaints (time frame).

Duration (months)	No. of patients with complaints
<3	6 (13.3%)
3-6	19 (42.2%)
7-12	14 (31.1%)
13-24	5 (11.1%)
>24	1 (2.2%)

Lump was the most consistent symptom in all the cases and distortion of nipple (retraction) was the next most common symptom (35.5%), (Table 2). The upper outer quadrant was the commonest quadrant involved in 53.3% cases. Majority of the patients (66.6%) had Pre-menopausal status.

Table 2: Symptoms at presentation.

Symptoms	No. of patients
Lump	45 (100%)
Retraction of nipple	16 (35.5%)
Pain	10 (22.2%)
Nipple discharge	8 (17.7%)
Swelling in axilla	8 (17.7%)
Skin ulceration	6 (13.3%)

The tumour size ranged from 4 to 12 cms with a mean size of 7.02 cms and majority of patients (77.7%) had tumour size of 5 to 8 cms. Axillary lymphadenopathy was seen in all the cases, but 51% cases had N1, 44.4% had N2 and only 4.4% of cases had N3 lymphnodal status.

Table 3: Sequencing of treatment.

Sequencing	No. of patients
S+C	19 (42.2%)
NC+S+C+R	15 (33.3%)
S+C+R	6 (13.3%)
NC+S+C	4 (8.8%)
NC+R	1 (2.2%)

S: Modified Radical Mastectomy; C: Adjuvant chemotherapy; NC: Neoadjuvant Chemotherapy; R: Adjuvant Radiotherapy

Out of total cases of LABC, 25(55.6%) were of stage IIIA, 17(37.8%) were stage IIIB, 2 (4.4%) were stage IIIC and 1 (2.2%) case was of inflammatory carcinoma. Even though the cases were of LABC, 55.6% cases were considered operable at presentation. Inoperable cases (44.4%) were subjected to neoadjuvant chemotherapy. Out of which 33.3% cases were subjected to neoadjuvant chemotherapy followed by surgery followed by adjuvant chemotherapy followed by adjuvant radiotherapy. The sequencing of treatments was shown in Table 3.

After neoadjuvant chemotherapy 70% of cases had a clinical Partial Response (cPR) and 25% of cases had a clinical Complete Response (cCR). All except one case were converted from inoperable to operable, after neoadjuvant chemotherapy. Histopathology was found to be infiltrating ductal carcinoma in 91.1% of cases. In patients who had clinical complete response postoperative histology was showing no residual tumor only microcalcification/dysmorphic calcification with hyalinization, fibrosis and sclerosis at the site of tumor.

Table 4: Complications of surgery and chemotherapy.

Complications of surgery	No. of patients
Flap necrosis	12 (27.2%)
Seroma	7 (15.9%)
Oedema of arm	4 (9.9%)
Wound dehiscence	4 (9.9%)
Toxicity of chemotherapy	
Alopecia	40 (88.8%)
Anemia	28 (62.2%)
Mucositis	12 (26.6%)
Nausea	08 (17.7%)
Emesis	08 (17.7%)
Fatigue	03 (6.6%)
Neutropenia	05 (11.1%)

Flap necrosis (27.2%) and seroma (15.9%) was the major complications of surgery while the alopecia (88.8%) and anemia (62.2%) were the major complications of chemotherapy, (Table 4). The patients were regularly

followed up and at the end of the study 77.7% patients doing well. One patient had expired after developing Distant Metastasis and 20% patients were lost to follow up.

DISCUSSION

LABC includes breast cancers with advanced primary tumors and also includes a rare subgroup, inflammatory breast cancer which has a particularly poor prognosis. When considering clinical presentation, most cases of LABC are visible and palpable, although in some cases, the breast is diffusely infiltrated and lacks a dominant mass. Careful palpation of the skin, breasts, and locoregional lymph nodes (axillary, supraclavicular, and cervical) is the initial step in evaluation. Large tumor size, fixation to the chest wall, ipsilateral satellite skin nodules, fixed or matted axillary nodes, and/or ipsilateral infraclavicular or supraclavicular lymph nodes connote LABC.³ Late diagnosis is a major factor for increased mortality as the majority of the patients present in advanced or metastatic stage. This is primarily attributed to lack of access to medical facilities, virtually non-existent breast cancer screening programs, lack of awareness and social-cultural attitudes.

LABC is best managed with multimodality therapy employing systemic and locoregional therapy. Neoadjuvant systemic therapy, in particular neoadjuvant chemotherapy, has become the standard approach for patients with locally advanced, inoperable breast cancer. The choice between neoadjuvant chemotherapy and adjuvant chemotherapy is based upon a woman's desire for breast preservation, since both approaches achieve comparable survival. Historically, patients with LABC had very poor prognosis. They were treated with either radical mastectomy or primary radiation therapy (RT). Despite aggressive surgical resection, they had an extremely high risk of local recurrence and distant metastases; fewer than 20 percent of patients survived beyond five years.⁴ The addition of postoperative radiation therapy (RT) to surgery showed an improvement in local control and disease-free survival.⁵⁻⁷ The addition of systemic therapy has further improved prognosis and may even permit breast preservation for patients with LABC.

In our hospital 37.5% of the patients admitted for the treatment of breast cancer were locally advanced. The mean age of patients was 42.4 years, ranging from 27 to 65 years. The incidence of LABC was more in age group of 41-50 years (40%) followed by 31-40 years (33.3%) while incidence to be less in 51 to 60 years age group and also in >60 years bracket. This age distribution of patients was similar to previous studies.⁸⁻¹⁰

Lump in breast was the commonest symptom noticed in 100% of cases in our study which was similar to other studies.¹¹⁻¹³ However, 53.3% of lumps were present in upper outer quadrant which was comparable to study

done by Sandhu et al.¹⁴ 40% of cases presented with 3 to 6 months of symptoms and 12% cases with symptoms duration less than 3 months. Only 8% of cases were noticed with symptoms more than 24 months which was slightly more than that noticed by Sandhu et al.¹⁴

In present study out of total cases, 25 (55.6%) were of stage IIIA, 17 (37.8%) were stage IIIB, 2 (4.4%) were stage IIIC. Only 1 (2.2%) patient had inflammatory carcinoma while previous studies did not notice any case of inflammatory carcinoma.¹⁵⁻¹⁷ 19 (42.2%) patients of stage IIIA with T3N1M0 were considered to be operable and hence subjected to modified radical mastectomy followed by adjuvant chemotherapy.

Present findings were similar to study done by Sandhu et al and Raina et al.^{14,18} In both these studies, post-operative chemotherapy was given in higher percentage than present study of 42.2% using Cyclophosphamide, 5 Flurouracil and Adriamycin. Only 6 (13.3%) patients of stage IIIA with N2 Lymph node status were subjects to adjuvant radiotherapy. Rustogi et al has commented that in premenopausal women surgery followed by chemotherapy followed by radiotherapy improves outcome reducing cardiac and pulmonary toxicities as compared to surgery followed by radiotherapy.¹⁹ In present study very few patients could afford ER/PR/HER 2 receptor status hence it was not tested. 20 (44.4%) patients presented as inoperable cases and hence were subjected to neoadjuvant chemotherapy.

The primary objectives of neoadjuvant chemotherapy is to downstage the tumours and in cases of inoperable tumours to convert them into operable ones. Out of 20 inoperable cases, 15 (33.3%) cases received radiotherapy after neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. 4 (8.8%) patients received neoadjuvant chemotherapy followed by local treatment in the form of surgery followed by adjuvant chemotherapy. 1 (2.2%) patient was subjected to neoadjuvant chemotherapy followed by radiotherapy.

Response to neo adjuvant chemotherapy was assessed by calculating the percentage decrease in the volume of tumour and response is classified according to the stage of disease. In our study of the 20 patients who received neo adjuvant chemotherapy, 5 (25%) patients had complete Clinical Response (cCR) which was similar to previous studies while 14 (70%) patients had clinical Partial Response (cPR).^{12,16} 1 (5%) patients had stable disease, (Inflammatory CA). 20 (44.4%) cases presenting as inoperable were treated with neoadjuvant chemotherapy, of these 19 (42.2%) were converted to operable and only 1 (2.2%) remained inoperable. Single patient, who remained inoperable, received radiotherapy as she could not be subjected to surgery.

Thus 95% of inoperable tumours were converted to operable ones. This data shows that in the present study fairly good objective response to neoadjuvant

chemotherapy was seen and that neoadjuvant chemotherapy downstages a good number of tumours and makes them operable and gives better locoregional control. This finding was correlated with the findings of study done by Yadav et al and Baldine et al.^{12,20}

The study at M.D Anderson Centre analyzed pathology specimens from patients treated with neoadjuvant chemotherapy using multivariate analysis showed that residual cancer burden correlated with prognosis independent of other factors like age, pretreatment clinical stage, hormone receptor status, hormonal; therapy and pathologic response.²¹

In current study, infiltrating ductal carcinoma was present in 91.1% cases, medullary carcinoma, colloid carcinoma and lobular carcinoma noted in 2.2% cases in each, these findings was comparable to study of Goel et al.⁹ Inflammatory carcinoma was noticed in 2.2% but was not seen in other studies. The present study found microcalcification, dysmorphic calcification, hyalinization, fibrosis and sclerosis at the site of tumor instead of tumor in those patients (20%) who had clinical complete (cCR) response to neoadjuvant chemotherapy. Similar findings were noted by Sethi et al.²²

The overall rate of complications of surgery was less than 30%. Flap necrosis was seen in 24.4% cases and was the most common complication in present study which was higher as compared to other studies.^{23,24} Incidence of Seroma was present in 15.9% cases. Wound dehiscence was seen in 9.9%. Ipsilateral arm oedema was noticed in 9.9% which was not seen at all in other studies.^{23,24} Chemotherapy has got its own complications and incidence wise alopecia, anemia, mucositis, nausea and vomiting are the commonest. In present study alopecia was found in 80% and anemia in 56% cases. Mucositis was the next common complication found in 24% cases. The incidence of nausea and vomiting was 16% and incidence of neutropenia was 11%.

CONCLUSION

The present study revealed that low educational status, health awareness and ignorance are the causes of LABC. The treatment of LABC is multimodal and neoadjuvant chemotherapy converts inoperable cases to operable cases and improves longevity of life of the patient. The result of inflammatory carcinoma remains to be dismal in spite of multimodality treatment.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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