



A STUDY ON INTERIM ANALYSIS OF THE EFFECTS OF NEO ADJUVANT CHEMOTHERAPY ON CARCINOMA BREAST

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KEYWORDS :

AIM AND OBJECTIVES

1. To determine the role and outcome of Neo adjuvant chemotherapy administered in Locally Advanced Breast Cancer (LABC).
2. To study the response of the tumour after chemotherapy regarding the Size of the tumour, Axillary status, Skin changes if any
3. To determine and study, to what extent the inoperable LABC becomes amenable to surgery.
4. To evaluate the role of NACT in improving the quality of life and morbidity in LABC patients.

LIMITATIONS OF THE STUDY

1. Unresolved issues are there like Selection of Patients, Tumor factors, Clinical factors, and Regional lymph nodes.
2. Some of the patients didn't turn up for review and follow up.
3. Limited availability of resources such as chemotherapy drugs on regular basis.
4. Non -availability of hormone receptor studies in trucut biopsy specimens
5. Many patients returned to their native for surgery after completion of chemotherapy.

MATERIALS AND METHODS

The study was done during the period from June 2018 to June 2019 in the department of General Surgery, Thanjavur Medical College and Hospital, Thanjavur. All the patients with Breast cancer were examined clinically. Patients with LABC were selected for the study.

Locally advanced carcinoma breast was defined as per AJCC staging and included stage IIB, Stage III A and stage III B tumors. Exclusion criteria included any contraindications for chemotherapy.

INCLUSION CRITERIA

- Stage IIb
- Stage IIIa
- Stage IIIb
- Stage IV with axillary metastasis

EXCLUSION CRITERIA

- LABC with Distant metastasis (except axillary mets)/ Palliative chemotherapy
- All early breast cancers who underwent surgery with or without adjuvant chemotherapy.
- Any contraindications for surgery
- Bilateral breast disease

INVESTIGATIONS

- Complete Haemogram
- Renal Function Tests
- Liver Function Tests
- FNAC
- X-Ray Chest
- CT chest
- ECG
- Ultrasonogram Abdomen
- Echocardiogram
- Skeletal survey

FNAC was done to confirm the diagnosis, in all patients. Routine investigations like complete hemogram, renal function tests, and liver

function tests were done. Metastatic work up was done. Cardiac assessment was done with echocardiogram for adriamycin based chemotherapy.

Detailed history and clinical examination of the patients were carried out as per the proforma. Tumor size assessed clinically two longest perpendicular diameter and the products of the perpendicular diameters were calculated. All Patients have taken CT scan breast before starting Neo adjuvant chemotherapy.

After completion of 3 cycles at the end of 3rd week, tumor size measured clinically and C.T. Breast taken regularly.

Chemotherapy was administered after admitting the patients and calculating body surface area. Antiemetic premedications which included Inj ondansetron 4 mg, Inj dexamethasone 8 mg, and Inj ranitidine 100mg were given.

Intravenous infusions of cyclophosphamide 600mg/m², adriamycin 60mg/m² were given as per AC regimen. Infusions of adriamycin and paclitaxel 175mg/ m² were given in AT regimen. Patients were observed for side effects and discharged with oral ondansetron prescription for 3 days.

Chemotherapy was repeated every 21 days after assessing the tumor response clinically for maximum of three to six cycles. After two weeks of the last preoperative cycle, tumor size was assessed clinically and with a repeat CT Breast. RECIST criteria were used to assess the tumor response clinically. Patients were worked up for modified radical mastectomy and surgery was done. All specimens showed tumor free margins.

DOSAGE AND SCHEDULE

Choosing the regimen

There is no single regimen that has emerged as the treatment of choice. Several trials have demonstrated that a 10% - 20% higher response rate has been observed with Doxorubicin / Epirubicin containing regimen with an increase in median survival from 14-18 months and an increase in median time of treatment failure from 5 to 7 months. The shorter duration of regimen and relative ease of administration favor this **AC regimen** as the first choice of therapy and in few patients **AT regimen** was used.

Regimens

FAC

- 5 FU 500mg/m²
- Adriamycin 60mg/m²
- Cyclophosphamide 600mg /m²
- On D1 every 3 weeks – 6 cycles

AC/ AT

- Adriamycin: 60mg/ m²
- Cyclophosphamide: 600 mg/ m² /Paclitaxel 175 mg/ m²
- On D1 every 3 weeks – 3 cycles

CAF

- Cyclophosphamide : 100mg/ m², D1-14
- Adriamycin : 30mg/ m² D1, 8
- 5FU : 500 mg/ m², D1, 8
- 6 cycles are given, once in 4 week

CMF

- Cyclophosphamide : 750 mg/ m²
- Methotrexate : 50mg/ m²
- 5-FU: 600mg/ m²
- Given once in every 3 weeks, for 6 cycles.

FEC

- 5FU 500mg/ m²
- Epirubicin 50mg/ m²
- Cyclophosphamide 500 mg/ m²
- On day one, every 3 weeks for 6 cycles

TAC

- Docetaxel 75 mg/ m² on D1
- Adriamycin 50mg/ m² on D1
- Cyclophosphamide 500 mg/ m² on D1
- 6 cycles are given, every 3 weeks

AC-T

- Adriamycin : 60mg/ m², D1
- Cyclophosphamide: 600 mg/ m²
- For 4 cycles once every 3 weeks
- Followed by Paclitaxel 175mg/m²
- Every 3 weeks for 4 cycles

RESULTS

The study was conducted between June 2018 and June 2019 at Thanjavur medical college. 40 patients were eligible for the study. Among them 5 patients didn't consent for the study, 4 patients lost for follow up. On evaluation, 2 patients had lung and spine metastasis. Hence, 29 patients were included for the final study.

DEMOGRAPHIC PROFILE

Clinical parameters of 29 patients were analyzed. The range of patient's age was 40 to 80 years and mean age at appearance was 55 years. 31% patients fell in the age group of 40-49 years & 51% fell in the age group of 50 to 59 years. 18% were above 60 years. Eighteen patients in the study group were post menopausal and 11 patients were pre menopausal. There was a predominance of right sided Breast cancer. Sixteen (55%) patients had cancer of the left Breast where as thirteen patients had left sided Breast cancer (45%). Fourteen patients (48%) had upper outer quadrant of the Breast. Seven patients (24%) had tumor in lower outer quadrant. 5 patients (17) had tumour in the central quadrant. Twelve patients (41%) had T3 tumor at presentation whereas seventeen patients (59%) had T4 presentation. 9 patients (31%) had III-A, 17 (59%) patients had III B, 3 (10%) patients had IV. The mean size of the tumor in its longest diameter was 7.04 cms.

COMPLICATIONS

Alopecia and vomiting were the commonest side effects noted in the study. All the patients developed alopecia of varying intensity. 12 patients had Black discoloration of nails, palms. Five patients developed anemia that was managed with Hematinics and transfusion.

Primary tumor response to neoadjuvant chemotherapy

29 patients were finally assessed for study of NACT in locally advanced Breast cancer. Among them, nineteen patients (65%) received AC regimen while 10 patients (35%) received AT regimen. Out of 29, seventeen patients (58.6%) had complete response. Ten patients (34.4%) patients had partial response and 2 patients (7%) had no response according to RECIST criteria.

Table – 1
Age Distribution Among The Patients In The Study Group

Age	No. of Cases	Percentage (%)
40-49	9	31
50-59	15	51
>60	5	18
Total	29	100

Chart – 1 Age Distribution Among The Patients In The Study Group

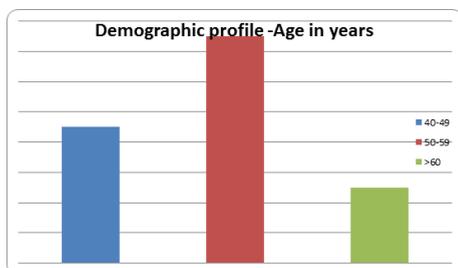


Table – 2 Quadrant Distribution Among The Patients In The Study Group

Quadrant	No. of Cases	Percentage (%)
UO	14	48.2
LO	7	24.1
C	5	17.2
UI	2	6.8
LI	1	3.4
Total	29	100

Chart – 2 Quadrant Distribution Among The Patients In The Study Group

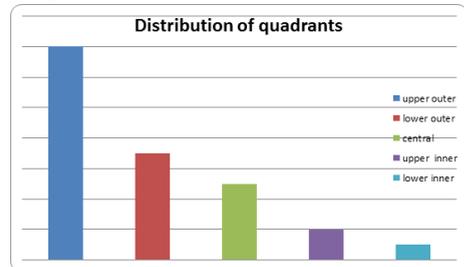


Table – 3 Side Distribution Among The Patients In The Study Group

Side	No. of Cases	Percentage (%)
Right	16	55.2
Left	13	44.8
Total	29	100

Chart – 3

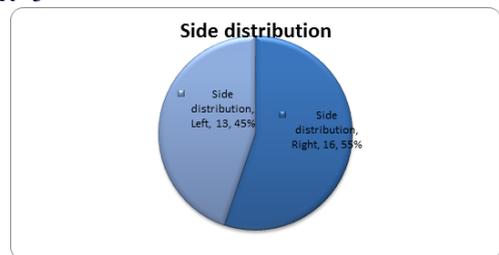


Table – 4 Distribution Of Patients According To Tnm Classification

TNM Classification	No. of Cases	Percentage (%)
T ₃ N ₁ M ₀	9	31
T _{4b} N ₀ M ₀	1	3.5
T _{4b} N ₁ M ₀	10	34.5
T _{4b} N ₂ M ₀	2	7
T _{4c} N ₁ M ₀	4	13.7
Others	3	10.3
Total	29	100

Chart - 4 Distribution Of Patients According To TNM Classification

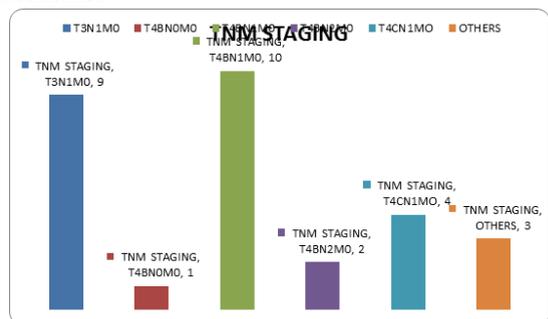


Table – 5 Distribution Of Patients According To T- Staging Of Tnm Classification

T	No. of Cases	Percentage (%)
T ₃	12	41.3
T ₄	17	58.7
Total	29	100

Chart 5 - Distribution Of Patients According To T-Staging

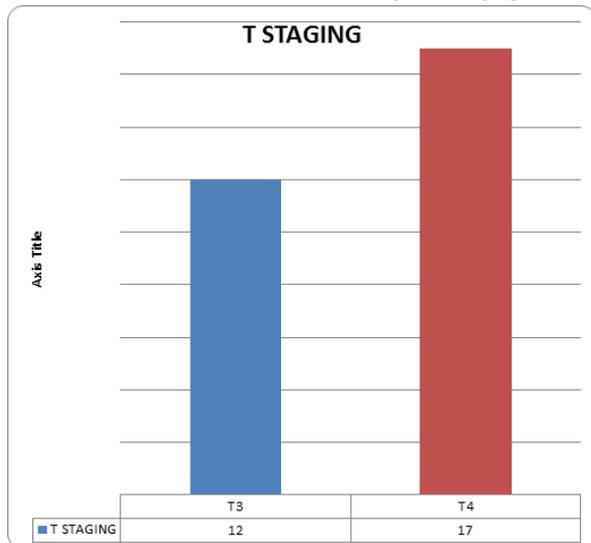


Table – 6 Distribution Of Patients According To Clinical Staging

Stages	No.of Cases	Percentage (%)
Stage IIIa	9	31
Stage IIIb	17	58.6
Stage IV	3	10.4
Total	29	100

Chart – 6 Distribution Of Patients According To Clinical Staging

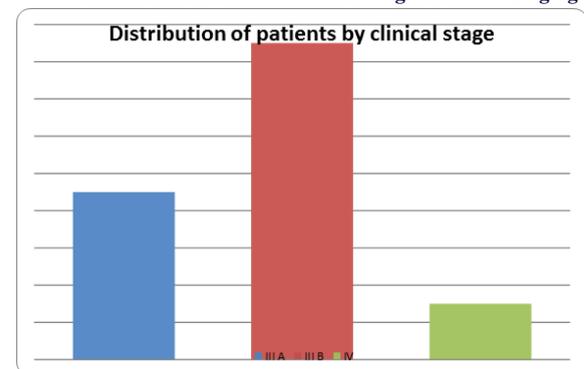


Table – 7 Chemotherapy Regimen Used

REGIMEN	No of patients	PERCENTAGE
AC	19	65.5
AT	10	34.5

Chart – 7 – Chemotherapy Regimen

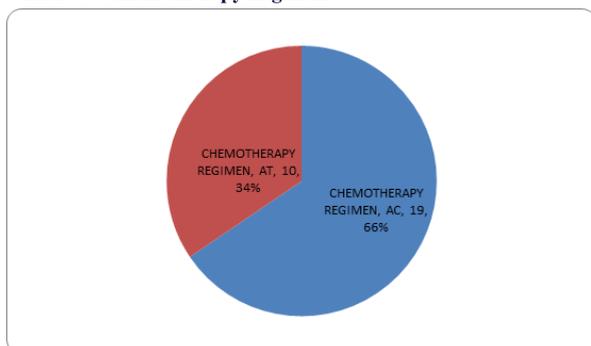
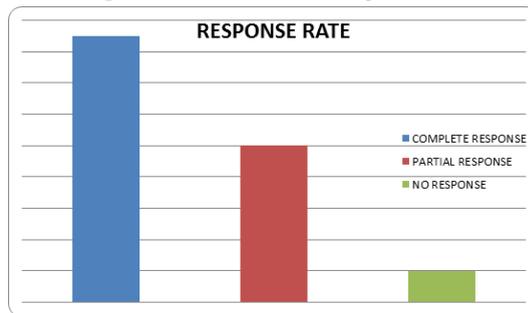


Table – 8 Response Rate Of Nact According The Recist Criteria

Response	No.of Cases	Percentage (%)
Complete	17	58.6
Partial	10	34.4
No Response	2	7
Total	29	100

Chart – 8 - Response Rate Of Nact According The Recist Criteria



Mean size of Tumor in cm for

Complete Response	: 5.53
Partial Response	: 6.33
No Response	: 8.83
Mean	: Before NACT 7.04 after NACT 3.5

DISCUSSION

Over the last decades Neo adjuvant Chemotherapy has changed the way in which locally advanced carcinoma breast is managed.

The study was designed with the aim of assessing the efficacy of Neo adjuvant chemotherapy in TMCH, THANJAVUR

An objective response to neo adjuvant chemotherapy in primary lesion provides important in vitro evidence that this therapy being used has antitumor activity. Tumor at remote sites will be sensitive as well.

Various Chemotherapy combinations have been described in literature. Over all, clinical response rates vary in different studies between 60% to 90%. Most common regimen used here is Adriamycin, cyclophosphamide.(AC regimen) and Adriamycin and Paclitaxel (AT regimen).

In 1978, Bill et al avowed a response rate of 82% to FAC regimen when compared with 62% response rate of 5-fluorouracil, methotrexate, cyclophosphamide. In a study of 372 patients who received NACT with four cycles of FAC regimen Keurer showed a complete response in 12% Boti et al in fifty six patients showed an overall outcome of 82%.

The response rate in European Organization for Research and Treatment of Cancer breast corporative group trial (EORTC) in 1991 using 4 cycles of pre-operative 5 – fluorouracil, epirubicin, cyclophosphamide was only 49%. The recent introduction of chemotherapy regimens using docetaxel have been shown to have significant better response rates. Expecting same line of better results we have followed A.C regimen primarily in our study in TMCH, Thanjavur.

40 patients were eligible for the study. Among them 5 patients didn't consent for the study.4 patients lost for follow up. On evaluation, 2 patients had lung and spine metastasis. Hence, 29 patients were included for the final study.

The reasons for this drop out could be the need for multiple hospital visits and side effects of the chemotherapy. Even in western studies like NSABP B-27 only 80% of the total patients inducted in the study had completed the treatment.

DEMOGRAPHIC PROFILE

The mean age at presentation to hospital 55 years with majority in 50-59 years. The mean longest diameter of tumor at presentation in this study was 7.04 and after NACT were 3.54.

RESPONSE TO NEO ADJUVANT CHEMOTHERAPY

All patients with LABC received three to six cycles of AC regime with cyclophosphamide 600mg/m², adriamycin 60 mg/m² or AT regime with adriamycin 60 mg/m², paclitaxel 175 mg/m² at intervals of 21 days.

In a study on preoperative chemotherapy conducted in patients with operable breast cancer, a response rate of 80% and complete pathologic response in 13% was seen.

The following are taken as predictor of response.

I. Clinical: Size of the Tumor

- Grave signs such as edema and ulceration.
- Nodal Status: Size, Number, Group and fixity of Tumor.

ii Epithelial elements i.e. FNAC

- Expression of differentiation of neoplastic cells.
- Pre and post operative size and shape staging of neoplasm.

iii Investigations:

- CT chest, as it is the most accurate non – invasive technique of identifying the extent of residual carcinoma.
- LFT is repeated to find out any rise in Alkaline phosphatase.
- X-Ray used for .skeletal survey.

SIZE AS A PREDICTOR OF RESPONSE

The mean size of tumor in patients with complete response was 5.53, 6.33 for partial response, and 8.83 for no response.

Kurer et al has found smaller tumor is associated with a complete pathological response in 372 patients receiving adriamycin based neo adjuvant chemotherapy (P.value <0.1). The size of the primary tumor has also been found to be associated with survival.

Valagussa shown the five year survival rate were 65%, 36, 16% for tumor volume measuring <5cm, 5-10cm and > 10cm respectively.

After completion of three cycles of NACT the tumor size, grave signs like edema and ulceration decreased in 78% of cases

AXILLARY NODE STATUS AND RESPONSE

Patients with clinically negative axilla had a significantly better chance of having complete response than in patients with clinically positive axilla. Out of 27 patients who were node positive 15 patients became clinically negative after completion of 3 cycles of chemotherapy. In the remaining 2 patients size of the node and their number has decreased.

SKIN INVOLVEMENT AND RESPONSE

Tumors without skin involvement showed a significantly better response to chemotherapy assessed by W.H.O. criteria. The better response shown by tumors with smaller size, clinically node negative and no skin involvement suggest that tumor cells may become more resistant as the tumor grows.

This is in concordance with the Goldie – cold man Hypothesis that the likelihood that resistant cells are present is a function of tumor size (or) the number of tumor cells and the spontaneous mutation rate of the cells. Histologically all the tumors turned out to be infiltrating ductal carcinoma(NOS type)

This study shows that the NACT with AC/AT regimen effects dramatic regression of the Breast lesion in apparently 70% to 80% The index lesion and axillary metastasis have disappeared following the 3 cycles of AC/AT regimen.

16 patients underwent modified radical mastectomy in our hospital.

2 patients were non-responders. 11 patients went to their native for undergoing surgery.

Out of 29 patients, 1 patient had malignant phyllodes and the rest all had invasive ductal carcinoma.

The study also shows that the tumor shrinkage and disappearance increased the sense of well being among of the patients, their confidence level enhanced: After the NACT technical operability of the tumor has improved. What seemed to be Inoperable became amenable to modified radical mastectomy in 60 to 70% of patients.

After establishing the loco regional control by above surgeries, these patients were followed up by adjuvant chemotherapy and adjuvant radiotherapy.

CONCLUSION

- Carcinoma Breast is a significant health problem attending surgical outpatient department in TMCH, THANJAVUR.
- Decreased awareness among patients about carcinoma breast makes them to present at late stages.

- As the patient need multiple visits, many lost for follow up.
- Locally advanced Cancer Breast with axillary node and grave signs like edema and ulceration is one of the presentation among all Carcinoma patients attending surgical Outpatients of TMCH, THANJAVUR.
- After Neo adjuvant chemotherapy, most of the Inoperable locally advanced Breast cancer became technically operable.
- Appropriate surgery done with or without post operative events in 78% of patients who became symptom free, and their quality of life improved. Survival period is prolonged and their disease free survival also improved.
- Neo adjuvant chemotherapy for locally advanced Breast cancer definitely paves the way for successful surgery in most cases, thereby making patients free from agonizing symptoms, giving satisfactory quality of life without much burden to the individual, family & society.