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A Study Protocol for Assessment of Outcomes of Adjuvant versus Neoadjuvant Chemotherapy in Stage-IIIA of Breast Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

Background: Locally advanced breast cancer (LABC) includes stage III along with stage IV breast cancer and consists of operable and inoperable advanced breast cancer and metastatic disease. LABC is among the most common breast malignancies with increasing incidence now a days. In India, it accounts for 30-35% of all cases. The use of neo-adjuvant chemotherapy (NACT) for the treatment of LABC offers benefits like initiation of early systemic treatment, the drugs can be delivered via intact vasculature, the tumours can be down staged which helps to convert inoperable tumours into operable tumours and renders tumours suitable for breast conserving surgery (BCS). This study is aimed to compare the outcomes of neoadjuvant and adjuvant chemotherapy using taxane based drugs for locally advanced breast cancers.
Methodology: This was an observational study will be undertaken in AVBRH. Total 40 patients will be enrolled in the study. Confirmed patients of breast malignancy either by FNAC or true cut histopathology with advanced breast malignancy confirmed on FNAC or true cut histopathology and planned for neo-adjuvant chemotherapy will be included in the study. For all the patients HER2, PR and ER status will be checked via immunohistopathology. Data will be analysed with appropriate statistical tests.

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Results: We expect neoadjuvant chemotherapy to have better surgical outcomes compared to neoadjuvant chemotherapy.
Conclusion: Neoadjuvant paclitaxel based chemotherapy can be a better option for patients undergoing BCS (breast conserving surgery).

Keywords: Locally advanced breast cancer; taxane based; neoadjuvant; adjuvant; chemotherapy; immunohistopathology.

1. INTRODUCTION

Locally advanced breast cancer (LABC) includes stage III along with stage IV breast cancer and consists of operable and inoperable advanced breast cancer and metastatic disease. According to National Comprehensive Cancer Network LABC as AGCC stage III breast cancer includes breast cancer that encompasses any of the following [1]:

- Tumor's of size > 5 cm with lymphadenopathy (N1-3)
- Tumor's including any size with direct extension to chest or skin or both (including ulcer or satellite nodules).
- Presence of regional lymphadenopathy independent of tumor stage.
  (Clinically set or matted axillary lymph nodes, or any infraclavicular, supraclavicular, or internal mammary lymphadenopathy)

LABC accounts for 10-20% of breast cancers in the West while in India, it accounts for 30-35% of all cases. LABC includes a wide multiple types of malignant breast tumours with different presentation and poses difficulty in treatment. The treatment of LABC has changed dramatically over last few decades. Use of neo-adjuvant chemotherapy (NACT) for the treatment of LABC offered us benefits like initiation of early systemic treatment which can be given at the earliest , the drugs can be delivered via intact vasculature, the tumour can be down-staged which helps to convert inoperable tumours into operable tumours and renders the tumours suitable for breast conserving surgery (BCS) and also it helps *in vivo* assessment of response [1].

Aim:

To study the outcome of adjuvant versus neoadjuvant chemotherapy in the management of stage IIIA of breast cancer.

Objectives:

- To study the outcome in relation with the molecular subtype of tumour
- To study the outcome of stage IIIA patients in Neoadjuvant setting
- To study the outcome of stage IIIA patients in Adjuvant setting.

Inclusion Criteria:

- All patients of stage IIIA carcinoma breast
- Gender: All female subjects
- Subjects who have given consent and who will be voluntarily willing to participate in the study.
- TNM stage IIIa – T1 N2a M0
  T1-2 N1/N2, M0

Exclusion Criteria:

- Patients who had neo-adjuvant therapy prior to admission
- Patient non-tolerant to chemotherapy
- Stage I breast cancer
- Stage II breast cancer
- Stage IV patients with distant metastasis
- Pregnancy /Lactation
- Recurrent breast cancer

2. MATERIALS AND METHODS

The materials and methods of the study are summarized below:

Place of Study-Department of Obstetrics and Gynaecology, Acharya Vinoba Bhave Rural Hospital (AVBRH), Datta Meghe Institute of Medical Sciences (DMIMS), Sawangi (Meghe), Wardha.

Duration of Study: 2020-2022

Sample Size: 40 patients

Sample size formula with desired error of margin

$$n = \frac{Z^2\ \alpha/1\ p\ (1-p)}{d^2}$$

Where

Z α/2 is a level of significance at 5% i.e.

95% confidence interval – 1.96

p = Prevalence = 25.8% / lakh population

= 0.058/1000 population = 0.0258

d = Desired error of margin = 5% = 0.05

$$n = \frac{1.96^2 \times 0.0258 \times (1-0.0258)}{0.05^2}$$

= 38.62

n = 40 patients need in the study.

Based on the n value patients will be equally divided among 2 arms. One being neoadjuvant chemotherapy and other arm being adjuvant chemotherapy.

Research Design: Observational Study.

Material (Study Subjects):

In the present study patients who are confirmed to have breast malignancy either by FNAC or true cut histopathology with advanced breast malignancy confirmed on FNAC or true cut histopathology were included. All female patients of all age group with locally advanced breast cancers as per inclusion criteria planned for neo-adjuvant chemotherapy will be included in the study.

For all the patients HER2, PR and ER status will be checked via immunohistopathology. With the above markers Ki67 will also be sent.

This will give an idea about the hormone receptor status along with the mitotic activity of the tumour within the breast tissue.

Method:

Patients who have stage IIIA breast cancer will be divided into two arms on the basis of the decision of (a) Neoadjuvant chemotherapy or (b) Primary surgery pursuant to which they will be treated with adjuvant chemotherapy. In cases where primary closure cannot be achieved, they will be subjected to Neoadjuvant chemotherapy, Patients who are eligible for primary defect closure will be subjected to adjuvant chemotherapy. Neoadjuvant chemotherapy will be taxane based and will be advised by a multidisciplinary team consisting of oncology physician, oncology-surgeon, pathologist and radiologist. Response will be assessed after 3 cycles of treatment based on clinical examination and ultrasound scan (USG) according to WHO criteria for assessing response to chemotherapy. In case of response, the patient will undergo MRM after completion of NACT chemotherapy or will continue with adjuvant chemotherapy. Patients with clinical progressive illness or incomplete reaction to first-line chemotherapy after 3 cycles of treatment will be re-discussed in the tumour board meeting for mastectomy or change of chemotherapy drug. The patients will be followed for 1 month, 3 months and 6 months. At each follow-up examination of local site, supraclavicular region and axillary region for early local recurrence and ultrasonography of abdomen and pelvis along with essential investigations will be undertaken if metastasis persists.

The following definitions will be adopted for the purpose of the study.

For all the subjects HER2, ER and PR will be checked. Along with above ki67 will be checked with regard to mitotic activity of the tumour.

Response - WHO criteria for response includes 4 categories-

- cCR- clinical complete response when tumor mass completely disapears.
- cPR – More than or equal to 50% reduction in the product of two perpendicular dimensions of tumour.
- cPD- when there was more than / equal to 25% rise in the product of two perpendicular dimensions with respect to the tumour.
- cSD- when the change did not fulfil the conditions for those types.

3. EXPECTED RESULT

Most probably neoadjuvant paclitaxel-based chemotherapy will show better outcomes in terms of reduction in tumour size, and more chances of operability of the tumour in comparison with adjuvant chemotherapy.

4. DISCUSSION

Locally advanced breast cancer (LABC) that is stage III and stage IV consisting of operable and inoperable advanced breast cancer and metastatic disease.

Commonly used regimens for LABC are Adriamycin along with cyclophosphamide based or taxane based which increase the rate of breast conservative surgeries and minimize the need for aggressive nodal surgery with axillary lymph node dissection as well as allows in vivo tumour response assessment and prognosis based on degree of tumour response to NACT. Patients with luminal status Her 2 neu enriched or triple negative disease also benefit from early treatment of distant micro-metastasis due to increased metastatic potential of these disease type [2].

At present, multimodal treatment therapy is the most effective management for cases diagnosed with breast carcinoma. Adjuvant or neoadjuvant chemotherapy can be given. In india, a large proportion of women with breast cancer have advanced disease [3,4].

The recommendations for the treatment of locally advanced diseases vary according to guidelines.NCCN suggested that all locally advan ced cases must first undergo chemotherapy and then urgical treatment, even though skin closure and surgery was necessary at the tim [5].

Whereas, ICMR guidelines advocates first surgical therapy in locally advanced cases provided skin closure is feasible and the tumour is operable and then chemotherapy adjuvant. In a previous study done in stage III patients of breast cancer, adjuvant chemotherapy had better outcome in terms of loco-regional recurrence and remote metastasis with neoadjuvant chemotherapy for stage IIIA & IIIB carcinoma of the breast. Hence, we have undertaken this study in order to evaluate the outcome in patient of stage IIIA where a dilemma arises whether to go for Neoadjuvant chemotherapy or whether to go forward with surgery followed by adjuvant chemotherapy in cases where primary skin closure is feasible.

All the subjects which would be included in the study will have their ER, PR and HER2 status checked. Along with that Ki67 marker will be looked upon mainly to look for mitotic activity of the tumour.

Delivering chemotherapy before surgery has advantages such as the potential to lower the microscopic metastatic disease, decreased drug resistance by treating tumours before development of resistance, increase the efficacy of treatment because the vascular system has not been disrupted by surgery, and permit evaluation of the response of the treatment in vivo. In principle, the reaction to in vivo therapy may help prevent inadequate therapy administration and help the clinician to modify the therapy for patient. In addition, it has shown that clinical outcomes are better with neoadjuvant chemotherapy compared to adjuvant. In the NSABP B-18 report, the dfs rate was 75% in patients with a full pathological response in the neoadjuvant therapy arm after 9 years of follow-up, compared with 58% in patients with some residual invasive disease after chemotherapy.

A meta-analysis of 12 randomized control trials evaluating neo adjuvant chemotherapy found that 18% of patients had no residual invasive disease in breast or axilla, with 13% among them had no residual disease. The association between pathological and long term complete results was strongest among patients who had aggressive tumour subtypes, including those having triple negative breast cancer and the ones with HER-2 Positive, hormone receptor-negative breast cancer. [Include the reference number].

By the end of systemic therapy, a percentage of patients will not have any disease on clinical examination but some residual disease can be detected with radiological imaging.

The percentage ranges from 10% to 15% in patients with hormone receptor positive tumours to approximately 50% in patients with HER-2 positive tumours.

Bhattacharyya T Et Al had done a study in which a total of 90 (60.8%) patients received mixed anthracycline and taxane-based chemotherapy. 119 patients (80.4 percent) responded to NACT either in the form of complete or partial response (PR). Complete response was seen in 27 (18.2%) patients and 92 (62.2%) patients showed PR after NACT. Pathological complete response was seen in 24 (16.2%) patients-. At a median follow-up period of 44 months 36 patients (24.3%) developed relapse of which six patients developed locoregional recurrence, while 28 (18.9%) patients developed distant metastasis. Major prognostic variables in this research were nodal status, chemotherapy response,

pathological tumour size <3 cm, and extracapsular extension (ECE). Neoadjuvant chemotherapy for LABC treatment is a reasonable alternative to early surgery. As this form of chemotherapy will reduce the size of tumour mass making it more favourable for breast conserving surgery.

Won HS et al had a study in which Twenty-five (62.5%) patients showed a partial response, and 15 (37.5%) patients showed a stable disease in the first response evaluation after two or three cycles of neoadjuvant chemotherapy. In the second response evaluation of nine patients who received six cycles of neoadjuvant chemotherapy, one patient achieved a complete response, but two patients with hormone receptor-negative, human epidermal growth factor receptor 2-positive breast cancer experienced disease progression. Twenty-five (62.5%) patients experienced downstaging after neoadjuvant chemotherapy. Patients with > 20% pre-treatment Ki-67 and decrease of Ki-67 between pre-neoadjuvant and post-neoadjuvant chemotherapy showed a trend for better response. In multivariate analysis, advanced pathological stage showed a significant negative effect on relapse-free survival. Study showed that Docetaxel and epirubicin neoadjuvant chemotherapy showed a good response in locally advanced breast cancer. Pre-treatment Ki-67 and change of Ki-67 may play a role as predictive factor for response to neoadjuvant chemotherapy.

According to the study conducted Thakur NA et al., where 120 cases with primary breast cancer who visited a tertiary care hospital were studied. Retrospective study of cases was carried out accordingly. Patients were interviewed and information was noted regarding identification, socio-demographic variables like residential, marital, socio-economic, educational status, etc. The delay since the patient detected the breast lump on self-examination and the time at which she presented to any health facility noted. Data were analyzed using statistical software STATA 10.1, 2009. Qualitative data were analyzed with percentage, c^2 test although quantitative data were summarized with mean and SD.

Few of the related studies to breast cancer were reported [6,7,8]. Hemant L et al. reported on correlation of Total Serum LDH levels with differentiation of breast carcinoma [9]. Kishor T. reflected on quadruple marker in breast carcinoma [10]. Studies by Dawande et al. [11] and Domakunti et al. [12-22] were reviewed.

Breast carcinoma is the prevalent cancer among the young to middle aged group of individuals, and the most common histological form of breast cancer is invasive ductal carcinoma of the breast. Self-breast assessment and early presentation to a health centre for improved management require health education. Hence, proper awareness and screening programs are essential.

5. CONCLUSION

This study will be a comparison study between the surgical outcomes of neoadjuvant and adjuvant-based chemotherapy using taxane based chemotherapy in stage 3a of breast cancer.

Most probably neoadjuvant paclitaxel-based chemotherapy will be a better option because it will be associated with lesser post chemotherapeutic complications and with a chance of patient undergoing BCS (breast conserving surgery).

All the subjects who would participate in this study, will have their ER, PR, HER2 sent for immunohistochemistry. Along with these markers additionally Ki-67 will also be sent.

CONSENT

As per international standard or university standard, patients' written consent will be collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval will be collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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