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ORIGINAL ARTICLE

IMPACT OF SEQUENTIAL NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER: A SERIES OF 10 CASES

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ABSTRACT: Breast cancer currently is a major health problem among women worldwide accounting for around 13.7% cancer deaths, nearly 1/3rd of it being due to Locally advanced breast cancer (LABC). Despite progress achieved in diagnosis & therapy of Breast cancer, LABC remains a major clinical challenge and in efforts to increase pCR, CCR & DFS in LABC, Neoadjuvant or primary chemotherapy followed by locoregional therapy and adjuvant systemic CT is well accepted treatment strategy since last 3 decades. Further to address the issue of drug resistance in NACT sequential anthracycline-taxane NACT has been evaluated by many researchers and has resulted in better outcome in terms of overall survival and pCR. In this study we have evaluated 4 cycles of sequential anthracycline-taxane, 2 cycles of Cyclophosphamide, Epirubicin, Fluracil +2 cycles of Docetaxel, Epirubicin (CEF- DE) NACT in a series of 10 cases of ER/PR +ve, Her -2 neu negative patients of LABC. 9/10 cases were rendered operable after primary chemotherapy and were subjected to further 4 cycles of adjuvant chemotherapy (1 cycle CEF, 1 cycle DE, 2cycles single agent Docetaxel, followed by locoregional RT. This tailored sequential NACT protocol in our subgroup of patient was well tolerated, well accepted and resulted in substantial increase in operability with CCR & DFS in 6/10 cases on 3 years follow up and pCR in one patient. Sequential NACT needs further validation by more RCT with extensive follow up.

KEYWORDS: NACT, LABC, sequential anthracycline–docetaxel.

INTRODUCTION: Breast cancer with an incidence of 1in 8 females in US and 1 in 30 females in India is the commonest female malignancy and a major health problem among women with an incidence of more than 1 million worldwide.[1] Breast cancer accounts for13.7% cancer deaths 1/3rd being Locally advanced breast cancer (LABC).[2] LABC encompasses a heterogeneous collection of (T3NI, T4N2/N3, M0) Breast neoplasm and constitutes 10- 20% of newly diagnosed breast cancer in western countries as compared to 30-60% in developing countries.[3] According to AJCC LABC may be defined as stage IIB, IIIA, IIIB, and IIIC breast cancer.[4]

Historically this subgroup of Breast cancer was treated with radicle Surgery/ RT but Radicle Mastectomy alone have survival data of 6%, chest wall Radiotherapy is also inadequate as revealed in studies of Guy's hospital & Mallkinrodt Institute of Radiology with survival of 16-30%. Neither combination of Surgery or Radiotherapy was of any significant benefit, with distant metastasis being the most common reason of treatment failure.[4,5] Hence with the aim of addressing systemic component of disease adjuvant CT has come in to existence in 70's and is an essential modality of treatment of both operable & inoperable LABC since then.[6] In last three decades Neoadjuvant chemotherapy (NACT) followed by locoregional therapy (Surgery or Radiotherapy) and adjuvant systemic CT has become the gold standard in management of LABC achieving local control in around

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70% cases, prolonged disease free survival (DFS)in 35-70% & Overall survival (OAS) significantly (25-40%) and even allows breast conservation in some.[5, 6]

Major rationale behind use of NACT are: [4-6]

- Early initiation of chemotherapy in view of systemic nature of Breast Cancer
- Primary tumour shrinkage or downstaging, hence NACT in LABC increases resectability & survival rates.
- Better drug delivery through intact vasculature.
- Assesment of in vivo chemosensivity
- Achieving pCR(Pathologic complete response)

Some early concerns regarding use of NACT were:

- Delay in definitive treatment and its effect on locoregional control.
- Lack of accurate initial pathologic staging
- Potential emergence of drug resistance.
  But most of the studies intended for evaluating complication rates and local control revealed primary chemo neither affects surgical complication rates nor delays treatment outcome adversely and result in to improved local control & 5 year survival.[4]

pCR (Pathologic complete response) is the best indicator of efficacy of NACT which eventually also is predictor of DFS(Disease free survival) & OAS(Ovearall survival) as seen in trials like NSABP 18& 27.[7,8] Hence all current and future therapies will be directed towards achieving pCR.

pCR in NACT may be defined as absence of malignant tissue in Breast, Lymphnode and surgical specimen.[9]

Doxorubicin based induction CT regimns had been most widely studied and results in 50% tumour shrinkage in around 75%cases, but currently Pacli & docetaxel containing regimns are strategies towards improving pCR.[10,11,12]

As docetaxel has been proved to be superior to Paclitaxel in MBC in many RCT 's,[10,11] its inclusion was considered prudent in neo adjuvant setting for best possible control of LABC. Sequential use of stronger drug like docetaxel after anthracycline has rationale of enhanced chances of elimination of strains resistant to anthracycline and many trials (Aberdeen trial) of sequential docetaxel after anthracycline based CT reflected not only increase in pCR but also improved OAS.[13-17]

In view of already proved efficacy of sequential anthracycline and taxane, sequential NACT with Docetaxel and Epirubicin (DE) after anthracycline based CEF has been evaluated in the present study.

MATERIAL & METHOD: 10 cases of LABC (T3, T4, N1N2M0) in age group of 45-60 years who reported between Jan 2009-Jan 2010 with uniform characteristics broadly constituted the study group.

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AGE	45-60
STAGE IIB/IIIA	4
IIIB/IIIC	6
Operability: Borderline operable	3
Inoperable	7
Menstrual status: Premenopausal	0
Post- menopausal	10
Hormonal receptor status: ER/PR +ve	9
ER-ve/ PR+ve	1
Her2neu+ve	NIL
Performance status (ECOG)	<2

Table 1: Patient characteristics

Investigative work up mainly included:

1. FNAC/ Trucut needle biopsy
2. Mammography of bilateral Breast.
3. Breast & axillary sonomammogram in patients with dense breast.
4. A baseline bone scan & chest & abdominal CT to rule out MBC.
5. Directed X rays for painful bony sites.
6. Head CT in patients with symptoms like headache & vertigo.

After routine investigations (CBC, LFT, KFT, Blood sugar etc) and baseline ECG/Echo all patients received sequential NACT comprising of 2cycles of anthracycline based CT (CEF) followed by 2 cycles of DE (Docetaxel & Epirubicin) in doses as follows:

CEF:	**DE:**
Cyclophosphamide -600mg/m^2	Docetaxel-75mg/m^2
Epirubicin-90mg/m^2	Epirubicin-90mg/m^2
5FU-600mg/m^2	

9/10 case were rendered operable after 4 cycles of sequential NACT and underwent MRM followed further by 4 cycles of sequential adjuvant CT [1cycles of CEF, 1 cycle of DE, 2cycles of single agent Docetaxel only at a dose of 75mg/m^2]. Total 8 cycles of chemotherapy were administered (4 NACT+4 Adjuvant) in our study. All patients were put on appropriate hormonal therapy post chemotherapy as patients of this series were ER/PR positive.

After completion of adjuvant CT, Radiotherapy of 50Gy to chest wall & axilla +10 Gy boost to the scar was delivered to all the patients. Median duration of treatment was around 11months in our study. Patient's were followed up regularly at monthly or two monthly intervals and assessed regularly with imaging studies like x ray chest, sonography abdomen/pelvis & bone scan & PET CT if possible to evaluate pCR, CCR (Complete clinical response) and OAS (Overall survival).

OBSERVATIONS: One patient(10%) who was borderline operable achieved pCR (negative surgical margin on histopathology), substantial CCR (complete clinical response) assessed by clinical

examination and imaging studies and DFS with objective response of 60% (6 cases) were observed in this study after 3 years of follow up. 3 recurred at distant metastatic sites like (lung, bone, brain) during the follow up. The sequential CEF-DE protocol in our series is well tolerated with acceptable and manageable hematologic, gastrointestinal and other toxicities.

DISCUSSION: Treatment of LABC has evolved with time from Halsted's radicle mastectomy (RM) in 19th century to MRM in in 20th century.[6] The failure of RM to cure many patients of breast cancer because of largely accepted systemic nature of the disease, identification of small breast cancer with introduction of mammography and ability of Radiotherapy (RT) to eliminate subclinical foci of disease led to emergence of less radicle surgery (MRM) as standard of care followed by RT. Use of RT as adjunct to surgery (pre or post op) evidenced significant improvement in local control and adjuvant RT became integral component in loco regional management stage III breast cancer.[4, 5]

But inspite of advocating this treatment line OAS in LABC is still dismal with distant metastasis being the most common reason of treatment failure. Hence with the aim of addressing systemic component of the disease adjuvant chemotherapy came in to existence and is cornerstone in the management of operable and inoperable LABC.[6, 10]

With the aim of early initiation of systemic treatment in this disease with high rate of distant metastasis and making inoperable disease operable, NACT was introduced and it further allows in vivo assessment of chemosensivity and achieving pCR.

NACT followed by Surgery and radiotherapy have now become the most widely practiced treatment of LABC. [10,11]

Large prospective studies have already proved efficacy of NACT in LABC. NSABP18 and NSABP27 are the two large prospective RCT of NACT so far.[5, 6] The biggest trial comparing preoperative vs post-operative CT is NSABP 18 in which 1523 patients with operative Breast cancer were randomized to preop doxorubicin and cyclophosphamide (AC) vs postop (AC) and demonstrated equal efficacy in NACT & postop CT group while NACT allowed more Breast conservation therapy and concluded that although there is no survival benefit there is no disadvantage from use of NACT.

The trial further concluded that NACT on an average leads to CCR (Complete clinical response) of 10-30% PR 50-60%, 1/3rd of patients with CR have pCR and patients with pCR have better survival outcome.[15]

In steps to increase pCR and OAS further in LABC, with the aim of overcoming drug resistance by using stronger drug sequentially, led to emergence of sequential Taxanes after anthracycline based CT.[10,11] Presently many trials of sequential AC-Docetaxel is in existence in Neoadjuvant setting and achieved higher pCR compared to dose dense Adriamycin or Docetaxel combination.[16]

In light of marked benefit of sequential AC-docetaxel as reflected in many recent studies in LABC, the present study was carried out to evaluate tailored sequential CEF –DE which yielded pCR of 10%, CCR and OAS of 60% and recurrence at distant metastatic site in 30% cases. The results of this case series is comparable to work of other researchers as discussed below.

Data from NSABP 27 reveals a pCR of 26% with addition of docetaxel sequentially to doxorubicin in preoperative setting and also better PR and CR in both ER +ve and –ve patients. Important issue in NACT being ¾ cycles vs NACT up to maximum response.[5,17]

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Aberdeen trial of sequential docetaxel after CVAP yielded 31% pCR, 93% survival at 63 months follow up and they concluded that most active drug in CVAP protocol include Adriamycin and cyclophosphamide, combination of AC has been extensively studied hence it would be appropriate to treat LABC with sequential AC-Docetaxel chemotherapy.[15]

In Geperduo study sequential AC-docetax was compared against dose dense Adriamycin-doce combination in T2-3, N0-2 patients with resultant higher pCR in sequential arm 22.4 vs 11.5% in dose dense arm. But few were LABC patients in this study majority were early Breast cancer (node negative & T size<4cm).[16]

Shahyar khan et al also reviewed sequential use of docetaxel after anthracycline based CT at standard doses and suggested that sequential CT not only increases pCR but also improves OS in patients with operable LABC.[9]

Miller KD etal also concluded that primary chemo with sequential doxorubicin and docetaxel is well tolerated and highly active with resultant more substantial node clearance than combination therapy.[17]

CONCLUSION: From present study it can be concluded that there is significant increase in operability and survival in our small series of locally advanced breast cancer with sequential anthracycline-docetaxel tailored Neoadjuvant chemotherapy.

In light of notable benefit of sequential Anthracycline- docetaxel NACT as proved by many prospective randomized trials and as observed in our study too there is need to further evaluate sequential Anthracycine- docetaxel in terms of pCR, CCR & OAS.

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