Original Article

Role of neo-adjuvant chemotherapy in locally advanced breast cancer

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Abstract

BACKGROUND AND AIMS: Locally advanced breast cancer (LABC) is common in developing countries. The advancement of disease leads to decreased probability of radical cure and increase in treatment cost. The study evaluated neo adjuvant chemotherapy with MRM and MRM followed by adjuvant chemotherapy and also the effectiveness of neo-adjuvant chemotherapy in down staging advanced disease and offering radical cure. **SETTINGS AND DESIGN:** A rural hospital-based prospective comparative study. **MATERIALS AND METHODS:** All histologically proven and investigated LABC (T3 N0, T3N1, Any T4, Any N2/N3, M0) were selected as subjects and divided into two groups. One group received neo adjuvant chemotherapy (5 fluorouracil, adriamycin and cyclophosphamide) followed by modified radical mastectomy and other group received adjuvant chemotherapy after modified radical mastectomy. Both groups were compared for disease free survival, overall survival and post-operative complications. Tumor response to chemotherapy in neo adjuvant group was also studied. **STATISTICAL ANALYSIS:** All continuous variables were analyzed using student's' test and categorical variable by Fischer exact test. **RESULTS:** Thirty one patients were enrolled, of these 16 patients received neo adjuvant chemotherapy. Clinical complete response was observed in two patients (12.5%). Clinical partial response was found in 12 patients (75%) and no response was seen in two patients (12.5%). Disease free survival and overall survival was 82% in neo adjuvant group while in adjuvant group disease free survival was 75% and overall survival was 83%. Post operative complications were similar in both groups. **CONCLUSION:** Neo adjuvant chemotherapy helps in down staging LABC and offers opportunity *in vivo* to assess the effect of chemotherapy on individual basis. There was no significant difference in disease free survival, overall survival and post operative complication in between two groups.

Key Words: Breast cancer, locally advanced breast cancer, neo adjuvant chemotherapy, adjuvant chemotherapy

Introduction

Carcinoma breast is the most common malignancy in women.[1] It is the second most common malignancy after cervical cancer in India. Around 90,000 new cases of breast cancer are diagnosed every year in India[2] and majority of them present as Locally Advanced Breast Cancer (LABC).[3] Because of local advancement of disease, patient cannot be offered radical cure and it also increases the cost of treatment and causes psychological and physical suffering. Neo adjuvant chemotherapy is a commonly used modality for LABC which offers an upfront systemic therapy in these high risk patients with expected micro-metastatic burden and also helps in down staging the disease thus making it emenable to radical surgical cure. Many clinical trials and randomized control trials have been done in patients with LABC with aim to improve therapeutic decision making and survival, but in Indian scenario with large number of cases presenting as LABC, an impending health problem, this is an important area of research to find out treatment solution for locally advanced disease and this study is an effort in rural population in central India.

Materials and Methods

The study was carried out at a tertiary care rural hospital between September 2009 and January 2013.

All pathologically proven and investigated cases of Carcinoma Breast were studied and patients with LABC (T3 N0, T3N1, Any T4, Any N2/N3, M0) were enrolled as subjects. Inflammatory breast carcinoma, metastatic breast carcinoma, breast cancers during pregnancy and malignant Phyllodes tumor were excluded from the study. Ethical clearance was obtained from the institutional review board of the institution.

LABC was defined as any tumor larger than 5 cm in size or that involved the skin or pectoralis major or chest wall. Locally advanced disease also included patients with fixed axillary lymph nodes or ipsilateral supraclavicular, infra-clavicular nodal involvement. Thus all of stage 3 disease, as is subset of stage 2B (T_3N0) was considered locally advanced.[4] These patients were further divided into operable (T3N0, T3N1) and inoperable disease (T4N2/N3).[5]

The chemotherapeutic regime used was 5- Fluorouracil, Adriamycin and cyclophosphamide (FAC). 5- Fluorouracil was given in dosage of 600 mg/m^2 body surface area (BSA) administered intravenous over 4 h. Adriamycin – 60 mg/m^2 BSA administered i/v over 4 h and Cyclophosphamide –600 mg/m^2 BSA administered intravenous over 4 h. In both adjuvant and neoadjuvant group, the allocation was done without formal randomization. Based on clinical judgement, patients with smaller tumor size (202 cc) were enrolled in adjuvant group as against bulkier lesions (282 cc) which were enrolled in the neo adjuvant group.

The Response to chemotherapy was studied in all patients who received neo adjuvant chemotherapy according to the Response Evaluation Criteria in Solid Tumors published in February 2000 by European Organization for Research and Treatment of Cancer[6] was used to evaluate the tumor response and it was documented as follows:

- Clinical Complete Response (cCR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm
- Clinical Partial Response (cPR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (cPD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative

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increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for Partial Response (PR) nor sufficient increase to qualify for Progressive Disease (PD), taking as reference the smallest sum diameters while on study.

Disease free survival was the secondary outcome measured from time of mastectomy and the appearance of loco-regional recurrence, or systemic metastasis was considered as end point of disease free survival. Overall survival was also measured from time of modified radical mastectomy till death of the patient as a consequence of breast cancer. Loco-regional relapse was defined as any recurrence in the wound, chest wall, axilla, skin or parasternal area on clinical examination and was confirmed by fine needle aspiration biopsy.

Post-operative complications of MRM such as local wound infection, development of seroma, flap necrosis, lymph edema of ipsilateral arm in both groups were recorded and compared.

Statistical analysis was done using statistical software Epi Info developed by cdc Atlanta USA. All continuous variables were analyzed using Student's *t* test after confirming the normality of the data and categorical variables by Fischer's exact test and the results were presented in tabular form.

Results

Out of total 73 females of carcinoma breast studied during the study period, 31 (42%) female patients of LABC were enrolled based on selection criterion. The mean age of presentation was 47 years (range 25-72 years). The mean volume of all the breast lumps was 508 cc. Of the 31 patients 17 (55%) were postmenopausal while 14 (45%) were premenopausal. Twenty three patients were sub classified as operable LABC (T3 N0, T3 N1) and remaining eight were inoperable LABC (T4 N2/N3) [Table 1]. Three patients (all inoperable) refused chemotherapy and surgery; these patients were referred for radiotherapy and were excluded from the study. Five patients belonging to the inoperable group though were not included for final analysis of survival, were only included in neo-adjuvant chemotherapy group with sole intention of assessing the tumor response to neo-adjuvant therapy and they were later on excluded from the analysis as MRM could not be done in them and hence they were not comparable to the other group and were excluded [Figure 1].

Neoadjuvant chemotherapy was given to 16 patients which included 5 inoperable LABCs, clinical complete response was observed in 2 patients (cCR = 12.5%). Clinical partial response was found in 12 patients (cPR = 75%) and Stable disease was seen in 2 patients (SD = 12.5%). Pathological complete response was observed in only 1 patient (pCR = 6.25%).

After above exclusions selected 23 cases were divided into two groups. The First group of 11 patients received neo-adjuvant chemotherapy followed by MRM three weeks after third cycle or if no response after second cycle. The second group of 12 patients underwent MRM followed by adjuvant chemotherapy.

As allocation to intervention was not done by randomization, to assess the equality of both groups, the basic characteristics of two groups were compared and it was found that age, menopausal status, lump size, stage of the disease were statistically equal in both the groups [Table 2].

Patient survival was secondary outcome measure with a mean follow up of 24 months, it was observed that the disease free survival and overall survival was similar in both the groups [Table 3]. These results suggest that neo adjuvant chemotherapy does not offer any survival advantage. Local recurrence and systemic metastasis were also not statistically different in two groups suggesting no advantage of neo adjuvant chemotherapy over adjuvant chemotherapy [Table 4].

Post-operative complications of MRM were compared between the two groups and were found to be statistically similar suggesting that preloading with chemotherapy does not affect post operative wound healing and complications.

Table 1: Distribution of LABC cases

Types of locally advanced breast carcinoma	No. of patients	Percentage (%)
Operable LABC		
Subset of stage 2b (T3N0M0) and	6	19.4
Subset of stage 3a (T3N1M0)	17	54.8
Inoperable LABC		
Remaining stage 3a, stage 3b and Stage 3c	8	25.8
Total	31	100

LABC=Locally advanced breast cancer

Table 2: Comparison of basic characteristics of two groups

Stage	Neo adjuvant chemotherapy (*n*=11)	Adjuvant chemotherapy (*n*=12)	*P* value
T3N0	3	3	0.63
T3N1	8	9	0.90
Mean age	47 years and 1 month	47 years and 7 months	0.89
Mean lump size	294.8 cc	202.68 cc	0.26
Premenopausal	5	6	0.82
Postmenopausal	6	6	0.82

Table 3: Mean follow-up, disease free survival and overall survival in neo-adjuvant and adjuvant group

Follow-up	Neo-adjuvant chemotherapy (*n*=11) (%)	Adjuvant chemotherapy (*n*=12) (%)	*P* value
Mean follow-up	16.3 months	16.5 months	>0.01
Disease free survival	9 (82)	9 (75)	>0.01
Overall survival	9 (82)	10 (83)	>0.01

Discussion

LABC poses a significant clinical challenge due to varied presentation and survival rates which differs from study to study solely due to differences in the institutional therapeutic policies and patient selection and overall poor long term survival.[7] These factors combined with multi modality treatment, financial constraints and compliance issues collectively makes LABC a major health problem in Indian scenario. Multi modality treatment, need for repeated visits to medical centers and financial constraints are major causes of non compliance and is the reason for attrition and follow- up losses.

The mean age of presentation in the current study was 47 years which is consistent with the Indian statistics.[7], but the patients from North America are older (median age of 57 years).[8] Premenopausal women constituted 45% of all LABC. These results are consistent with the world literature available.[7,9,10]

Neo adjuvant or induction chemotherapy helps convert inoperable cases to resectability and increases the rate of breast conservation therapy.[11-14] It also gives a theoretical advantage of early initiation of systemic therapy, delivery of drug through intact vasculature and gives a window to access the response rate. In present study, the tumor response rate was found to be similar to that reported in literature[15-22] [Table 5]. The comparison included studies with taxanes and the results of our study are equal to taxanes and considering the cost factor and affordability. FAC with similar outcome is a good alternative in chemotherapeutic regime in rural Indian population with financial constraints.

The overall survival and disease free survival and occurrence of metastasis was similar in both adjuvant and neo adjuvant group. There was no survival benefit noted in the neoadjuvant group which is similar to the results of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27 trial[15,16] [Table 6].

The result of the present study suggests that neo adjuvant chemotherapy does not offer additional short term (2 years) survival benefit to patients of LABC however it definitely downstages the disease and helps offer surgical resection, so also give an invivo opportunity to assess tumor response to chemotherapy. Due to financial constraints the hormonal status and human epidermal growth factor receptor 2 (Her2) status evaluation was not done in present study except in two cases where no clinical response was noted and they were Her2 positive cases.

Table 4: Mean follow up of cases according to recurrence and death in neo adjuvant and adjuvant group

Follow up	Neo-adjuvant Chemotherapy (*n*=11)	Adjuvant Chemotherapy (*n*=12)	*P* value (ns)
Local recurrence	1	1	0.73
Systemic metastasis	1	2	0.53
Expired	2	2	0.67

ns=Not significant

Table 5: Comparison of results of tumor response from literature with present study

Study	pCR (in %)	cCR (in %)	cPR (in %)
Perloffand Lesnick 1988[17]	NA	22	55
Hortobagyi *et al.* 1988[18]	8	17	71
Banadonna *et al.* 1990[19]	4	17	60
Fisher *et al.* 1998[14]	21	17	58
Powles *et al.* 1995[13]	10	28	51
Semiglazov *et al.* 1994[20]	29	35	57
Van der Hage *et al.* 2001[21]	3.7	6.6	42.3
Raina *et al.* 2011[22]	7.8	13.3	71.1
Gupta *et al.* 2011[7]	13.2	16.7	37
Present study 2011	6.6	13.3	73.4

pCR=Pathological complete response; cCR=Clinical complete response; cPR=Clinical partial response

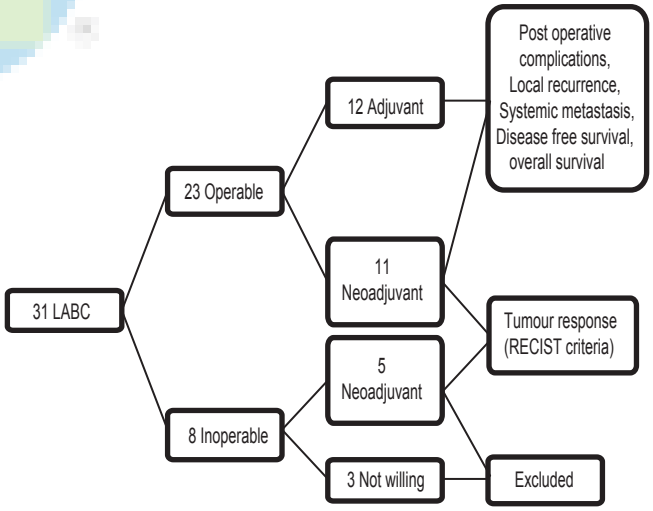

Figure 1: Algorithm of patient's treatment

Table 6: Comparison of DFS and OS from literature with present study

Study	No. of patients	Median follow-up	Neo-adjuvant (%)		Adjuvant (%)	
			DFS	OS	DFS	OS
Van der Hage *et al.*[21]	698	56 months	65	82	70	84
Fisher *et al.*[14]	1523	9.5 years	55	69	53	70
Raina *etal.*[22]	128	5 years	41	58	Not compared	Not compared
Gupta *et al.*[7]	54	3 years	61.1	78.5	Not compared	Not compared
Present study	31	2 years	82	82	75	83

DFS=Disease free survival; OS=Overall survival

Conclusion

LABC is a common presentation of carcinoma breast in Indian population. Advancement of the disease ultimately affects the overall prognosis and increases the cost of treatment. FAC, a financially affordable chemotherapeutic regime helps in down staging the disease and surgical resection and the results are similar to MRM with adjuvant chemotherapy. It is important to note that in patients with LABC with large tumor mass upfront chemotherapy offers only chance of curative resection. However large randomized control trials from multiple centers across India will help in establishing the treatment guidelines of LABC patients in the Indian scenario.

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