Locally Advanced Breast Cancer, Its Management with Neoadjuvant Chemotherapy and Its Response in Southern Part of Odisha

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ABSTRACT

BACKGROUND

Locally Advanced Breast Cancer (LABC) is a subset of breast cancers characterized by advanced breast tumours in the absence of distant metastasis. The need to identify LABC as a separate group of breast cancers arose in view of the high associated rate of locoregional and systemic failure. Management includes multimodality treatment which is complex. LABC is the most common mode of presentation in the region of study i.e. the southern part of Odisha. Aim is to study the multimodal treatment and its response as provided in this institution.

METHODS

This prospective study was conducted in the Postgraduate Department of General Surgery, M.K.C.G. Medical College & Hospital, Berhampur, Orissa, from July 2017 to June 2019 including 6 months of follow up period. 49 cases of locally advanced breast cancer were included in the study. Multimodal treatment including surgery and chemotherapy was offered. Response to surgery and various chemotherapeutic agents was evaluated.

RESULTS

Combination of neoadjuvant chemotherapy, modified radical mastectomy, adjuvant chemotherapy achieved superior locoregional control and delayed systemic dissemination. Maximum clinical response was seen in paclitaxel receivers i.e. complete response in 22 % and partial response in 77 % of cases with 0 no response rates. After 6 months of follow up of multimodal treatment of LABC, the overall survival rate is maximum in stage IIIA with 95.8 %, followed by 83.3 % in stage IIIB and 42.8 % in stage IIIC.

CONCLUSIONS

Surgery and chemotherapy are more effective in locally advanced breast cancer than surgery alone and paclitaxel as chemotherapy displays high level of antitumour activity.

KEYWORDS

Locally Advanced Breast Cancer (LABC), Neo-Adjuvant Chemo-Therapy (NACT), AC (Adriamycin Cyclophosphamide), CAF (Cyclophosphamide Adriamycin 5 - Fluorouracil) Paclitaxel

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BACKGROUND

Breast cancer is a very common site-specific cancer in women in the region of study, and is associated with social stigma, morbidity and mortality in women of the southern part of Odisha. Locally Advanced Breast Cancer (LABC) is a subset of breast cancer characterized by the most advanced breast tumours in the absence of distant metastasis. The need to identify LABC as a separate group of breast cancers arose in view of the high associated rate of loco regional and systemic failure (in the absence of distant metastasis at presentation) despite the best efforts of surgeons to remove loco regional spread of the tumour in its entirety. Management is complex and multimodality treatment (surgery, chemotherapy, and radiotherapy in combination with hormonal and targeted therapy if required) can significantly improve outcomes in this selected group of patients.

We wanted to evaluate the efficacy of multimodality treatment as provided in this institution for treating breast cancer. We also wanted to compare the various chemotherapeutic agents that are available and their efficacy in patients of southern part of Odisha.

METHODS

This prospective study was conducted in the Postgraduate Department of General Surgery, M.K.C.G. Medical College & Hospital, Berhampur, Orissa from July 2017 up to June 2019 including 6 months of follow up period. The total number of patients with a confirmed diagnosis of breast cancer and treated at our hospital was 78 of which 49 patients were included in the study as they fall into the category of locally advanced breast cancer. A detailed clinical history was taken and thorough clinical examination was done to arrive at a provisional diagnosis of carcinoma breast. The patients were then subjected to undergo complete haemogram, F.N.A.C. of the breast lump and / or lymph node, core-needle biopsy, U.S.G., mammography, Chest X ray, Hormone receptor study (ER / PR) and C. T. Scan thorax / abdomen to identify distant metastasis. All confirmed breast cancer cases with stages IIIA IIIB IIIC were included in the study. Depending upon operability patients were undertaken for surgery (modified radical mastectomy) and adjuvant chemotherapy or neoadjuvant chemotherapy (NACT) followed by surgery. According to the chemotherapeutic agents available in the institution 3 regimen of chemotherapeutic agents were tried namely

AC (Doxorubicin 60 mg / m^2 Cyclophosphamide 600 mg / m^2 4 cycles at 21 days interval) regimen,

CAF (Doxorubicin 60 mg / m^2 Cyclophosphamide 600 mg / m^2 5-fluorouracil 600 mg / m^2 6 cycles at 21 days interval) regimen.

Paclitaxel single drug (180 mg / m^2 I.V. 3-hour infusion 3 - 4 cycles every 21 days) regimen.

The response rate was evaluated. Toxicities were evaluated before each cycle according to national cancer institute common toxicity criteria. Dose adjustments were made based on blood counts, renal and liver function test. Patients were followed up after surgery for 6 months. Recurrence and disease free survival was seen. The prospective study was approved by the Ethics Committee of MKCG MCH, Berhampur Odisha.

RESULTS

Out of 78 diagnosed breast cancer cases, 23 were grouped as early breast cancer which accounts for 29.4 % of total, 49 were grouped as locally advanced breast cancer accounting for 62.8 % of cases and remaining 6 were metastatic disease i.e. 7.7 %. Maximum presentation was locally advanced breast cancer. LABC comprises 62.8 % of our series.

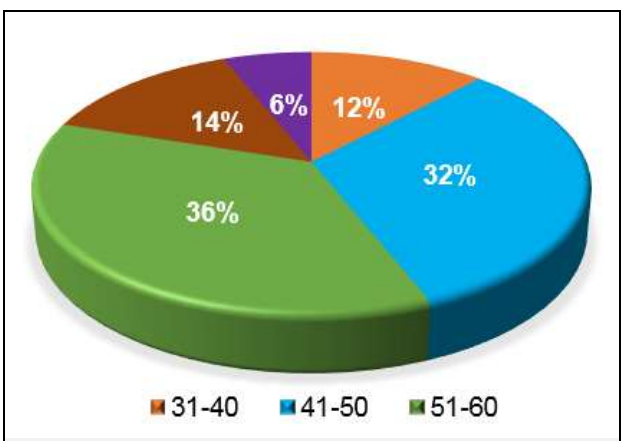

Table 1 - Age Distribution of Locally Advanced Breast Cancer

Among LABC patients maximum number of cases were seen in the age group of 41-50 and 51-60 with 16 and 18 patients respectively. 7 cases were in age group 61-70, 5 cases were seen in younger age group 31-40 and 3 cases were seen in the 71-80 age group.

The majority of patients presented as LABC between 41-60 years. They formed 68 % of the study.

Youngest patient in our series was 32 years old and oldest patient was 74 years old.

Out of 49 patients 5 belonged to upper socioeconomic society, 16 were from middle class and 28 patients belonged to lower class. The incidence of LABC in high socioeconomic class was 10.2 % whereas in middle SES it rose to 32.7 % and majority of patients belonged to low SES and comprised 57 % of the study.

Stage of Disease	Number of Patients	Percentage
Stage IIIA	24	48.9 %
Stage IIIB	18	36.7 %
Stage IIIC	7	14.3 %

Table 2. Staging of Cases as Per AJCC Classification

48.9 % of total LABC patients belonged to stage IIIA and 36.7 % of patients belonged to stage IIIB. Remaining 14.3 % cases were in stage IIIC.

Patients presented to the hospital with a large lump in the breast due to their ignorance and low socioeconomic status and social stigma associated with the disease.

Out of 49 patients, at the time of diagnosis 18 patients were operable which accounts to 36.7 % of cases and 31 patients were initially unresectable LABC which accounts for 63.3 % of cases. 32.7 % patients underwent surgery first followed by chemotherapy. 31 unresectable patients received neoadjuvant chemotherapy followed by surgery and then remaining cycles of chemotherapy.

Therapeutic Option	Number of Cases	Percentage
Surgery + chemotherapy	16	32.7 %
Neoadjuvant chemo + surgery + adjuvant chemo + radiotherapy	31	63.3 %
Surgery	2	4 %

Table 3. Multimodal Treatment Options for Locally Advanced Breast Cancer

Regimen used	No. of Patients	Clinical Complete Response after 3-4 Cycles	Clinical Partial Response after 3-4 Cycles	Clinical no Response after 3-4 Cycles	% of CR:PR
AC	12	1	8	3	8:67
CAF	10	2	7	1	20:70
Paclitaxel	9	2	7	0	22:77
Total	**31**	**5**	**22**	**4**	**16:71**

Table 4. Chemotherapy Regimen Used and Its Response

Maximum clinical response was seen in paclitaxel receivers i.e. complete response in 22 % and partial response in 77 % of cases with 0 no response rates. CAF regimen also has good results with 20 % complete response and 70 % partial response as compared to AC alone which gave only 8 % complete response. After 6 months of follow up of multimodal treatment of LABC the overall survival rate was maximum in stage IIIA with 95.8 %, followed by 83.3 % in stage IIIB and 42.8 % in stage IIIC.

DISCUSSION

A total of 78 patients was involved in the study. 49 out of 78 were diagnosed as locally advanced breast cancer. In our study early breast cancer was seen in 29 % whereas 62.8 % presented with locally advanced breast cancer. These locally advanced breast cancers were mostly seen in low socioeconomic group which is at 57.1 % in this study. Maximum number of locally advanced breast cancer is seen in age group of 51-60 years followed by 41-50 years. Youngest patient in our series was 32 years old and oldest patient was 74 years old. Only 12 % of patients were below 40 years of age. The average age at presentation was 52.3 years in our research which was slightly higher than the 43-46 years reported by Bangal et al.[1] According to Chopra et al.[2] mean age of subjects was 50.1 ± 10.5 years. Age distribution showed two peaks at 41-50 years and 51-60 years to which this study is comparable. Chopra et al**.** study shows that 45 % of the total patients were having advanced carcinoma breast (Stage III) at the time of reporting and 77 % of these patients were below 50 years of age.

Maximum number of locally advanced breast cancer presented in stage IIIA i.e. 48.9 % and stage IIIB i.e. 36.7 % followed by IIIC at 14.3 % in this study. It is comparable to Saxena et al.**[3]** study at a New Delhi hospital, stage III-b (35 %) followed by stage III-a (27 %) and II-b (16 %).

Breast cancer has more prevalence in upper middle class according to international journal of western lifestyle but in our study, it is seen more commonly in low socioeconomic class because of ignorance of the population. India is mainly a rural population and there is lack of awareness among the people. There is a lack of rigid screening programme to detect breast cancer at an early stage. So, patients mainly present as locally advanced cases. Other factors are social and religious causes, fear of mutilating surgery and social inhibition and stigma associated with the disease.

The delay in diagnosis and consecutive challenges in management pose a hidden economic burden over the government as the treatment cost for breast cancer detected at stages I, II and III cost significantly much less than at stage IV disease in developing countries. A study conducted by Groot et al**.** established this fact with cost figures[4] recognizing the increasing burden of cancer in India as per the GLOBOCAN and ICMR predictions.

In our present study NACT was given to 63 % of patients. Clinical complete response was observed in 16 % of patients and partial response was observed in 71 % patients.

Table 5. Outcome of Management

In paclitaxel based NACT complete response was 22 % and partial response in 77 % while in CAF regimen complete response was seen in 20 % and partial response in 70 %. And in CA regimen complete response was seen in 8 % and partial response in 67 %.

Ghersi et al.[5] reviewed 28 studies and found statistically significant survival advantage of taxane-containing regimens. According to Formenti et al.[6] in 2003 offered 8 cycles of paclitaxel to the 44 patients with stage IIb / III and complete response rate was 9 %.

As first- or second-line treatment, a 24 -h infusion of 250 mg / m^2 paclitaxel every 21 days displayed high levels of antitumor activity, with overall response rates of 56 % and 62 %, as reported by investigators at the MD Anderson Cancer Centre (MDACC) and the Memorial Sloan-Kettering Cancer Centre (MSKCC), respectively.[7] These studies provided the first evidence that paclitaxel was very active as single-agent therapy for metastatic and locally advanced breast cancer. Phase I studies have indicated that the maximum tolerated dose of paclitaxel given by 24 -h infusion every three weeks is 175-200 mg / m^2 without G-CSF support and 200 - 250 mg / m^2 with G-CSF support.[7]

We followed up the patients for 6 months after multimodality therapy overall survival rates were found to be stage IIIA 95.8 % in stage IIIB 83.3 % and 42.8 % in stage IIIC. Locoregional recurrence was seen in 5 patients in our series. According to Klein et al.[8] study breast cancer treated with NACT followed by surgery and RT is associated with low rates of LRR (approximately 10 % at 5 years) and relatively high OS (greater than 75 % at 5 years)

In the present study we could not arrive at 3 years or 5 years overall survival and disease free survival rate due to limited time period.

CONCLUSIONS

Locally advanced breast cancer is a major problem in the region of study. Patients mainly present in late stages because of lack of rigid screening programs, lack of awareness, and social stigma attached with the disease. For similar reasons, it is more prevalent in low socioeconomic status in the region of study. In LABC, the combination of neoadjuvant chemotherapy, modified radical mastectomy, and adjuvant chemotherapy achieved superior locoregional control and delayed systemic dissemination. In this study, maximum clinical response was seen in paclitaxel receivers followed by CAF regimen.

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