CASE STUDY ON AN APPROACH TO THE MANAGEMENT OF LOCALLY ADVANCED CARCINOMA OF BREAST

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ABSTRACT

BACKGROUND

Locally Advanced Carcinoma Breast

Breast cancer is one of the most common malignancies in female and in developing countries, majority of them present in locally advanced stages. Patients presenting with LABC constitute a diverse group for which a variety of treatment modalities have been instituted with co-ordinated treatment planning among the medical oncologist, surgical oncologist and radiation oncologist. The study is conducted to know the incidence, age distribution and common modes of presentation.

MATERIALS AND METHODS

This is a prospective study of 50 patients presenting with Stage III and inflammatory breast cancer to MNR Medical College and Hospital, Department of General Surgery from December 2014 to December 2015.

RESULTS

Majority of the patients, 35 (70%) of the patients were doing well at the end of the study. The most distressing outcome was development of distant metastasis in 4 (8%) of the patients. These cases included one inflammatory carcinoma and other three were Stage IIIB, two of which had not responded to NACT and had remained inoperable. Local recurrence was seen in 3 (6%) of the patients. Two of these cases were of Stage IIIA and was not on radiotherapy. One case belonged to Stage IIIB and had completed radiotherapy; 8 (16%) of the cases were lost to followup.

CONCLUSION

Multimodality therapy is effective in treatment of locally advanced carcinoma of breast, but distant metastasis is seen in four patients and local recurrence in 3 patients shows that management is still a challenge and improvements in current therapies and newer modalities are needed to further reduce disease free and overall survival.

KEYWORDS

Locally Advanced Breast Carcinoma, Neoadjuvant Chemotherapy.

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BACKGROUND

Worldwide breast cancer is the most frequent cancer in women and represents the second leading cause of cancer death among women (after lung cancer).^{1,2} Locally Advanced Breast Cancer (LABC) constitutes more than 50% to 70% of the patients presenting for treatment.³

The Locally Advanced Breast Cancer (LABC) is characterised by varying clinical presentations such as presence of a large primary tumour (> 5 cm) associated with or without skin or chest wall involvement or with fixed (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. These are tumours belonging to Stages IIIA, IIIB, IIIC and inflammatory breast cancer.

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Although, the clinical features at presentation and prognosis among women with LABC vary, there are two common problems in the treatment. Achieving local control and prolonging survival by preventing or delaying distant metastasis.

Today treatment of LABC requires a combination of systemic and local/regional therapies.

Chemotherapy Regimens

CMF

Cyclophosphamide 500 mg/m², Methotrexate 50 mg/m² and 5 fluorouracil 500 mg/m².

All three drugs IV day 1 and day 8 every 4 weeks for 6 cycles (includes pre-op and post-op).

AC

Adriamycin 60 mg/m², Cyclophosphamide 600 mg/m².

Both IV day 1 every 3 weeks for 4 cycles (includes pre-op and post-op).

AC for 4 cycles followed by paclitaxel 175 mg/m² every 3 weeks for 4 cycles (includes pre-op and post-op).

Surgery⁴

Modified radical mastectomy implies removal of entire breast tissue from clavicle to rectus abdominis and between sternal

edge and latissimus dorsi together with nipple areolar complex, excess skin of the breast and fascia of pectoralis major muscle. It includes axillary dissection.

Prognostic Indicators

Axillary lymph nodes- The extent of axillary lymph node involvement by breast cancer is the most established and reliable prognostic factor for subsequent metastatic disease and survival.

The other factors are-

- Tumour size.
- Histologic grading.
- ER/PR status.
- Age- Very young (35 years or less) breast cancer patients have poorer prognosis than older patients.
- HER-2 amplification or overexpression, poorer prognosis.

Objective

The study is conducted to know the incidence, age distribution, common modes of presentation. To study the multimodality management including neoadjuvant chemotherapy, surgery and adjuvant therapies.

MATERIALS AND METHODS

This is a prospective study of 50 patients presenting with Stage III and inflammatory breast cancer to MNR Medical College and Hospital, Department of General Surgery from December 2014 to December 2015.

Sample Size- 50 patients.

Inclusion Criteria

All patients presenting in MNR Hospital, Sangareddy with Stage IIIA, IIIB, IIIC and inflammatory carcinoma were included in the study.

Exclusion Criteria

Patients who were clinically diagnosed as having locally advanced breast cancer (i.e. IIIA, IIIB, IIIC and inflammatory carcinoma), but on investigations found to have distant metastasis were excluded.

Anatomy

Extent

The breasts are modified sweat glands, which extend from the level of second to sixth rib. It extends transversely from the lateral border of the sternum to the anterior axillary line.⁵ The deep surface of the breast rests on the fascia of the pectoralis major, serratus anterior and external oblique abdominal muscles. The axillary tail of Spence extends laterally across the anterior axillary fold.

Blood Supply

The breast receives its principal blood supply from-

1. Perforating branches of the internal mammary.
2. The lateral thoracic artery is a branch of axillary artery and courses along the lateral border of pectoralis minor muscle.
3. The pectoral branch of the acromiothoracic artery, also a branch of axillary artery, this supplies the posterior part of the breast.

Blood Supply of Breast

Venous Drainage

Can broadly be classified into deep veins and superficial veins.

- A. The deep veins of the breast drain along routes of corresponding arterial supply, so major drainage is via perforating veins into the internal mammary veins.
- B. The superficial veins are quite rich and sometimes dilated during pregnancy and neoplasm. The majority of these veins drain into the internal mammary vein and axillary vein.

Nerve Supply

Lateral cutaneous branches of third through sixth intercostal nerves provide sensory innervations of the breast (lateral mammary branches) and of the anterolateral chest wall. Cutaneous branches that arise from cervical plexus, specifically the anterior branches of the supraclavicular nerve supply a limited area of skin over the upper portion of the breast.

Lymphatic Drainage of Breast⁶

Group 1- External mammary nodes or anterior pectoral nodes.

Group 2- Scapular nodes.

Group 3- Central nodes.

Group 4- Interpectoral nodes (Rotter's nodes). These lie between the pectoralis major and minor muscles.

Group 5- Axillary vein nodes.

Group 6- Subclavicular nodes.

RESULTS

Proportion of Cases

The total number of patients with carcinoma breast admitted during the study period was 136. Out of these, 60 patients were identified as patients of LABC based on the accepted definition. Thus 44% of patients admitted with carcinoma breast presenting for treatment were identified as patients with LABC.

Age Distribution

The age of the presenting patients ranged from 27 to 65 years. The highest number of patients were in age group of 41 - 50 years' age group with 17 (34%) followed by 31 - 40 years' age group with 13 (26%). The mean age of patients was 45.1 years.

Duration of Symptoms

The highest number of patients had symptoms for 3 - 6 months, i.e. 19 (38%). The duration of symptoms ranged from 1 - 28 months. The mean duration of symptoms was found to be 8.84 months.

Symptoms at Presentation

Lump is the most consistent symptom and present in all the patients; 8 (16%) of these patients presented with an ulcer over the lump. Pain was the complaint in 13 (26%) of the patients; 6 (12%) patients complained of lump in the ipsilateral axilla.

Symptom	Number of Cases	%
Lump	50	100%
Ulcer with Lump	8	16%
Pain	13	26%
Retraction of Nipple	14	28%
Nipple Discharge	6	12%
Swelling in Axilla	6	12%

Table 1. Symptoms at Presentation

Quadrants Involved

The upper outer quadrant is the most common predominantly involved quadrant with a total of 29 (58%) cases. Since most of the lumps were large, they spanned more than one quadrant.

Predominantly Involved Quadrant	Number of Cases	Percentage
Upper Outer	29	58%
Upper Inner	5	10%
Lower Outer	8	16%
Lower Inner	3	6%
Central	5	10%

Table 2. Quadrants Involved

Tumour Size

The tumour size ranged from 4 cm to 12 cm in the highest dimension. The smallest tumour measured 4 x 3 cms, while the largest 12 x 10 cms. Majority of the tumours were 5 - 8 cms size. The mean size of the tumours is 6.6 cms.

One patient presenting with inflammatory carcinoma had diffuse lump.

Fixity to Skin and Chest Wall

24 (48%) of 50 cases were found to have fixity to either skin

or chest wall. Highest number 12 (24%) were found to have Peau d'orange implying skin fixity and 8 (16%) had ulcer over the lump. Chest wall fixity was found in 5 (10%) cases.

Fixity	Feature	Number of Patients	%
	Peau d'orange	12	24%
Skin	Ulcer	8	16%
	Sat Nodule	1	2%
Chest Wall		5	10%

Table 3. Fixity to Skin and Chest Wall

Lymph Node Status

The axillary node status seen in the study is depicted in the following table and graph.

Lymph Node Status	Number of Patients	Percentage
N1	26	52%
N2	22	44%
N3	2	4%

Table 4. Lymph Node Status

Stage of the Disease

24 of the 50 cases studies 23 (46%) were of Stage IIIA, 24 (48%) are Stage IIIB, 2 cases (4%) are Stage IIIC and 1 case (2%) is inflammatory carcinoma.

Group	TNM	Number of Patients	Number of Patients	%
IIIA	T3N1M0	12		
	T3N2M0	10	23	46%
	T2N2	1		
IIIB	T4aN1M0	1	24	48%
	T4aN2M0	4		
	T4bN1M0	13		
	T4bN2M0	6		
IIIC	T3N3M0	2	2	4%
Inflammatory Ca	T4d	1	1	2%

Table 5. Stage of the Disease

Chemotherapy Regimen

Three standard regimen were used in the study. CMF was used the most in 26 (52%) of the patients. AC regimen was used in 24 (48%).

Response to Neoadjuvant Chemotherapy

Response to neoadjuvant chemotherapy was assessed by calculating the percentage decrease in the volume of the tumour.

In our study of the 38 patients who received neoadjuvant chemotherapy, 5 (13.2%) patients had complete clinical response (cCR), 25 (65.8%) patients had partial clinical response (pCR); 8 (21%) had stable disease. One case of inflammatory carcinoma had no response to therapy.

Proportion of Inoperable Tumours Converted to Operable Stages

38 (76%) cases presenting as inoperable were subjected to NACT, of these 35 were converted to operable and only 3

remained inoperable. These tumours which remained inoperable were subjected to radiotherapy.

Receptor Status

Both ER and PR were positive in 23 (46%) of the cases, both ER/PR were negative in 20 (40%). ER positivity with PR negativity was seen in 5 (10%). ER negativity with PR positivity was seen in 2 (4%). Overall receptor positivity is seen in 30 (60%) patients. Tamoxifen 20 mg O.D for 5 years was advised to all patients with hormone receptor positive status.

Histopathology

Infiltrating intraductal carcinoma was the predominant type seen in 46 (92%) of the patients. Other types seen were 1 (2%) each of Medullary, Colloid, Lobular and Inflammatory types.

Outcome

The patients were regularly followed up and at the end of the study 35 (70%) of the patients were doing well; 4 (8%) of the patients developed distant metastasis and 3 (6%) of the patients developing local recurrence; 8 (16%) of the patients were lost to followup.

DISCUSSION

Proportion of Cases

In our hospital, 44% of the patients admitted for the treatment of breast cancer were locally advanced. Chopra R states the proportion of LABC to the total number of reported breast cases to be 28.9%, 40.5% and 52% in Mumbai, Trivandrum and Chennai respectively.

Age Distribution

The highest number of cases are seen in the age group of 41 - 50 years in all the studies including ours.

The mean age is 46.5 years and 47.39 years in Amit Aggarwal et al⁷ and D S Sandhu et al⁸ series respectively. The mean age in our study, i.e. 45.1 years matches closely with the above-mentioned studies.

In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their Western counterparts. While the majority of breast cancer patients in Western countries are postmenopausal and in their 60s and 70s, the picture is quite different in India with premenopausal patients constituting about 50% of all patients.⁹

Symptoms at Presentation

The presenting features are compared with the percentages of presenting features in some of the similar series from India. The most consistent symptom is that of a lump and is seen in all cases in our study and 87.9%, 74%, 96.5% in Sandhu D S et al, Gang et al and Raina et al series respectively.

Quadrants Involved

In all the series, the percentage in the upper outer quadrant by far exceeds the percentage of location in other quadrants. The percentages of lump in the upper outer quadrants are 58%, 47%, 49% and 48% in the current, Sandhu DS et al, Sen and Dasgupta et al and Fields et al series.

The possible explanation is that the upper outer quadrant has a relatively larger volume of breast tissue.

Duration of Symptoms

Most of the cases present with 3 - 6 months' duration. The percentage of patients in this range was 38% and 32.9% in our study and in D S Sandhu et al series respectively. The cases with less than 3 months' duration were higher in D S Sandhu series compared to our study.

Tumour Size

The tumour sizes in our study are compared with Chintamani et al and Aggarwal Himanshu et al studies. Maximum tumours are in the range of 5 - 8 cms. The percentage of tumours in that range is considerably higher in our study.

The patients ignore the mass, as it is commonly painless and does not interfere with the regular lifestyle of the patient. There is also considerable delay in presenting to the hospitals due to ignorance allowing the lump to attain larger proportions.

Lymph Node Status

Jai Ganesh Vishambaran L K et al reported N1 stages to be 93% and N2 stages to be 7%. Compared to this study, our patients showed a higher incidence of N2 disease. But results similar to ours were seen in series of Chintamani et al and Aggarwal Himanshu et al. The percentages are shown in the above table.

Stage of the Disease

In the present study more percentage of cases were of IIIB (48%) than stage IIIA (46%); 4% and 2% of cases were of IIIC and inflammatory carcinoma.

Jaiganesh Vishambaran L K et al have reported 70% IIIA and 30% IIIB stages among their patients.

The percentages for IIIA were 24%, 55% and 27.2% respectively in B S Yadav et al, William G et al and Brian Nolen et al.

Stage IIIB cases were 33%, 27% and 36.4% respectively in B S Yadav et al, William G et al and Brian Nolen et al.

IIIC cases were reported in BS Yadav et al and William G et al with 25% and 2% of cases respectively.

Response to Neoadjuvant Chemotherapy

38 (76%) patients who presented in operable states were subjected to neoadjuvant chemotherapy. CMF and an anthracycline based regimen AC were used.

The primary objectives of neoadjuvant chemotherapy is to downstage the tumours and in cases of inoperable tumours to convert them into operable ones. In our study also maximum number of cases 25 of 38 (65.8%) had partial response.

The rates of partial response were 45.45%, 65%, 73% and 56.3% in Brian Nolen et al, B S Yadav et al, Jaiganesh Vishambaran L K et al and Amit Aggarwal et al respectively.

In their article, Nirmal Raut and Nilesh Chordiya present data related to response rates of various trials.¹⁰

Our data compares closely with the results mentioned in the above table.

Conversion Rates of Inoperable Tumours

Out of 38 inoperable tumours treated with neoadjuvant chemotherapy, 35 were rendered operable. Thus, 92% of

inoperable tumours were converted to operable ones. This data shows that in our 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.

Receptor Status

Receptor status of our study compares closely with the results of receptor status study by Tanuja Shet et al conducted at Tata Memorial Hospital, Mumbai from 1999 to 2006. The receptor positivity is 60% in our population and 55.8% in Tanuja Shet et al study.

Complications of Therapy

Toxicity of Chemotherapy regimen. The toxicities of chemotherapy noted in our study are compared with study conducted by Sambasivaiah Kurapathy¹¹ et al. In both the studies, overall the toxicity rates are higher in anthracycline based regimen like AC than in CMF. Most common adverse effect noted is alopecia followed by emesis and anaemia in AC regimen and anaemia and mucositis in CMF regimen. Neutropenia was noted in only one patient on AC regimen. The rates of toxicity are comparable to the above-mentioned study.

Outcome

Majority of the patients, 35 (70%) of the patients were doing well at the end of the study. The most distressing outcome was development of distant metastasis in 4 (8%) of the patients. These cases included one inflammatory carcinoma and other three were stage IIIB, two of which had not responded to NACT and had remained inoperable.

Local recurrence was seen in 3 (6%) of the patients. Two of these cases were of Stage IIIA and was not on radiotherapy. One case belonged to Stage IIIB and had completed radiotherapy.

8 (16%) of the cases were lost to followup.

CONCLUSION

- About half of the cases presenting with breast cancer are in locally advanced stages.
- Lump in the breast is the most common symptom, upper outer quadrant being its most common location and most of the lumps were 5 - 8 cms in size.
- Highest number of cases were presented in 5th decade followed by 4th decade indicating the presentation is a decade earlier in Indian patients compared to the West.
- Fixity to skin was seen in about 48% of the cases and was the most common cause of inoperability.
- Only a quarter of the cases were operable, rest inoperable.
- Patients administered NACT showed good response with 13.2% and 65.8% of the patients showed clinically complete and partial response respectively; 92% of inoperable tumours became operable confirming that NACT is an effective method of down staging the tumour.
- Infiltrating ductal carcinoma is overwhelmingly the most common histological variant seen.
- Multimodality therapy is effective in treatment of locally advanced carcinoma of breast, but distant metastasis is seen in four patients and local recurrence in 3 patients shows that management is still a challenge and

improvements in current therapies and newer modalities are needed to further reduce disease free and overall survival.

SUMMARY

- A very high number of cases, 44% presented in locally advanced stage of breast cancer in tune with trend in developing countries.
- Highest incidence was seen in 5th decade with 17 (34%) of patients presenting in this age group followed by 4th decade with 13 (26%) of patients. Mean age being 45.1 years.
- Lump in the breast is the overwhelmingly common presentation and was seen in all the patients; the most common location of the tumour being upper outer quadrant 29 (58%).
- Most of the patients 19 (38%) present with duration of symptoms from 3 to 6 months with mean duration being 8.8 months.
- Size of 75% of tumours were in range of 5 - 8 cms with mean size being 6.6 cms.
- Fixity to skin and chest wall was seen in 38% and 10% of cases respectively, making them inoperable at presentation; 24% of cases were operable at presentation and 76% inoperable.
- 46% presented in Stage IIIA, 44% presented in Stage IIIB and 4% in Stage IIIC and 2% inflammatory breast cancer.
- Neoadjuvant chemotherapy was administered to these all inoperable cases converting 92% of these to operable stages. Clinical complete response was seen in 13.2%, clinical partial response seen in 65.8% and 21% had stable disease.
- Chemotherapy was well tolerated in patients with alopecia being most common toxicity.
- 60% of patients are hormone receptor positive.
- Infiltrating ductal carcinoma is by far the most common histopathological variant seen in 92% of patients.

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