RESEARCH

A STUDY OF CLINICAL AND PATHOLOGICAL RISK FACTORS IN CARCINOMA BREAST AND ITS CORRELATION TO RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN A TERTIARY CANCER INSTITUTE

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Background: Neoadjuvant chemotherapy (NAC) of breast cancer (BC) improves outcomes, especially in patients with locally advanced and inflammatory cancer. Further insight into clinic-pathological factors influencing outcomes is essential to define the optimal therapeutic strategy for each category of patients and to predict the response to the treatment. The aim is to present study is to correlate clinical and pathological risk factors of carcinoma breast with the response of study subjects to neoadjuvant chemotherapy. **Materials and Methods:** This is a single institutional cross-sectional trial done in females who are known cases of locally advanced breast cancer treated by Neoadjuvant chemotherapy in 50 histological proven diagnosed and treated cases of carcinoma breast eligible. Study included patients aged 18-70 years, histologically proven breast cancer stage IIB to III, ECOG performance status Grades 1,2, adequate baseline haematological, hepatic and renal functions and in Well controlled diabetes / hypertension in patients on medications. **Result:** There is strong association between tumor size and response after neoadjuvant chemotherapy with p value of <0.0000001. There is a significant correlation between NACT response and tumor staging, nodal stage with p value of 0.001. Most of the patients presented with grade 2 followed by grade 3. 23 are PR positive, 6 showing complete response and 17 are partial responders. 27 were PR negative, 5 showing partial response. P value 0.27 hence not significant. 15 are HER2 positive, 35 are HER2 negative, patients with HER2 positive showing complete response are 3 and partial are 12. Her2 negative patients are 8 in complete response and 27 in partial, with p value 0.4, hence not significant. In present study patient with luminal A subtype are 16 among which 5 showed complete response and 11 are partial. Luminal B patient are 1 with complete response and 7 are with partial response, HER2 + are 7 in number with 2 complete response and 5 are with partial response.in triple negative subtype among 19 patients 16 were partial responders and 3 were complete responders. 11 achieved complete response (22%) and 31 patients (62%) has partial response.2 patients progressed and there is not response in 1 patient (2%). **Conclusion:** There is no correlation between the majority of clinical risk factors, such as age at presentation, age at first pregnancy, breast-feeding, and body mass index, but the parity showed a close correlation with tumor response. Histopathological examination of tumor is the gold standard for evaluating response to chemotherapy.

INTRODUCTION

Breast cancer is one of the most frequently diagnosed cancer in women and a leading cause of death. As per GLOBOCON 2020 female breast cancer has now surpassed lung cancer as the most commonly diagnosed cancer worldwide. The estimated 2.3 million new cases indicate that one in every 8 cancers diagnosed in 2020 is breast cancer. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths in 2020. In women, breast cancer accounts for one in 4 cancer cases and one in 6 cancer deaths, and the disease ranks first in terms of incidence and mortality in most countries around the world. In India as per GLOBOCON 2020 total number of new cases of cancer in 2020 are 1,324,413 and breast cancers include 13.5% of it i.e.,178,361.[1]
Breast cancer incidence rates are converging worldwide, yet breast cancer mortality rates and survival proportion are lower in settings with lower HDI (human development indices), largely because of advanced stage of presentation. Marked changes in lifestyle, sociocultural context, and built environments are having a major impact on the prevalence of risk factors for breast cancer in many countries with low and medium HDI. This risk factor includes the postponement of childbearing and having fewer children, as well as greater levels of excess bodyweight and physical inactivity.
Neo-adjuvant chemotherapy (NACT) has been accepted as a standard therapeutic strategy for patients with locally advanced Breast cancer and inflammatory Breast cancer, as it can provide timely and individualized chemo sensitivity information, reduces tumor burden prior to surgery, and improves the success rates of operation and the chances of breast conservation surgery.[2]
Currently, pathological assessment of breast tissue and metastatic lymph nodes after surgery is the main approach for evaluating the treatment response to NACT which is the gold standard. The studies states that pathological complete response to neo-adjuvant chemotherapy is the best predictor of overall survival (OS).[3] Complete histological response following neo adjuvant chemotherapy for breast cancer has great prognostic value. All patients do not benefit from NACT, as some patients develop drug resistance and present with stable disease or even disease progression during NACT, their by missing the surgical opportunity. Therefore, identification of more bio markers is important for improving response evaluation and risk stratification before and after NACT, selecting appropriate candidates of NACT, and avoiding unnecessary chemotherapy-related toxicity for patients who respond less to NACT. Furthermore, as a large number of patients with breast cancer who do not achieve complete pathological response usually suffer from high risk of recurrence and death, it is important to identify more pathological response assessment approaches for evaluating morphological changes and cancer cells regression of tumors in patients with residual disease after NACT.[4]
Assessment of pre-treatment bio markers including histological grade and molecular sub types of breast cancer and post treatment pathological grading, hormone receptors and lymph node status after treatment have been shown to provide prognostic information for patients treated with NACT.[5] This study was conducted to understand the variation of response to breast cancers to NACT with a focus on Indian population and to study the correlation between clinical and pathological risk factors of carcinoma breast and response to NACT. This study will also aid in tailoring the screening programs accordingly.

MATERIALS AND METHODS

This is a single institutional cross-sectional trial done in females who are known cases of locally advanced breast cancer treated by Neoadjuvant chemotherapy in Department of Radiation Oncology, MNJ institute of oncology and Regional Cancer Centre, red hills, Hyderabad. A total of 50 histological proven diagnosed and treated cases of carcinoma breast eligible according to inclusion and exclusion criteria for neoadjuvant chemotherapy will be enrolled for the study. The study is conducted during the period of July 2018 to June 2020.
Inclusion criteria: Aged 18-70 years, histologically proven breast cancer stage IIB to III, ECOG performance status Grades 1,2, adequate baseline haematological, hepatic and renal functions and in Well controlled diabetes / hypertension in patients on medications.
Exclusion criteria: Pregnant and nursing mother, active uncontrolled tuberculosis or other comorbidities which preclude the use of radiotherapy and concurrent chemotherapy, post-operative cases of carcinoma breast, double primary (synchronous/metachronous malignancy). Noncompliance to treatment
Approval for the study was taken from the Institutional Ethics committee of Osmania Medical College. A minimum of 50 histologically proven cases of carcinoma breast eligible accordingly to the inclusion and exclusion criteria for neoadjuvant chemotherapy will be enrolled for the study. They were informed about the study and consent was taken. After the consent was taken, the patients were enrolled in the study.
Clinical examination, General examination, basic parameters including weight, height, and body surface area, complete systemic examination, local breast examination, assessment of axillary lymph nodal status and palpation of bilateral supraclavicular fossa for presence of lymph nodes. TNM-AJCC 8TH edition cancer staging Guidelines are followed for classification. For staging ECOG performance status grading and TNM—AJCC cancer staging proforma was obtained.

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Patient must undergo biopsy and HPE and IHC or obtained. Patients were given 8 cycles of neoadjuvant chemotherapy and lesions were measure clinically at the time of diagnosis after 4 cycles of NACT (AC) and after 8 cycles (completion of 4 cycles taxon) i.e., assessment was done just prior to surgery and pathological response (complete CPR) and PPR was taken after the surgery and compared with clinical and pathological risk factors.

For this study clinical complete response has been defined as absence of any palpable tumor in the breast. Specimen assessment include size at the time of grossing and histological grading of response to the chemotherapy by the pathologist.

Hormone receptor status for estrogen receptor (ER), progesterone receptor (PR) and Her-2/new (erb-2) was evaluated using immune histological staging (IHC). Pathological response was classified as nil response (p NR), partial response (p PR) and complete response (pCR).

RESULTS

Age of patient, age at menarche, age of first child, breast feeding, menopause, family history, personal habits BMI and NACT response has found to be statically not significant. Parity is significant among groups [Table 1].

There is strong association between tumor size and response after neoadjuvant chemotherapy with p value of <0.0000001. There is a significant correlation between NACT response and tumor staging, nodal stage with p value of 0.001. [Table 2]. Most of the patients presented with grade 2 followed by grade 3. Among the patients having the complete response most of them are among 50 patients, 23 are PR positive, 6 showing complete response and 17 are partial responders. 27 were PR negative, 5 showing partial response. P value 0.27 hence not significant.

Among patients studied, 15 are HER2 positive, 35 are HER2 negative, patients with HER2 positive showing complete response are 3 and partial are 12. Her2 negative patients are 8 in complete response and 27 in partial, with p value 0.4, hence not significant.

In present study patient with luminal A subtype are 16 among which 5 showed complete response and 11 are partial. Luminal B patient are 1 with complete response and 7 are with partial response, HER2 + are 7 in number with 2 complete response and 5 are with partial response. In triple negative subtype among 19 patients 16 were partial responders and 3 were complete responders.

Among 50 patients 11 achieved complete response (22%) and 31 patients (62%) has partial response.2 patients progressed and there is not response in 1 patient (2%).

Table 1: Correlation of age at first child birth with complete response in the study patient.

	Complete response		Total	Chi Square P value
	Present	Absent		
Age in years				
Less than or equal to 50	5 (10%)	26 (52%)	31(62%)	0.1
Greater than 50	6(12%)	13(26%)	19 (38%)	
Total	11(22%)	39(78%)	50 (100%)	
Age at menarche in years				
Less than 14	6 (12%)	23 (46%)	29(58%)	0.3
Greater than or equal to 14	5(10%)	16(32%)	21 (42%)	
Age at first child in years				
Less than or equal to 20	5 (10%)	25(50%)	30(60%)	0.4
Greater than 20	6(12%)	14(28%)	20(40%)	
Parity				
Less than 2	3 (6%)	21 (42%)	24(48%)	0.05
Greater than or equal to 2	8(16%)	18(36%)	26(52%)	
Breast Feeding				
No	1 (2%)	8(16%)	9(18%)	
Yes	10(20%)	31(62%)	20(82%)	0.2
Menopause				
Yes	6	24	30	0. 34
No	5	15	20	
Family History				
No	10 (20%)	36(72%)	46(18%)	
Yes	1(2%)	3(6%)	4(8%)	0.4
Personal habits				
Tobacco/Alcoholism	2(4%)	13(26%)	15(30%)	0.16
None	9(18%)	26(52%)	35(70%)	
BMI(kg/m2)				
Up to 24.99	4(8%)	12(24%)	16(32%)	0.3
>24.99	7(14%)	27(54%)	34(68%)	

Table 2: Showing tumor and node staging before and after neoadjuvant chemotherapy

Tumor staging	Before NACT	After NACT	P Value
0	0	15	Chi square value = 62.4 Degree of freedom = 5 P value = <0.0000001 (Significant)
1	0	8	
2	4	17	
3	20	7	

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4	26	1	
X	0	2	
Total	50	50	
Node staging			
0	11	29	Chi square value = 15.82 Degree of freedom = 3 P value = 0.001 (Significant)
1	30	13	
2	8	8	
3	1	0	
Total	50	50	

Table 3: Showing staging before and after NACT.

	0	1	2	3	4	X	Total
Staging before NACT							
T	0	0	4 (8.00%)	20 (40.00%)	26 (52.00%)	0	50 (100.00%)
N	11 (22.00%)	30 (60.00%)	8 (16.00%)	1 (2.00%)	0	0	50 (100.00%)
M	48 (96.00%)	0	0	0	0	2 (4.00%)	50 (100.00%)
Staging after NACT							
T	15 (30.00%)	8 (16.00%)	17 (34.00%)	7 (14.00%)	1(2.00%)	2 (4.00%)	50 (100.00%)
N	29 (58.00%)	13 (26.00%)	8 (16.00%)	0	0	0	50 (100.00%)
M	40 (80.00%)	2 (4.00%)	0	0	0	8 (16.00%)	50 (100.00%)

Table 4: Correlation of grade, ER, PR and HER status with response to NACT.

Grade	Complete response		Total	Chi Square P value
	Present	Absent		
1	3	1	4	
2	8	29	37	0.01
3	0	9	9	
ER status				
Positive	6	19	25	0.3
Negative	5	20	25	
Total	11	39	50	
PR status				
Positive	6	17	23	
Negative	5	22	27	0.27
Total	11	39	50	
HER status				
Positive	3	12	15	
Negative	8	27	35	
Total	11	39	50	

Table 5: Showing response of different molecular sub types with response to NACT.

Subtype	ER	PR	HER2NEU	Complete response	Partial Response	Total
LUMINAL A	+	+/-	-	5	11	16
LUMINAL B	+	+/-	+	1	7	8
HER2+	-	-	+	2	5	7
TNBC	-	-	-	3	16	19
Total				11	39	50

Table 6: Showing response to NACT in the study.

Response	Frequency	Percent
Complete response	11	22.00%
Tumor complete response	5	10.00%
No response	1	2.00%
Partial response	31	62.00%
Progressed	2	4.00%
Total	50	100.00%

DISCUSSION

Breast cancer is one of the most frequent malignancies in the world. Upto 20% present with advanced breast cancer that is associated with poor prognosis and remain challenging for medical and surgical oncologists in developing countries. NACT is an accepted standard therapy for LABC, it is not only reducing the tumor burden prior to surgery but also improves success rate of operation. It provides chemo sensitive information and chance to select candidates for NACT.

Large number of studies shows PCR was predilection for improved outcome with significant better DFS and OS compared to patients having residual tumor after NACT.[5,6,7,8] Currently pathological breast tissue and metastatic lymph nodes after surgery is main approach for treatment response for NACT (which is gold standard). Although NACT standard therapy for locally advanced breast cancer some people do not benefit for NACT and develop drug

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resistance and present as stable disease or progressive disease after NACT missing surgical option. Most of the studies has assessed response correlating with the pathological risk factors like tumor size nodal status and hormonal status and some of the clinical risk factors like age and BMI and its correlation to response to NACT, in addition to the previous studies a correlation of risk factors like age at menarche, age at menopause, parity, breast feeding was studied in the present study to customize subsequent strategies for treatment and also help in selecting the patients before neoadjuvant chemotherapy and improved outcome Among the study all patients are diagnosed with invasive ductal cell carcinoma in a study conducted by Ellison and Ellis and study by Galal the most common type of cancer was invasive ductal cell carcinoma.[6]

The frequency of patients in the study with carcinoma breast were more in age between 40-59 and Mean age of patients in our study was 46.6 with standard deviation (9.28) as in the study conducted by sexena et al where the mean age of presentation is 47.8 with SD(6.3).[7]

In the study patients who received neo adjuvant chemotherapy Among 50 patients 11 (22%) 36 patients (72%) attain partial response 2 patients has progressive disease and one patient has no response. Studies that conducted before on response to NACT showed pathological complete response between 3% to 46% and partial response between 30% to 90% which was seen in our study.[8]

In the study patients the mean at menarche is 13.36 years with SD of (1.72) and mean age at menopause was 44.5 year (SD 6.33) which is near to the meta-analysis study and study by Chantal C organ et al. With a mean age of menarche is 13years and mean age at menopause is 46 years. And younger age at menarche and late menopause are risk factors for breast cancer. when we correlate these age-related risk factors with the response to Neo adjuvant chemotherapy there is no correlation. Many studies have shown parity induced protection to breast cancer. Dalle et al found parity in young women (below 20 years) decreases breast cancer risk.[9] It was well known that early pregnancy (before age 20) reduces breast risk and one of the natural protective events that reduce breast cancer. In present study most of patients 60% are before age 20 years and 2% are above 30 years. age at first pregnancy later in life (after 35years) increases breast cancer risk, there is no correlation between this risk factor with the NACT response.

In the study patients there are 24% are with parity less than two and 52%are with parity greater than two when we correlated with the response to neoadjuvant chemotherapy there is 6%complete response and 42%partial response in patients with parity less than two and 16%complete response and 36% partial response in patients with parity more than two with p value of 0.05 [Table 6] showing near correlation to NACT response. Most of the patient in the study 82% has breast fed their children. breast feeding is of particular interest for breast cancer prevention as it is a modifiable risk factor.[10] Estimated that breast feeding prevents annul deaths from breast cancer newer research suggest it is limited to hormone receptors subtypes. In our study when we correlate breast with NACT response there is no correlation found. Though there are many studies on use of oral contraceptive pills and risk of breast cancer in study no patient has history of use of oral contraceptive pills so its correlation with response to NACT was not done.

Among 50 patients 9 patients has habit of drinking toddy 4 has habit of chewing tobacco and 1 has both alcohol and tobacco chewing habits. 2 patients have developed completed response and 13 patients (26%) has no response compared to 9 patients (18%) and partial response 26 (52%) with a P value of 0.16 thus indicating no correlation between personal habitats response.

Many studies showed overweight and obesity breast cancer patients had low PCR rate compared to patient with underweight and normal weight patients. Patients more than 25 of BMI shows 14% complete response and 54% partial response and BMI up to 24.9 shows 8% complete response and 24% partial response with P value of 0.3 showing no correlation with response to NACT.[11]

In the present study out of 50 patients 26 presented with T4 stage at the time of diagnosis most of the patient has clinical tumor size of 5.6cm. In the studies that conducted previously states that clinically small sized tumors respond better than large tumors.[12]

Among the study group participated majority of patients with T4(52%) and T3(40%) most of patients with complete response are of T3(24%) showing larger tumors has partial response as study by Gala et al and has significant correlation with NACT response with p value (0.00001). Most of patients in the study has nodal stage of N1 (60%) followed by N2 (18%) and most of PCR was seen in N1 showing a significant correlation with response to NACT with p value. Among 50 patients most were grade 2 (74%) and 4(8%) were grade 1and 9(18%) are grade 3.and among patients with complete response 72.72% were grade 2 and 27.72% are grade one. Among study conducted previously smith and Barer et al 12PCR is between19%-31%. Which correlates with the study. Study that conducted previously showed tumors with positive ER had worse pathological response. Among 50 patients 25 are ER positive and 25 are ER Negative. with no significant p value hence not correlate with response.56% of patients are PR negative and 46% are PR positive. Her 2neu correlation with NACT response.[13]

Limitations of the Study

The limitations to this study group are small study group

- The study was conducted only with one NACT regimen and response was assessed other regiments were not included in the study. The study has not included the targeted therapy like

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tansuzumab which has better outcomes in Her2 positive patients.

- As there is no facility of doing other molecular studies in our institute, further molecular study cannot be done.

CONCLUSION

From our study we concluded that histopathological examination of tumor is goal standard for assessing response to chemotherapy and there is no correlation found with the most of clinical risk factors like age at presentation ,age at first pregnancy ,breast feeding ,Body mass index but the parity showed near correlation tumor response. Pathological complete response can be used as biomarker to assess tumor response to paclitaxel-based chemotherapy regimen as all the patient in the study treated with one regimen. For increasing PCR in patients new approaches according to each subtype to be considered like Trastuzumab for HER2 and for Luminal B subtypes convectional approach of early surgery followed by adjuvant chemotherapy and endocrine therapy and for Triple negative subtypes extension of NACT and neoadjuvant trail with new chemotherapeutics should be consider.

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