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Assessment of Neoadjuvant Chemotherapy Response In Carcinoma Breast Patient By High Frequeny Ultrasound.

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Abstract--- *Neoadjuvant chemotherapy for carcinoma breast was discovered historically for inoperable tumor. This Study is about neoadjuvant chemotherapy response between caf and taxane in carcinoma breast patients by high frequency ultrasound in female patients. With the discovery of new neoadjuvant type of chemotherapy for locallyadvanced or dispersed carcinoma breast patients , the cure rate and metastasis rates have been decreased. While caf is the 1st line neoadjuvant chemotherapy in cases of locally advanced carcinoma breast, the new evolving 2nd line paclitaxel neoadjuvant type chemotherapy is working wonders in the same group of patient creating a new path for study of these new chemotherapy drugs. High high frequency Ultrasound is used to study the response of both of these neoadjuvant type chemotherapy and the best of them is further decided and hence then proved. In patients with axilla positive the new use of neoadjuvant taxane based chemotherapy shows a path breaking result than Adriamycin based neoadjuvant chemotherapy thus increasing the overall survival rate and disease free rate in patients of metastatic and locoregional spread of carcinoma breast patients.*

Keywords--- *CARCINOMA BREAST, NEOADJUVANT CHEMOTHERAPY, USG , AXILLARY LYMPHNODES*

I INTRODUCTION:

There is higher burden of breast cancer in both developed and also the developing countries with very high death rate in developing countries. Late medical help may be because of ignorance of the disease, painless nature, and fear of losing the breast, economical constraints or lack of access to medical facilities. There are different methods to assess axillary lymph nodes. Physical examination by physician- 25-32.3% sensitivity with very low specificity, Magnetic resonance imaging has sensitivity 36-78% and specificity 93-100%, There is technical difficulty in imaging the axillary lymph nodes in mammography, but if lymph nodes are detected it's specificity is 99.5% for identification metastasis. Ultrasonography which is easily available tool has 45.2 - 86.2% sensitivity and 40.5%- 86.6% specificity. An ultrasonographic feature of breast cancer varies as per the hormonal behavior of the tumor i.e. triple negative breast cancers and HER overexpression (1-8).

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sensitivity with very low specificity, 2) Magnetic resonance imaging has sensitivity 36-78% and specificity 93-100%, 3) There is technical difficulty in imaging the axillary lymph nodes in mammography, but if lymph nodes are detected it's specificity is 99.5% for identification metastasis. Ultrasonography which is easily available tool has 45.2 - 86.2% sensitivity and 40.5%- 86.6% specificity. An ultrasonographic feature of breast cancer varies as per the hormonal behavior of the tumor i.e. triple negative breast cancers and HER overexpression . Maximum cortical thickening has a positive metastatic association more with histopathology than cytology, where as other imaging features like size and contour, cortical morphology and hilar fat failed to predict its correlation in patient of clinically node absent axilla. Enlarge lymph node of 5mm diameter showed the 87% sensitivity and 56% specificity, isolated size has poor sensitivity for metastasis. In advanced stage of metastatic burden in the lymph node there is rounding and loss of fatty hilum, these features on ultrasound are highly specific for metastatis (9-15). Additional use of colour Doppler/ power Doppler or elastography or use of contrast media increases sensitivity 83.33% specificity 84.38% but it is not recommended for routine use by European society. Updated guidelines of American. Society of Clinical Oncology 2014 and European. Society for Medical Oncology 2015, it is emphasized that clinical evaluation should be assisted by ultrasound (US) of axilla and if suspicious lymph node is identified, FNAC or FNAB from particular site of suspicion. (Evidence IIIA) SLNB was considered to be standard of care in N0 axilla. Studies have demonstrated that abnormal lymph nodes with larger tumour had higher rates of metastasis and ultimately recommended its use in tumour stage T1C. It also does not delay the initiation of the definitive therapy. Sonologically positive axilla in NACT patients should considered for axillary lymph node detection. There is different response to chemotherapy depending on the immunological subtypes of breast malignancy. Mammography and USG shown better correlation with pCR, i.e. sensitivity 78.6%and specificity 92.5%.it sis observed that micro metastasis present in early stages and larger tumour are prone develop resistance to chemotherapeutic agents. Outcome of NACT will depend on size and cellularity of primary tumours and size and number of the lymph nodes. Extent of residual tumour has significant impact on distant relapse. pCR of primary tumour has lower higher rates negative residual metastasis. Prognosis in the NACT patient will depend on response to chemotherapy and biological markers of the tumour which are not a part of traditional staging of the breast cancer (13-25). Different pathological response is observed to anthracycline based chemotherapy regime and taxane based regimes. Thirty percent complete pathological response (pCR) with Anthracycline based chemotherapy and 40% with taxane based chemotherapeutic agents in triple negative tumours was observed in breast cancer patients, addition of immunotherapeutic agents to chemotherapy in HER-2 positive tumour increased response to 70%. There are issues related radiological imaging and histopathological evaluation as well tumour behavior as pointed out by ICMR, at present there are to established recommendation for imaging surveillance during NACT and routinely used method i.e. physical examination of breast lump and axillary lymph nodes is grossly inaccurate, hence present study is undertaken.

Comparation is between two types of chemotherapies 1) cyclophosphamide-adriamycin-5 fluro-uracil and 2) paclitaxel with response shown on High frequency ultrasound after 3 cycles of neoadjuvant chemotherapy.

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II OBJECTIVES:

- To study molecular biology of carcinoma breast.
- To study the response of anthracycline based and taxane based neoadjuvant chemotherapy regime by using high frequency ultrasonography.

Trial design: Single blind observation and comparative study**.**

III MATERIALS AND METHODOLOGY:

Present study will be conducted in "Acharya Vinoba Bhave Rural Hospital (AVBRH)", a tertiary care teaching hospital situated in rural area of Wardha district, in central India in association with Jawaharlal Nehru medical college Sawangi Meghe Wardha for 3 years , with sample size of 50 with materials as study confirmed patients of 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 neoadjuvant chemotherapy will be included in the study.

Method:

Step-1: Clinical examination of breast and axilla will be performed for tumour and nodal staging which include size of tumour, anterior or posterior fixation of tumour to skin and muscle , number, size and fixation of axillary lymph nodes. Included patients of carcinoma breast will be first assessed by high frequency ultrasound (7.5 to 16 MHz) for size of breast lump before neoadjuvant chemotherapy. For the purpose of examination of tumour size and axillary nodal status, the patient will be placed supine, with the forearm positioned upwards adjacent to her head or her forehead. Thorough assessment of all quadrants of breast, retro-areolar region, and axillary tail of Spence, anteromedial aspect of the axilla extending into the upper quadrant or the axillary tail of Spence and the Level I, Level II and supraclavicular lymph nodes will be assessed.

Following features will be studied on Ultrasound-

- Size and number of the breast lump
- Size and number of lymph nodes.
- Eccentric cortical thickness > 3 mm.
- Absent fatty hilum.
- Rounded Morphology.
- Increase in the Blood Flow in the Thickened Cortex on the Doppler.(13)

Doppler study will be done from the tumour vessels since there is a greater sensitivity of the tumour vessels for Doppler ultrasound. A decreasing or increasing pattern of the tumour vascularity will be evaluated by the doppler ultrasonography which will reflect the response to chemotherapy.

Designated ultra-sonologist will assess chemotherapy response who will not be able to review the chemotherapy regime of the patients.

Serial Ultrasound will be done after 3 weeks of chemotherapy after each cycle

Patients will randomized to CAF or paclitaxel chemotherapy regime arm using random number table. Dose of the chemotherapeutic agent will calculated as per standard dose per meter square of body surface.

Size of the breast lump and lymph and US features before initiation of chemotherapy and size breast lump and lymph nodes and feature after 21 day of receiving chemotherapy after each cycle will be assessed. Tumour burden increase or decrease or no change to chemotherapy will be assessed by comparing the 3 imaging findings during the treatments regimens and the response to the treatment at the time of surgery will be taken as the end point according to the response evaluation criteria in solid tumours.

Tumour response/burden to the first of the three cycles of NACT will be calulated as -(15)

Tumour Response = 100 X (Before T - After T) / Before T

Step 2: Histopathological Examination

Patients will be thoroughly investigated for fitness and all down staged patient where skin closure after surgery is possible will be subjected to surgical interventions i.e. modified radical mastectomy (MRM). Excised specimens of MRM will be sent for histopathological examination which will be considered as the gold standard, with special emphasis for size of the primary tumour, histopathological variant of breast malignancy, grade of the malignancy and lymphovascular invasion.

(er/pr) Estrogen/progesterone receptor status and HER2/neu expression and Ki67 index will be assessed by immuno-histochemistry. Depending on receptor positive or negative expression on IHC, response to chemotherapy regime will be assessed.

The high frequency ultrasound and color doppler findings will be associated with the histopathological findings post surgery As per response found in both chemotherapy arms, patients will be divided into 2 groups after completion of three chemotherapy cycles:

- Responders: Complete Response (CR): No radiological evidence of residual tumour.
- Partial Response (PR): Reduction in the size of the tumour more than 30%.
- Non responders: Stable Disease (SD): Reduction in size of the tumour inferior than 30%.
- Progressive disease (PD): Increase in the size of tumour or appearance of new lesions.

INCLUSION CRITERIA

- All patients with LABC
- T3 with any N
- Any T1-T3 with N2
- T4 with any N
- Any T with N3

EXCLUSION CRITERIA

- Early stage cancer
- Metastatic cancer
- Patients unfit for chemotherapy i.e. cardiac dysfunction, hepatic or renal derangements.
- Postponement of chemotherapy due to toxicity more than 15 days
- Pregnancy/lactation
- Recurrent breast cancer
- Bilateral breast cancer
- Concomitant radiotherapy
- Received prior chemotherapy-

Interventions: ultrasonography for first 3 cycles of neoadjuvant chemotherapy.

IV OUTCOMES:

The study is a randomized controlled study which is based on intervention and definitive treatment in patients particularly females of carcinoma breast with locoregional spread ie axillary lymphnodes and supraclavicular lymphnodes. The response to neoadjuvant chemotherapy is described after assessment of tumor in the breast and axillary lymphnodes on high frequency ultrasound and response to monotherapy and individual regimen and result of the both neoadjuvant chemotherapy is evaluated. The molecular biology of the tumor

Sample size: 50

Method

Female patients with stage 3 carcinoma breast are allocated and discussed in the tumor board and then neoadjuvant therapy is decided as randomization of 1:1 ratio.

Allocation is During tumor board discussion, the neoadjuvant chemotherapy is randomized in the ratio of 1:1 by th oncologist .

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Implementation Will be done by the author

The ultrasonologist is blinded as he/she is the one who is documenting the response for 3 cycles of neoadjuvant chemotherapy as response is documented by high frequency ultrasound.

V ETHICS AND DISSEMINATION:

The consent from the patient is taken by the author after explaining the patient there disease and medical management given to them and explaining the pros and cons of this management.after obtaining the informed consent from the patients in their own language, thee patient is selected in the study.

The present study is approved by the institution ethic committee of the avbrh.

VI EXPECTED OUTCOMES/RESULTS:

In patients with locoregional carcinoma breast patients who will receive cyclophosphamide-adriamycin-5 flurouracil chemotherapy and paclitaxel chemotherapy , the expected outcome will be expected that the neoadjuvant chemotherapy is exceptional in treating patients of carcinoma breast with locoregional spread. The previously stated 2nd line chemotherapy with paclitaxel is now to be proved revolutionary and evolving in decreasing the tumor burden in breast and axilla in patients with carcinoma breast in comparison to caf chemotherapy.

VII DISCUSSION:

With the discovery of neoadjuvant chemotherapy for locally advanced carcinoma breast patients , the cure rate and metastasis rates have been decreased. Most commonly used in clinical practice is Adriamycin based chemotherapy, though new protocol with taxanes based chemotherapy has rebellious results. The neoadjuvant therapy reduces the tumor load to reduce thereby allowing for decreasing the tumor bulk during surgery, thus decreasing the mental health problems of the patient and increasing the cosmetic value of a definitive intervention. Couple of articles on similar aspect of study and related factors were reviewed (26-74).

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