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Pathological Patterns and Complete Response Rates after Neoadjuvant Chemotherapy and Chemoradiation in Locally Advanced Breast Cancer- an audit of 104 Patients

(Original Article)

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Abstract

Introduction: *Locally advanced breast cancer (LABC) is a disease with relatively poor prognosis. The incidence of LABC is high in India constituting about 30-35% of all cases. Neoadjuvant chemotherapy is the standard of care for patients with LABC. Concurrent chemoradiation is also investigated in LABC in neoadjuvant setting.*

Aim: *In this study we aimed to evaluate the histopathological patterns including the incidence of pathological complete response (pCR) after neoadjuvant chemotherapy or chemoradiation in our patient population with LABC and also to correlate various pathological and immunohistochemical parameters with pCR.*

Materials and methods: *We retrospectively analysed locally advanced breast cancer patients who underwent neoadjuvant chemotherapy (NACT) and neo-adjuvant chemoradiation (NACTRT) during the period Nov 2011-Jan 2014. The histopathological patterns and the incidence of pCR were assessed and correlated various pathological and immunohistochemical parameters with pCR. For statistical analysis Pearson's Chi-Square test and a binary logistic regression model were applied.*

Results: *Out of total 104 patients, 91 received NACT and 13 underwent NACTRT. pCR was 14.4%(15/104). 23% in (3/13) of NACTRT and 13.2% (12/91) of NACT group achieved pCR. In our study none of the pre-treatment parameters showed statistically significant association with pCR. The presence of LVE in the core biopsy and post-therapy surgical specimen (p-value 0.025) was significantly associated with axillary lymph node metastasis.*

Conclusions: *With limitations of being a retrospective analysis with small sample size, our study shows that in LABC following NACT or NACTRT, the probability of pCR is higher in tumors of high grade, ER negative, PR negative and Her2neu negative. The pCR after neoadjuvant chemoradiation was higher than neoadjuvant chemotherapy but was not found statistically significant.*

Key-words: *Locally advanced, neoadjuvant, chemotherapy, chemoradiation. retrospective.*

Introduction

Breast cancer ranks among most common malignancies in females worldwide. Breast cancer incidence in India varies from 12-31/1,000,000 [1]. Locally advanced breast cancer (LABC) is a disease with relatively poor prognosis with 5 year survival rates less than 50% [2] and it accounts for about 30-35% of all cases in India while it is 4.6% in the United States [1,2]. Neoadjuvant chemotherapy is the standard of care for patients with locally advanced breast cancer. Neoadjuvant Concurrent chemoradiation (NACTRT) is also investigated in LABC in neoadjuvant setting before surgery [3].

Pathologic assessment of the final surgical resection specimen is the gold standard for determining the response to the neoadjuvant treatment. Pathological complete response (pCR) is defined as no evidence of malignancy in both breast and axillary nodes. The optimum utilisation of NACT versus NACTRT in breast cancer is not known and the studies based on comparison between the two approaches are limited. In this study, we have retrospectively analysed the incidence of pCR to neoadjuvant chemotherapy / chemoradiation in our patient population with LABC and also tried to determine correlation if any between various pathological and immunohistochemical parameters with pCR. We have also described the various histopathological findings including gross and microscopy in post surgery specimens that are seen after neoadjuvant strategies in breast cancer.

Materials and Methods

The retrospective analysis of LABC patients who underwent Neo-adjuvant chemotherapy (NACT) or chemoradiation (NACTRT) during the period Nov,2011 -Jan, 2014. The majority of patients with LABC are treated by Neoadjuvant chemotherapy at our institution. An institutional ethics committee approved randomised clinical trial between neoadjuvant chemotherapy and neoadjuvant chemoradiation in locally advanced breast cancer has been started at our center since 2011. The NACTRT patients belong to the study group whereas the NACT group comprises of all the patients with LABC who were treated with NACT. FEC chemotherapy was given to patients in the NACT versus NACTRT trial. FEC also was the standard regimen used in our institution prior to constitution of a new Medical Oncology team after which the institutional policy shifted to use of AC regimen the majority of patient received 3 cycles of FEC chemotherapy.

All patients who had pre treatment core biopsy were included. NACT regimen included 3 to 6 cycles of FEC (5fluorouracil-600mg/m2, epirubicin-90mg/m2 and cyclophosphamide-600mg/m2 every 3weekly) or 4 cycles of AC (Doxorubicin 60mg/m2 and cyclophosphamide 600mg/m2). In NACTRT patients, chemotherapy (5-fluorouracil600mg/m2, epirubicin-60mg/m2 and cyclophosphamide-600mg/m2) first dose was given on day 1 of radiation and second dose on Day 22 of RT (RT dose-40Gy/20fractions-5fractions/wk).The total dose of RT was 4000cGy/ 20 fractions/ 4 weeks. This study protocol was approved by Institutional Review Board

Data regarding clinical parameters like age, pre-treatment TNM status, core biopsy findings and immunohistochemical results were obtained from the case records. Tumor grade, presence or absence of features like carcinoma insitu component, necrosis, lymphovascular emboli (LVE) and perineural infiltrate (PNI) were assessed from core biopsies. TNM stage by baseline physical examination was recorded. Tumor grade was based on modified Scarff-Bloom –Richardson classification. After NACT/NACTRT, patients underwent mastectomy /breast conservation surgery. Formalin fixed specimens were studied in detail, for therapy induced changes. Post treatment TNM staging was determined according to the guidelines given in 7th edition AJCC cancer staging manual.

Statistics Analysis

The associations between Pathological Response and pre-treatment variables, like age, tumor size, grade, ER, PR, Her2/neu status, etc. were determined using Pearson's Chi-Square test. A binary logistic regression model was applied to determine whether a factor was independent predictor of pCR in a multivariate analysis. All statistical tests were two-sided, and P values <0.05 were considered statistically significant. The statistical analyses were performed using SPSS 20.0 software (IBM©SPSS, India, 2011).

Results

A total o 386 patients underwent surgery for carcinoma breast during the study period. 104 patient's belonged LABC category, constituting 26.94% of all breast cancer patients. Median age was 50 years (range 26-78). Patient characteristics are given in Table 1. Most common histology was invasive ductal carcinoma, NST (103/104). Pre-treatment TNM stage was IIIA-65.4% (68 /104), IIIB-30.8% (32 /104) and IIIC-3.8% (4/104). Tumor grade based on core biopsy was low in 75 and high in 16 cases. It was not assessed in 13 cases as there were only few neoplastic cells in the core. NACT regimen included 3 to 6 cycles of FEC in 83 patients, and 4 cycles of AC in 8 patients.13 patients underwent NACTRT The majority of patients received 3 cycles of FEC chemotherapy (90.4%). Very few patients (<5%) received 6 cycles of FEC due to poor clinical response. Post-treatment surgery was breast conservation surgery in 8 patients and modified radical mastectomy in remaining 96. Pathological complete response (pCR) was seen in 15 patients (14.4%) and 23% (3/13) of NACTRT & 13.2% (12/91) of NACT achieved pCR. 82(78%) patients were pathological partial responders and 7 (7%) non responders. Majority of tumors were ER positive (55.8%) and of all patients, the rate of Her2/neu negative was 52.9%. Triple negative breast cancer was found in 23% (22/94of the cases).

Correlation between pre-treatment factors and pCR is given in Table 2. Tumor having smaller size, higher grade, ER negative, PR negative and Her2 negative tumors achieved higher rate of pCR. None of the patients with carcinoma in situ component, lymphovascular emboli or perineural infiltrate in the core biopsy showed pCR. All the 3 patients with presence of LVE in core biopsy and 16 out of 19 patients with LVE in post treatment surgical specimen had axillary lymph node metastasis. The presence of lymphovascular emboli in the core biopsy and post therapy surgical specimen (p-value 0.025) was significantly associated with axillary lymph node metastasis.

Gross evaluation of post treatment surgical specimens revealed poorly defined fibrotic appearance of the tumor bed in majority of cases. Residual tumor appeared as fleshy nodular areas . Microscopically the most common morphological change was stromal hyalinization (83%). Other changes included presence of patchy lymphohistiocytic infiltrate (34%), necrosis (25%), calcification (8%) and foreign body giant cell reaction in 7% of cases. Atrophy of the terminal duct lobular unit was the striking change seen in the benign breast tissue. Most important change noticed in the axillary lymph nodes was presence of intra nodal sclerosis.

Table 1 Patient characteristics

Characteristics	N =104	%
Age		
>50	50	48
<=50	54	52
Tumor size		
<=5 cm	18	17.3
>5 cm	86	82.7
Tumor grade		
1	3	2.9
2	72	69.2
3	16	15.4
Not possible	13	12.5

Table 2. Univariate analysis of pCR by pre treatment parameters

Parameters	Number (%)	pCR Number(%)	p-value
Age			0.906
>50	50	7(14)	
<=50	54	8(14.8)	
Tumor size			0.660
<=5 cm	18	5(16.1	
>5 cm	86	12(13.9)	
Tumor grade			0.625
1&2	75	9 (12)	
3	16	3 (18.75)	
ER			0.60
Positive	59	7(12.7)	
Negative	45	8(16.3)	
PR			0.139
Positive	46	4(8.7)	
Negative	58	11(19)	
Her2/neu			0.258
Positive	38	3(10.3)	
Negative	56	11(19.6)	

Discussion

LABC is defined as stage III disease and is represented by stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage III B (T4N0–2M0), and stage IIIC (TanyN3M0) (4). pCR after neoadjuvant treatment is considered as one of the most important factor predicting prolonged survival in LABC patients [5]. In this study we have analysed the incidence of pCR to neoadjuvant chemotherapy and chemoradiation in our patient population. In various studies, incidence of pCR ranges from 12-30% in anthracycline based therapy[6]. The pCR rate in this study (14.4%) is comparable to other published series using anthracycline based chemotherapy [6,7,8]. In a study by Prisack et al [9] pCR was seen more frequent in tumors that received radio-chemotherapy (28.3%) compared to chemotherapy alone (11.9%).We also noticed a higher pCR in neoadjuvant chemoradiation (23%) though the sample size is not comparable.

The clinical course of breast cancer patients treated with neoadjuvant chemotherapy is difficult to predict. Histologically homogenous breast cancers can differ in their response to treatment. Many researchers have assessed the predictive role of pre-treatment clinical, histological and immunohistochemical parameters to neoadjuvant chemotherapy. These studies but have yielded different results. Tewari et al, in a study of 50 LABC patients evaluated different parameters like tumor grade, ER, PR, HER2, Ki-67, p53, Bcl-2 and BAX. Of all parameters studied, only the apoptosis –related genes seemed to exert some influence on the response to therapy. The author suggested the possible role of genomic profiling of breast cancer to predict the response to neoadjuvant chemotherapy[10]. Pu RT et al also found no significant association between parameters like higher histologic and nuclear grade, ER,PR status and HER-2/neu over expression with pCR [11]. In the present study also, there was no significant association between the above parameters with pathologic response. Many studies have shown that ER and PR negative tumors achieved significantly higher rate of pCR and [12,16]. Tomofumi et al in his study showed that patients with ER-negative tumors were 18.6 times more likely to achieve pCR than those with greater than or equal to 30% ER-positive tumor cells. Yao et al observed that ER or PR negative, small sized and higher grade tumors are more sensitive to neoadjuvant chemotherapy. In our study also, though statistically significant association was not seen, higher numerical probability of pCR was seen with ER negative, PR negative and Her2neu negative tumors

Prior studies have proven significant association of presence of lymphovascular emboli [LVE] in the core biopsy and axillary lymph node metastasis in post-therapy surgical specimen [8,11].Our study also confirms the same finding but any significant association between presence of necrosis in core biopsy and pCR was not seen when compared to those studies. In the present study, none of the cases with perineural infiltrate (PNI) in the core biopsy achieved pCR. The previous studies have not looked upon such an association between PNI and pCR.

Limitations of study: This study is a retrospective analysis of case records of LABC patients who underwent either neoadjuvant chemotherapy or neoadjuvant chemoradiation. Hence, direct comparison on pathological outcomes of treatment between the two groups cannot be drawn. Alsos, the study sample is small.

Conclusion

With the limitations outlined above, our study shows that in locally advanced breast cancer, following neoadjuvant chemotherapy or chemoradiation, the probability of pathologic CR is higher in tumors with higher grade, ER negative, PR negative and Her2neu negative. The most common histological picture in post surgery specimen after neoadjuvant stategies in breast cancer is stromal hyalinisation followed by patchy lymphohistiocytic infiltrate. The pathological complete response rate after neoadjuvant chemoradiation was higher than neoadjuvant chemotherapy but was not found statistically significant. In view of low pCR rates with current anthracycline based neoadjuvant protocols, the benefit of neoadjuvant chemoradiation must be prospectively studied especially in patient subgroups with tumors of large size, low grade and ER positive which have not showed optimum pCR rates with neoadjuvant chemotherapy.

References

1. Raina V, Kunjahari M, Shukla NK, Deo SV, Sharma A, Mohanti BK, et al. Outcome of combined modality treatment including neoadjuvant chemotherapy of 128 cases of locally advanced breast cancer: Data from a tertiary cancer center in northern India. Indian J Cancer 2011;48:80-85.
2. Yalcin, B. "Overview on locally advanced breast cancer: Defining, Epidemiology, and Overview on Neoadjuvant Therapy." Experimental oncology 35.4 (2013): 250-252.
3. Ismaili, Nabil. "Concurrent chemo-radiotherapy in the treatment of early breast cancer: Current status." Clinical Cancer Investigation Journal 2.1 (2013): 1. Ismaili N. Concurrent chemo-radiotherapy in the treatment of early breast cancer: Current status. Clin Cancer Investig J 2013;2:1-8
4. American Joint Commission on Cancer. Breast. In: SB Edge, DR Byrd, CC Compton, AG Fritz, FL Greene, A Trotti III, eds. AJCC cancer staging manual. 7th edition. New York, NY: Springer; 2010: 345–377.
5. Estevez LG, Gradishar WJ: Evidence-based use of neoadjuvant taxane in operable and inoperable breast cancer. Clin Cancer.Res 2004, 10:3249-61.
6. Gharbi O, Trabelsi A, Chafai R, Zayen A, Ezzair F, Hochlef M, et al. Clinical and pathological response to neoadjuvant anthracycline based chemotherapy in women with breast cancer. World J Oncol 2010;1:167-72.
7. Gharbi O, Trabelsi A, Chafai R, Zayen A, Ezzair F, Hochlef M, et al. Clinical and pathological response to neoadjuvant anthracycline based chemotherapy in women with breast cancer. World J Oncol 2010;1:167-72.
8. Yao L, Liu Y, Li Z et al. HER2 and response to anthracycline-based neoadjuvant chemotherapy in breast cancer. Ann Oncol 2011; 22: 1326–1331.
9. Patel T, Gupta A, Shah M (2013). Pathological predictive factors for tumor response in locally advanced breast carcinomastreated with anthracyclin-based neoadjuvant chemotherapy.J Cancer Res Ther, 9, 245-9
10. Prisack HB,Karreman C,Modlich O, et al. Predictive biological markers for response of invasive breast cancer to anthracycline/ cyclophosphamide-based primary (radio-)

chemotherapy. Anticancer Res. 2005; 25: 4615–4621.)

11. Tewari M, Pradhan S, Singh U, Singh TB, Shukla HS: Assessment of predictive markers of response to neoadjuvant chemotherapy in breast cancer. Asian J Surg 2010, 33(4):157–167
12. Pu RT, Schott AF, Sturtz DE, Griffith KA, Kleer CG. Pathologic features of breast cancer associated with complete response to neoadjuvant chemotherapy: importance of tumor necrosis. Am J Surg Pathol. 2005; 29: 354– 358.
13. Colleoni M, Minchella I, Mazzarol G, Nolè F, Peruzzotti G, et al. (2000) Response to primary chemotherapy in breast cancer patients with tumors not expressing estrogen and progesterone receptors. Ann Onco 11: 1057–1059..
14. Ring AE, Smith IE, Ashley S, et al. Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. Br J Cancer.2004;91:2012–2017.
15. 14.Lee, Ho-chang, et al. "Expression of Immunohistochemical Markers before and after Neoadjuvant Chemotherapy in Breast Carcinoma, and Their Use as Predictors of Response." Journal of breast cancer 16.4 (2013): 395-403.
16. Osako T, Nishimura R, Okumura Y, et al (2012). Predictive significance of the proportion of ER-positive or PgR-positive tumor cells in response to neoadjuvant chemotherapy for operable HER2-negative breast cancer. Exp Ther Med, 3, 66-71
17. Keam B, Im SA, Kim HJ, Oh DY, Kim JH, Lee SH, Chie EK, Han W, Kim DW, Moon WK, et al.: Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple negative breast cancer.BMC Cancer 2007, 7(1):203.