Study of feasibility and efficacy of neoadjuvant chemotherapy in cases of locally advanced breast cancer

Arun V Dawle\textsuperscript{1}, Satish Girebinwad\textsuperscript{2}

\textsuperscript{1}Associate Professor, Department of General Surgery, SRTR Medical College, Ambajogai, Maharashtra
\textsuperscript{2}Lecturer, Department of Surgery, SRTR Medical College, Ambejogai, Maharashtra

Corresponding Author:
Dr. Arun Dawle
Email: drarundawle@gmail.com

Abstract:
Chemotherapy regimens most commonly used are Bonnadonna designed CMF (Cyclophosphamide Methotrexate 5fluorouracil), doxorubicin based CAF (Cyclophosphamide Adriamycin 5fluorouracil) or AC (Adriamycin Cyclophosphamide) regimen along with hormonal therapies which have been shown to significantly control disease progression, relief from symptoms and improve survival. Because of substantial evolution in the management of advanced breast carcinoma neoadjuvant treatment with chemotherapy is being used increasingly with minimal possible side-effects. Hence CMF and CAF have been tried in the present study to observe the feasibility and efficacy of neoadjuvant chemotherapy in cases of locally advanced breast cancer. CMF (Cyclophosphamide Methotrexate 5fluorouracil) was used in 66.67\% of cases and, doxorubicin based CAF (Cyclophosphamide Adriamycin 5fluorouracil) was used in 33.33\% of cases. All patients on chemotherapy developed the side effects of GIT, Hematological and alopecia. Of all the patients, 25 needed all six cycles of chemotherapy, three were given only one cycle and two patients were given only two cycles of chemotherapy. Radiotherapy was given in 92\% of patients.

The response of advanced breast cancer to treatment with combination chemotherapy along with hormonal therapy is an index of nature of the carcinoma and this response provide a guide for the selection of further treatment. Therefore, careful serial recording of the objective measurements of any change in lesions is invaluable as an aid in evaluating the nature of the response.

Key words: Neoadjuvant chemotherapy, Locally advanced breast cancer, Chemotherapy

INTRODUCTION:
Cancer of the breast is the commonest malignant tumor occurring in females worldwide.\textsuperscript{1,2} In India it is the second most common malignancy in females surpassed only by the incidence of carcinoma cervix.\textsuperscript{3,4,5}

Cervical and breast cancer accounts for 38 to 50\% of total cancer load in females. The incidence of Ca. breast is about 21.9 to 28.3 per 10000 population and is a leading cause of cancer deaths in females in India with age adjusted mortality of 5.4 per lac population.\textsuperscript{6,7}

With the knowledge of CA BREAST as a SYSTEMIC DISEASE rather than a local one, the role of SYSTEMIC CHEMOTHERAPY came in the picture.\textsuperscript{8} Initially surgery used to play a major role in the diagnosis and management of CA Breast.\textsuperscript{9}

Till 1970s classical radical mastectomy as described by Halsted in 1894 used to be the standard surgical procedure for breast cancer management.\textsuperscript{10}

Nowadays, however, the treatment of breast cancer involves multimodal therapy.\textsuperscript{11}

Multiple randomized studies have demonstrated that the addition of chemotherapy and hormone therapy to surgery or/and radiotherapy improves overall survival in patients with breast cancer.\textsuperscript{12,13}
Chemotherapy regimens most commonly used are Bonnadonna designed CMF (Cyclophosphamide Methotrexate 5fluorouracil), doxorubicin based CAF (Cyclophosphamide Adriamycin 5fluorouracil) or AC (Adriamycin Cyclophosphamide) regimen along with hormonal therapies which have been shown to significantly control disease progression, relief from symptoms and improve survival. Because of substantial evolution in the management of advanced breast carcinoma neoadjuvant treatment with chemotherapy is being used increasingly with minimal possible side-effects. Hence CAF and CMF have been tried in the present study to observe the feasibility and efficacy of neoadjuvant chemotherapy in cases of locally advanced breast cancer.

METHODS:
The present study was carried out in the Department of Surgery, S.R.T.R. Medical College & Hospital, Ambajogai, from June 2004 to December 2006. 30 female patients of age 30 to 80 years having LABC without any systemic metastasis were included in this study.

DIAGNOSTIC WORKUP
At first detailed history was taken & complete physical examination and systemic examination was done. Detailed description of primary growth & regional L.N was noted. Routine Blood investigations chest x-rays KFT, LFT, USG, Abdomen & ECG were performed in each patients at their first presentation.

INCLUSION CRITERIA
i) Histopathologically confirmed breast cancer.
ii) Patient presenting as locally advanced breast cancer
   a) Skin involvement in the form of edema ulceration, infiltration, satellite nodules.
   b) Matted or fixed axillary L.N.
   c) Ipsilateral Supraclavicular / Internal mammary L.N.
   d) Fixity to chest wall.
   e) Arm edema.
iii) No evidence of distant metastasis.
iv) Patients taken no prior treatment viz, Radiotherapy, chemotherapy or surgery.
v) Patients having normal haematocrit, blood counts, Renal & Liver Function Tests.
vi) Patients having no uncontrolled medical conditions like TB, cardiac failure, etc.
vii) Patients much give informed consent for the treatment (in written) after explaining the side effects and probable effectiveness.
viii) She must undergo the definitive procedure wherever appropriate.

MANAGEMENT PROTOCOL
It includes initial 3 cycles of chemotherapy CAF (Cyclophosphamide Adriamycin 5fluorouracil) or CMF (Cyclophosphamide Methotrexate 5fluorouracil) regimens followed by surgery and or radiation as appropriate and later followed by 3 more cycles of chemotherapy during the entire treatment & also during follow-up.

All patients were kept on tamoxifen twice daily for 5 years.

Chemotherapy: - prior to course of chemotherapy complete blood counts renal function tests & liver function tests & ECG were performed and chemotherapy was given when only when the investigations were within normal limits.

Operative Treatment:-
Patients were subjected to modified radical mastectomy or simple mastectomy with axillary clearance as appropriate.

Radiotherapy:-
Patients were given external beam radiotherapy to the whole breast & peripheral lymphatics to the whole breast peripheral lymphatics in the dose of 200 cGy daily four 5 days in a week for 5 weeks up to total dose of 5000 cGy.

In post on patients boost to scar of disease site was given in the dose of 1000 to 1600 cGy at 200 cGy per fraction. On completion of locoregional treatment all patients received the remaining 3 cycles of chemotherapy.

FOLLOW-UP
Response was evaluated on clinical examination every one monthly for 3 months then at 6 months & then 6 monthly.

RESULTS:
The maximum number of patients were in 40-60 years of age. The prevalence of breast cancer was more in post menopausal women compared to pre-menopausal women. Left side was more affected 56.67% vs 40% than right side. The upper outer quadrant of the breast was most commonly affected (60%) than any other quadrant. Lump was the most common presenting symptom (46.2%) followed by pain (43%) and discharge in 10.8%. Family history of carcinoma breast was present in only one patient. Infiltrating Duct Carcinoma (IDC) was present in majority i.e. 86.67% of patients followed by Invasive Lobular Carcinoma (6.67%), Medullary Carcinoma (3.33%) and adenocarcinoma in 3.33%. CMF (Cyclophosphamide Methotrexate 5fluorouracil) was used in 66.67% of cases and, doxorubicin based CAF (Cyclophosphamide Adriamycin 5fluorouracil) was used in 33.33% of cases. All patients on chemotherapy developed the side effects of GIT, Hematological and alopecia. Of all the patients, 25 needed all six cycles of chemotherapy, three were given only one cycle and two patients were given only two cycles of chemotherapy. Radiotherapy was given in 92% of patients.

Table 1: Tumor size and nodal status in NACT group
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### a) Tumor size

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Pre-treatment (NACT)</th>
<th>Post-treatment (NACT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>T1</td>
<td>00</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>00</td>
<td>0</td>
</tr>
<tr>
<td>T3</td>
<td>07</td>
<td>23.33</td>
</tr>
<tr>
<td>T4</td>
<td>23</td>
<td>76.67</td>
</tr>
</tbody>
</table>

Most patients included in our study had tumors of the T4 category (23) and 7 patients were from T3 Category, after NACT administration 9 patient down staged to T2 Category and 2 more patient added in T3 Category.

### b) Nodal status

<table>
<thead>
<tr>
<th>Axillary nodes</th>
<th>No. of Patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically present</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>Clinically absent</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1(b) shows that axillary nodes were affected in 60% of the cases.

### Table 2: Surgical Treatment used in NACT group

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Operation</th>
<th>No. of Patients</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MRM</td>
<td>18</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Simple mastectomy with axillary clearance</td>
<td>05</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Not done</td>
<td>02</td>
<td>08</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Of the 25 patients who completed all the 3 cycles of NACT, 18 underwent MRM, 5 patients underwent simple mastectomy with axillary clearance while no surgery was done in 2 patients.

### Table 3: Response Rate in NACT group

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Response</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Complete response</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>Partial Response</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>Stable disease</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Progressive disease</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Objective response rate (CR+PR)</td>
<td>19</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Clinical benefit rate (ORR + SD)</td>
<td>24</td>
<td>88</td>
</tr>
</tbody>
</table>

Above table shows an objective response rate in 68% of patients and a clinical benefit rate of 88%.

### Table 4: Comparison of post-op outcome between NACT group (group A) and Adjuvant CT group (Group B)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to achieve primary closure</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Wound gape</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Persistent raw area over chest</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Additional surgery</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Above table shows greater post-operative morbidity in Group B patients.
DISCUSSION:

In our study slight preponderance was seen on the left side which was involved in 56.67% and right side in 40% of cases. Bilateral cancer was found in 3.33% patients. As per Paul Peter Rosen, breast cancer shows a predilection for left side (52%) than right (48%).\(^\text{15,16}\)

In our study, upper outer quadrant was the most frequent site of disease progression in either group. Spratt J., Donegan W reported 48% of the tumour in upper outer quadrant.\(^\text{17}\)

In our study, most of the patients had complaints of lump (100%), pain (93.33%) and discharge (23.33%). Roger Ghys, reported presence of lump in 50% of cases and discharge in 35% of cases.\(^\text{18}\)

We found infiltrating duct carcinoma in 86.67% of patients. H. Stephen Gallager reported infiltrating duct carcinoma to be the most frequent of all carcinoma of breast, comprising nearly 75% of all cases.\(^\text{19}\) As have been noted by Foote and later supported by findings of Fisher from NSABP protocols, 78% of the cases were of the infiltrating duct carcinoma variety.\(^\text{20}\)

66.67% of patients were given NACT with CMF while remaining patients were given CAF regimes. Coskun U, Gunel N et al evaluated locally advanced breast cancer (LABC) patients who had been treated with different neoadjuvant chemotherapy regimens, viz., FAC (5-Fluorouracil, doxorubicin, cyclophosphamide), CA (cyclophosphamide, doxorubicin), FEC (5-Fluorouracil, epirubicin, cyclophosphamide), CE (cyclophosphamide, epirubicin) and with CMF (cyclophosphamide, methotrexate, 5-Fluorouracil) combination in neoadjuvant setting. In their study, overall response rates were found to be higher in anthracycline-based combinations than CMF, but these regimens had no additional survival advantage over CMF regimen. They recommended that the long-term effects of these regimens should be investigated in further randomized trials.\(^\text{21}\)

An Indian study involving cases of locally advanced breast cancer (T\(_4\), N\(_0\)-3, M\(_0\); Stage III B) were treated with 3 cycles of either neoadjuvant cyclophosphamide, doxorubicin and 5-fluorouracil, being the CAF group, or cyclophosphamide, methotrexate and 5-fluorouracil, being the CMF group: Patients achieving complete response or with residual disease of < 2 cm in diameter received radical radiotherapy while those with more residual disease underwent radical mastectomy. Nine cycles of adjuvant chemotherapy were administered. Complete responses and disease control by radiotherapy with complete breast preservation were more frequently observed after CAF than CMF. Overall response rates, adverse effects, disease control following radiotherapy/ surgery, local relapses and metastases were similar for both regimes. This study suggests that in locally advanced breast cancer, a greater proportion of patients can be rendered disease free after neoadjuvant CAF and radiotherapy compared to neoadjuvant CMF and radiotherapy.\(^\text{22}\)

Radiotherapy as an approach in LABC has been studied by Dalena M et al as early as 1978\(^\text{23}\) and more recently studied in the primary management of regionally confined breast cancer by Fletcher GH in 1985.\(^\text{24}\) Grim KL studied the role of adjuvant radiotherapy followed by chemotherapy in breast cancer patient treated with mastectomy.\(^\text{24}\)

The toxicities of chemotherapeutic agents have been studied by numerous authors such as Weiss RB,\(^\text{25}\) Alam Lysee.\(^\text{26}\) The toxicities of Doxorubicin and Cyclophosphamide were studied in particular by Andrew Bothnley and Martine Piccart.\(^\text{24}\) Symptomatic physical toxicity is common in patients receiving NACT. Though all patients experienced toxic effects of the drugs used during the treatment, most of the adverse events observed were mild to moderate in severity as a consequence of multimodality approach. Hormonal therapy with Tamoxifen or Letrozole has been repeatedly shown to be useful as adjuvant treatment of breast cancer (Brodie et al, 2003,\(^\text{28}\) Becher et al 1981).\(^\text{29}\) Hence all patients in our series were given Tamoxifen as adjuvant hormonal treatment in the dose of 10 mg. twice daily.

Objective response rates to NACT regime was 68% and the clinical benefit rate was 88 % (Al Herrn RP, Smith IE, and Ebbs SR) showed an overall response rate of 40-65% with CAF regime in locally advanced cases.\(^\text{14}\)

Out of the total patients on follow up, no local recurrence were seen. No patients out of 25 have died during the follow up. However this study was of short duration to comment on responses to this multimodality treatment or any long term side effect affecting quality of life of patients.

Also being a study over only two and half years it has become difficult to compare the results with long term significant trials such as the Bonnadonna series (Milan) published in 1981,\(^\text{8}\) in which 79% of the cases who received more than 85% of the optimal dose were disease free, after 3 years.

In order to have an objective evaluation of the role of NACT we have also compared the results of treatment of the NACT group of patients to an equal number of patients of the same stage (T and N status) who had undergone simple/toilet mastectomy with adjuvant chemotherapy with radiotherapy (retrospective comparison) in our institution.

Nissen et al also studied the effect of pre-operative adjuvant chemotherapy of breast cancer and reported good results with patients receiving preoperative CT.\(^\text{30}\) It was found that due to downsizing of the tumour, the post-operative outcome was better in patients who underwent NACT before undergoing surgery compared to those who

M R I M S  J o u r n a l  o f  H e a l t h  S c i e n c e s ,  V o l .  3 ,  N o .  3 ,  O c t o b e r - D e c e m b e r  2 0 1 5  P a g e  1 7 1
had first undergone surgery and were then given adjuvant chemotherapy.

The requirement for blood transfusions was found to be greater in the group undergoing surgery before adjuvant CT, both in terms of number of patients requiring transfusions and number of pints of blood transfused.

In the NACT group 22 patients out of 25 required peri-operative blood transfusions while all 30 patients of the latter group required peri-operative blood transfusions.

In the NACT group only 3 patients required 3 transfusions (12%) and none required more than 3 units of blood, while in the latter group, 9 patients (30%) required 3 units of blood and 6 patients (20%) required more than 3 units of blood.

The decreased requirement of blood transfusions in the NACT group could be due to the fact that downsized tumours are easier to resect with less intra-operative blood loss. Decreased blood transfusion requirement also lessens the chances of avoiding other potential complications of blood transfusions.

An added advantage that might accrue is that NACT patients stand a better chance of experiencing haematological toxicity as their pre-chemotherapy blood counts are higher than in patients of the adjuvant chemotherapy group.

CONCLUSION:

The response of advanced breast cancer to treatment with combination chemotherapy along with hormonal therapy is an index of nature of the carcinoma and this response provide a guide for the selection of further treatment. Therefore, careful serial recording of the objective measurements of any change in lesions is invaluable as an aid in evaluating the nature of the response.

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Source of Support: Nil. Conflict of Interest: None.