Section: Surgery

Original Research Article

NEUTROPHIL-TO-LYMPHOCYTE RATIO AND TUMOR INFILTRATING LYMPHOCYES AS A PREDICTOR OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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ABSTRACT

Background: Aim: To evaluate whether the pre-treatment Neutrophil-to-Lymphocyte ratio (NLR) and Tumor infiltrating lymphocytes (TIL) can predict the response to Neoadjuvant Chemotherapy (NACT) in breast cancer (BC) patients. **Materials and Methods:** This Prospective Observational predictive Study of patients of 90 locally advanced breast cancer LABC was conducted in Department of General Surgery, Pathology and Radiology from July 2018 to April 2020. Patients are included after taking informed consent. Inclusion criteria was newly diagnosed LABC, not received any prior treatment. An exclusion criterion wasconcurrent acute infections, chronic infections, inflammatory and autoimmune diseases, steroid intake in last 2 weeks, associated other malignancies, pregnancy. NLR was calculated by dividing absolute neutrophil count to absolute lymphocyte count before commencement of NACT. TIL was calculated from pre-therapeutic core needle biopsy taken from the tumor. Histopathologic analysis of the lymphocyte infiltrate was performed on hematoxylin and eosin stained sections. Radiological assessment will be done at presentation and after 3 cycles of NACT. Response is evaluated according to RECIST 1.1 criteria. The statistical analysis was done using SPSS for Windows version 23.0 software (IBM Inc.). **Results:** Approximately one-third (30%) patients had complete response of the tumor. Majority of patients (63.3%) patients had partial response to NACT and rest 6.7% had stable disease. The NLR cut-off value was ≤ 1.80 (area under the ROC curve = .852, p=0.006) with 76.2% sensitivity and 78% specificity. The low ratio group demonstrated a better response to NACT than the high ratio group. A total of 27 patients had complete response of which 77.8% had NLR less that 1.80 and 22.2% had NLR more than 1.80 which is statistically significant (p value= 0.006). Majority of the patients (70%) had Grade 2 TIL of which 43.3% patients had partial response and 26.6% patients had complete response. All patients (16.6%) of Grade 1 TIL had partial response. Only 13.3% patients had Grade 3 TIL of which 10% patients had partial response and 3.3% patients had complete response. **Conclusions:** The easily available inflammatory marker NLR can be used as potential screening tool to identify patients, who will be more responsive to NACT, thus help in individualizing thetreatment plan with better outcome. Tumor Infiltrating Lymphocytes cannot be used as a predictor of response to NACT in Breast cancer patients.

INTRODUCTION

Globally, breast cancer (BC) ranks the second most frequent cancer, but it is by far the most common cancer among women with approximately 1.7 million new cases every year.[1] As of Indian scenario, BC is the most common cancer with age adjusted incidence rate of 25.8 per 100,000 women and mortality 12.7 per 100,000 women. The highest of noted in Delhi followed by Chennai.[2]

A number of host and tumor characteristics have been found to prognosticate the severity of disease, risk of recurrence or death. These include tumor size, tumor grade (histologic, nuclear), biologic or

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molecular subtypes, number of axillary lymph node involvement, lymphatic, vascular and perineural invasion, receptor status and others.

More recently neutrophil to lymphocyte ratio (NLR) and TIL (TIL) has been used to prognosticate the breast cancer. These parameters has been studied as a predictor of response to chemotherapy.

Since the concept of neoadjuvant chemotherapy (NACT) has been introduced and used continously, significant efforts to determine those patients who would most likely to be benefitted from NACT have consistently been made by the clinicians and the researchers. A few parameters have been suggested as predictors of NACT response.

TIL are the most important immune cells in the tumor microenvironment. Inflammation play an important role in each step of tumorogenesis, be it tumor initiation, tumor progression or metastatic progression. Important inflammatory cells includes neutrophils, lymphocytes, platelet.

The current study is to evaluate whether the pre-treatment TIL and NLR can predict the response to NACT in BC.

MATERIALS AND METHODS

This prospective observational predictive study was carried out in Department of General Surgery, Heritage Institute of Medical Sciences, Varanasi; over a period of 20 months from September 2018 to April 2020.

A total of 90 patients of newly diagnosed locally advanced breast cancer (LABC), not received any prior treatment were included in this study after taking informed consent. Patients with concurrent acute infection, chronic infection, inflammatory and autoimmune diseases, steroid intake in last 2 weeks, associated other malignancies and pregnancy were excluded.

TIL was calculated from pre-therapeutic core needle biopsy on hematoxylin and eosin stained sections (Image 1a & 1b). One section (4-5mm, magnification x 200-400) per patient was considered to be sufficient (Salgado R et al 2015). TIL is defined as lymphocytes in direct contact with tumor cells. Proportional score of 3, 2, 1, 0 will given if the area of stroma containing lymphoplasmaticinfilteration around invasive tumor cell nests comprised >50%, >10-50%, <10% and 0% respectively (Asano et al. BMC Cancer 2017).

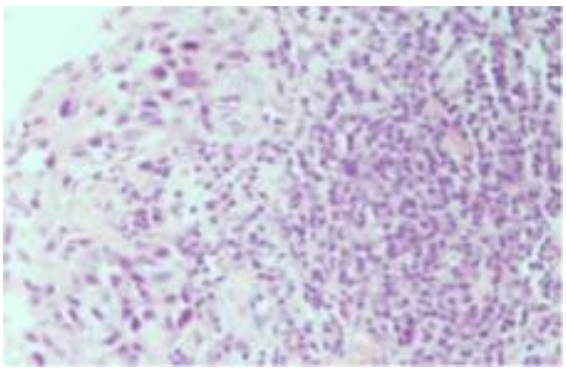

Image 1a: Grade 2 Tumor Infiltrating Lymphocytes in Breast Cancer (400 X)

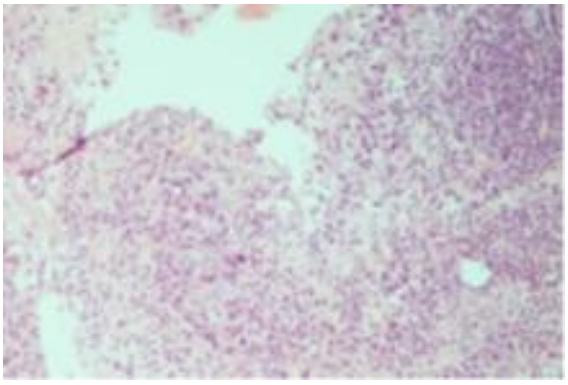

Image 1b: Grade 2 Tumor Infiltrating Lymphocytes in Breast Cancer (200 X)

NLR was calculated as the ratio of neutrophil to lymphocyte, absolute counts obtained from blood sample taken before commencement of NACT.

The response after 3 cycles of NACT was evaluated according to the RECIST 1.1 criteria and correlation with TIL and NLR is studied (Adapted from Revised RECIST Guideline Version 1.1: What Oncologists Want to Know and What Radiologists Need to Know by Mizuki Nishino et al AJR 2010).

Statistical Analysis: The statistical analysis was done using SPSS for Windows version 23.0 software (IBM Inc.). For categorical data Chi-square and Fischer's Exact Test was used. For comparing two groups of mean independent Student's 't' test was used. For paired samples Paired t test was applied for statistical analysis. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

RESULTS

We studied on 90 patients of LABC who did not received prior treatment. The baseline characteristics of the study subjects are summarized in table 1.

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Table1: The characteristics of 90 patients of BC

Age (years)	**n (%)**
<50	63 (70.0%)
>50	27 (30.0%)
Variable	
Pain in lump	30 (33.3%)
Nipple discharge	0 (0%)
Benign Breast Disease	6 (6.7%)
Menstrual status Pre-menopausal Post-menopausal	 60 (66.6%) 30 (33.3%)
Parity <2 >2	 42 (46.7%) 48 (53.3%)
Family history	0 (0%)
Hypertension	9 (10%)
Diabetes	3 (3.3%)
Parameters	
Lump in quadrant Upper outer Lower outer Lower inner Upper inner Central	 57 (63.3%) 18 (20%) 3 (3.3%) 6 (6.7%) 6 (6.7%)
Ulceration	6 (6.7%)
LN(before NACT) Non palpable Palpable	 0 90 (100%)
TNM Classification	
Stage II B	15 (16.7%)
Stage III A	69 (76.7%)
Stage III B	6 (6.7%)
Stage III C	0 (0%)
Grade Well differentiated Moderately differentiated Poorly differentiated	 0 (0%) 72 (80%) 18 (20%)
MBR score 6 7 8 9	 57 (63.3%) 15 (16.7%) 9 (10.0%) 9 (10.0%)
LVI Absent	 63 (70%)
Present	**27 (30%)**
PNI Absent Present	 78 (86.7%) 12 (13.3%)
ECE Absent Present	 72 (80%) 18 (20%)
ER Negative Positive	 45 (50%) 45 (50%)
PR Negative Positive	 57 (63.3%) 33 (36.7%)
Her2 Negative Positive	 54 (60%) 36 (40%)
Receptor status	
HR+ , Her2 +	21 (23.3%)
HR+ , Her2 -	27 (30%)
HR - , Her2 +	15 (16.7%)
HR - , Her2 -	27 (30%)

Approximately one-third (30%) patients had complete response of the tumor (Table 2). But majority of patients (63.3%) patients had partial response to NACT whereas 6.7% patients had stable disease and none of patients showed progressive disease. For the study purpose the partial responder and stable disease were considered under single category.

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Table 2: Distribution of patients according to response to NACT

Response	n (%)
Complete response	27 (30%)
Partial response	57 (63.3%)
Stable disease	6 (6.7%)
Progressive disease	0 (0%)
Total	90 (100%)

For NLR, the cut off value was calculated using the ROC curve. It was considered as a value where the specificity and the sensitivity of NLR to detect response to NACT were same or similar. For our study the cut off value came out to be 1.80. The Sensitivity and Specificity is 76.2% and 78% respectively.

Table 3: Area under the Receiver Operator Characteristic (ROC) Curve

Area	Cutoff value	p-value	Sensitivity	Specificity
.852	1.80	.003	76.2	78.0

Majority of the patients (60%) had Neutrophil to Lymphocyte ratio >1.80, whereas 40% patients had value of <1.80. [Table 4]

Table 4: Distribution of patients according to the Neutrophil to Lymphocyte ratio

NLR-0	n (%)
<1.80	36 (40%)
>1.80	54 (60%)
Total	90 (100%)

A total of 27 patients had complete response of which 77.8% had NLR less that 1.80 and 22.2% had more than 1.80 which is statistically significant with p value 0.006. Among the rest 63 partially responsive patients 76.2% had NLR more than 1.80.

Table 5: Correlation between Neutrophil to Lymphocyte Ratio and response to NACT

NLR-0	Response	
	Complete	Partial
	n (%)	n (%)
<1.80	21 (77.8%)	15 (23.8%)
>1.80	6 (22.2%)	48 (76.2%)
Total	27 (100%)	63 (100%)
p=0.006		

Majority of the patients (70%) had Grade 2 TIL followed by Grade 1 in 16.6% patients and Grade 3 in 13.3% before commencement of NACT. [Table 6]

Table 6: Distribution of patients according to TIL grading.

TIL Grade	n (%)
0	0 (0%)
1	15 (16.6%)
2	63 (70%)
3	12 (13.3%)
Total	90 (100%)

A total of 27 patients had complete response of which 88.9% had Grade 2 TIL and 11.1% patients had Grade 3 TIL. However, none of the patients had Grade 1 or Grade 0 TIL. The rest 63 patients had partial response to NACT, among which majority of patients (61.9%) again had Grade 2 TIL followed by Grade 1 TIL (23.8%) and Grade 3 TIL (14.3%). The correlation is not significant.

Table 7: Correlation between TIL Grade to Response to NACT

TIL Grade	Response	
	Complete	Partial
	n (%)	n (%)
0	0 (0%)	0 (0%)
1	0 (0%)	15 (23.8%)
2	24 (88.9%)	39 (61.9%)
3	9 (11.1%)	9 (14.3%)
Total	27 (100%)	63 (100%)
p=0.241		

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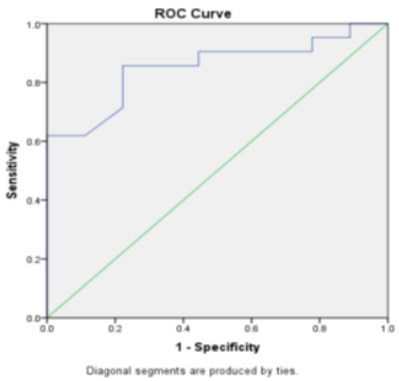

Figure 1

DISCUSSION

LABC account for 10 15% of newly diagnosed breast cancer cases in United States while in India, they account for 30 60% of breast cancer cases. LABC constitutes more than 50 to 70% of the patients presenting for treatment.[3]

NACT which is designed to administer systemic chemotherapy prior to surgery in patients with LABC in order to convert inoperable BC to operable BC, has got significant attention. Other scenarios where NACT is being commonly used is prior to conservative surgeries due to its reduced morbidity and a better acceptable self image, and palliative management of metastatic breast disease.[4]

The study showed that complete response of the tumor is 30% following 3 cycles of NACT. But majority of patients (63.3%) were partial responder and 6.7% patients had stable disease and none of patients showed progressive disease. A study by Salvatore Del Prete showed the complete radiological response rate after NACT to be 76%.[5]

Previous studies has predicted that the response rate varies from 15-30%, that depends on the type of chemotherapy used and the nature of tumor (Sahoo S et al. 2012) (Dawood S et al. 2011). The complete responder group has shown to experience better outcomes, in terms of long term disease free survival and overall survival.[6]

The study showed that a total of 27 patients had complete response to NACT, of which 77.8% patients had NLR of less than 1.80 compared to the rest 22.2% patients who had a NLR of more than 1.80, which is statistically significant. There are multiple studies conducted in the recent past to identify if there is any correlation between these inflammatory blood markers and response to NACT. Among them a study conducted by Chae et al demonstrated that a low NLR is predictive of better response to NACT.[7] Chae showed that the response rate was higher in patients having a low NLR (≤1.7) than in those having a high NLR (42.1% vs. 18.4%, p = 0.018), and in his multiple logistic analysis, a low NLR value remained the only predictive factor for response with odds ratio: 4.274 & p value = 0.008. Also the recurrence free survival was significantly higher in the low NLR group (5-year recurrence free survival rate: 83.7% vs. 66.9%; log-rank p value= 0.016).

The role of inflammation in malignancy is well established.[8] The importance of inflammation has been described at different stages of cancer development including initiation, promotion, invasion, and lastly metastasis. There is evidence that the neutrophils can promote tumor growth and play a role in metastatic development.[9,10]

IléanaCorbeau et al 2020 recently published a systemic review on NLR as Prognostic and Predictive Factor in BC Patients, involving a total of 45 articles and found NLR to be an independent prognosticfactor for the survival in most of the adjuvant setting but no significant correlation was found in BC patients receiving NACT.[11]

In the recent years, the role of TIL, especially in the BC patients, has also been studied (Ravelli A et al. 2017). TIL are a set of T cells that show a high specific immunological reactivity against the cancer cells. These lymphocytes, which are part of the innate immune system, can detect malignant cells and thus alert the immune system that will destroy them. Therefore, it is considered that a low TIL count could be predictive of a lower response to neo-adjuvant chemotherapy,[12]and might be associated with poor prognosis.[13,14] The same way higher TIL are associated with better response to NACT.

Thus by evaluating the pretreatment TIL in core biopsy specimen, it will be easy to identify a group of individual, who will be more benefitted by NACT thus providing the patients with a better management plan and outcome.

Majority of the patients (70%)in the present study had Grade 2 TIL followed by Grade 1 in 16.6% patients and Grade 2 in 13.3% before the commencement of NACT.

A total of 27 patients had complete response of which 88.9% had Grade 2 TIL and only 11.1% patients had Grade 3 TIL. However, none of the patients had Grade 1 or Grade 0 TIL. The rest 63 patients had partial response to NACT, among which majority of patients (61.9%) again had Grade 2 TIL followed by Grade 1 TIL (23.8%) and Grade 3 TIL (14.3%). In our study we could not establish a significant correlation between TIL and response to NACT.

However, study by Miao Ruan et al 2018 concluded that both the stromal and intra-tumoral TIL are independent predictor of pathological complete response to NACT in triple negative breast cancers.

Ruan M demonstrated that stromal TIL had a p value of 0.0001 by multivariate logistic regression analysis in predicting the response. Ruan used ROC curve analysis to identify a cut off value of TIL and showed that a higher TIL was associated with higher pathological complete response rates in univariate analysis. Also, multivariate analysis showed that a 20% threshold of stromal TIL was an independent predictive factor for pathological complete response (P = 0.005).[15]

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Ke Wang et al 2016 conducted a meta-analysis on 23 studies including 13,100 patients over a period of 16years. He found that a high TIL level was associated with a significantly improved response rate to chemotherapy, when compared with a low TIL level (Odds Ratio, 2.81; P < 0.001), commonly in the triple-negative breast cancer (Odds Ratio, 4.67; P < 0.001). He also illustrated that a high TIL level was associated with significantly longer disease-free survival and overall survival.[16]

Again a very recent meta-analysis by Guoxuan Gao showed that triple negative Breast Cancer patients with high TIL level had a higher rate of pathological complete response to treatment (odds ratio 2.14, 95% confidence interval 1.43–3.19) and found to have a better overall survival and disease free survival when compared to patients with low TIL.[17]

CONCLUSION

Although there is a continuous ongoing evolution of multimodality management in Breast Cancer, many of the Breast Cancer patients are still being treated by conventional protocol. However, individualizing the treatment as per the patient's characteristics is the need of hour. A number of biomarkers are already evaluated and many are under evaluation as a predictive and prognostic tool. By an early assessment of tumor response to a treatment plan, may provide a patient with better outcome. Thus an easily available inflammatory biomarker, the Neutrophil to Lymphocyte ratio can be significantly used to predict the response of breast cancer to Neo-Adjuvant Chemotherapy with a Sensitivity of 76.2% and a Specificity of 78%. However, no correlation could be established between TumorInfiltrationg Lymphocytes and response to Neo-Adjuvant Chemotherapy.

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