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Pathologic Predictors of Chemotherapy Response in Post Neo-Adjuvant Breast Cancer

Sabiha Rizwan [a*], Rufina Soomro [a], Atif Ali Hashmi [b] and Muhammad Irfan [c]

[a] Department of Surgery, Liaquat National Hospital and Medical College, Karachi, Pakistan.
[b] Department of Pathology, Liaquat National Hospital and Medical College, Karachi, Pakistan.
[c] Department of Statistics, Liaquat National Hospital and Medical College, Karachi, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. Authors SR, AAH and RS have made substantial contributions to conception and design of study. Authors SR and MI have been involved in requisition and analysis of the data and revision of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Pathological complete response (pCR) is the most important prognostic factor in determining survival in post-neoadjuvant breast cancer. In this study, we evaluated the pathologic predictors that are associated with pCR in post-neoadjuvant breast cancer.
Methods: It was a retrospective observational study conducted in Liaquat National Hospital and Medical College, Pakistan, from January 2019 to December 2020 over a period of two years. All patients with primary breast cancer that received neo-adjuvant chemotherapy at Liaquat National Hospital were included in the study. Pathological parameters from pre-chemotherapy specimens like tumor type, grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal

**Corresponding author: E-mail: sabiha_rizwan89@hotmail.com;*

growth factor receptor 2 (HER2/neu) and proliferative index Ki67 status were recorded. Pathological response to chemotherapy from post-chemotherapy specimens was recorded as complete or partial responses to chemotherapy.

Results: A total of 287 patients were included in the study, among whom pCR was noted in 65 (22.6%) cases. A significant association of pCR was noted with Ki67 proliferative index, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) statuses, whereas no significant association was noted with tumor size, histological type, grade, or nodal metastasis.

Conclusion: The pCR was significantly seen more in cases with higher Ki67 index, hormone receptor negativity and HER2/neu positivity. These pathological predictors can help develop post-neoadjuvant chemotherapy protocols and guide patients regarding their likely chemotherapy response and prognosis.

Keywords: Post-neoadjuvant breast cancer; estrogen receptor (ER); progesterone receptor (PR); human epidermal growth factor receptor 2 (HER2neu); Ki67 proliferation index.

ABBREVIATIONS

pCR : Pathological complete response
ER : Estrogen receptor
PR : Progesterone receptor
HER2/neu : Human epidermal growth factor receptor 2

1. INTRODUCTION

Breast cancer is one of the most prevalent cancers in women worldwide with high frequency of its occurrence in Pakistan [1–3]. In western countries owing to highly efficient screening programs including mammography have led to early detection of this disease, especially at tumor stages T1 and T2 that results in upfront curative surgery. In contrast, in this part of world, due to lack of resources, many patients present at late stages and therefore, initial surgery is impossible. In these circumstances neo-adjuvant chemotherapy is given to reduce the bulk of the disease, followed by surgical resection. In the surgically resected specimens, pathological response is determined based on the viability of residual tumor cells in the specimens, which is one of the most important prognostic factors in these patients [4]. There are various pathological schemes to evaluate the initial response to chemotherapy and complete pathological response (pCR) is labeled when there are no residual invasive cancer cells in either the breast or lymph nodes [5–7]. It is noted that same stage breast cancers with similar biomarker status have different pathological responses. Whether there are any specific pathological parameters like histologic type, tumor grade that drives pathological response is unknown in our population, therefore, in this study we evaluated the pathologic predictors of response to neo-adjuvant chemotherapy in breast cancer that would help to see the statistics in our subset of population.

2. METHODS

It was a retrospective observational study conducted in Liaquat National Hospital and Medical College, Pakistan, from January 2019 to December 2020 over a period of two years. All patients with primary breast cancer that received neo-adjuvant chemotherapy at Liaquat National Hospital were included in the study. Patients with surgery before chemotherapy or with recurrent cancers were excluded from the study. The chemotherapy regimen used in the neoadjuvant setting was anthracycline based along with taxanes with/without anti-HER/2neu therapy depending upon their human epidermal growth factor receptor 2 (HER2/neu) status.

After ethical approval from the institutional research committee, pathological and oncology records were searched and slides of histopathological specimens were retrieved. Pathological parameters from pre-chemotherapy specimens like tumor type, grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu) and proliferative index Ki67 status were recorded. Pathological response to chemotherapy from post-chemotherapy specimens were recorded as complete or partial responses to chemotherapy.

2.1 Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (Version 26.0, IBM Inc., Armonk, USA). Chi-square and Fisher's

exact tests were used to verify the association. The odds ratio was calculated using Univariate binary logistic regression. P-values < 0.05 were considered as significant.

3. RESULTS

A total of 287 patients were included in the study. The demographics and clinical characteristics of the study population are presented in Table 1. The mean age of the patients at the time of diagnosis was 47.33±10.49 years with majority (54.4%) were between 36 and 50-year age group. The mean tumor size was 5.32±2.59 cm, while the mean Ki67 index was 37.26±22.68.

The majority of cases (89.5%) were of infiltrating ductal carcinoma (IDC) and 47% were of grade II. Most common tumor (T)-stage group was T2 (49.8%), and nodal metastasis was present in 59% of cases. Estrogen receptor (ER), progesterone receptor (PR) and HER2/neu positivity were noted in 56.4%, 40.8%, and 23% cases, respectively. pCR was noted in 65 (22.6%) cases. After the completion of systemic therapy, breast conservation surgery was performed in 35.2 % of cases and modified radical mastectomy in 41.1% cases.

Table 2 and 3 depict the association of pCR with various clinicopathological parameters. A significant association of pCR was noted with the Ki67 index, ER, PR, and HER2/neu status. The pCR was significantly seen more in cases with higher Ki67 index, hormone receptor negativity and HER2/neu positivity.

Table 1. Clinicopathological characteristics of the population under study

Clinicopathological parameters	Values
Age (years), mean±SD	47.33±10.49
Age groups	
≤35 years, n (%)	32(11.1)
36-50 years, n (%)	156(54.4)
>50 years, n (%)	99(34.5)
Tumor size (cm), mean±SD	**5.32±2.59**
Tumor size groups	
≤5 cm, n (%)	164(57.1)
>5 cm, n (%)	123(42.9)
Ki67 (%), mean±SD (n=244)	37.26±22.68
Ki67 groups (n=244)	
≤25%, n (%)	94(38.5)
>25%, n (%)	150(61.5)
Histological subtype	
DCIS, n (%)	7(2.4)
Invasive ductal carcinoma, n (%)	257(89.5)
Invasive lobular carcinoma, n (%)	16(5.6)
Invasive mucinous carcinoma, n (%)	5(1.7)
Invasive metaplastic carcinoma, n (%)	2(0.7)
ER	
Positive, n (%)	162(56.4)
Negative, n (%)	125(43.6)
PR	
Positive, n (%)	117(40.8)
Negative, n (%)	170(59.2)
HER2/neu	
Positive, n (%)	66(23)
Negative, n (%)	221(77)
Nodal status (n=273)	
Positive, n (%)	161(59)
Negative, n (%)	112(41)
Nodal Status (n=273)	
N0, n (%)	112 (41)
N1, n (%)	125 (45.8)
N2, n (%)	33 (12.1)
N3, n (%)	3 (1.1)
Presence of metastasis(n=273)	
Present, n (%)	4(1.5)
Absent, n (%)	269(98.5)

Clinicopathological parameters	Values
Pathological stage(n=273)	
Stage I, n (%)	17(6.2)
Stage II, n (%)	144(52.7)
Stage III, n (%)	108(37.6)
Stage IV, n (%)	4(1.5)
Procedure	
BCS, n (%)	101(35.2)
MRM, n (%)	118(41.1)
Simple mastectomy, n (%)	68(23.7)
Laterality	
Right, n (%)	146(50.9)
Left, n (%)	141(49.1)
Tumor grade	
Grade I, n (%)	51(17.8)
Grade II, n (%)	135(47)
Grade III, n (%)	101(35.2)
T Stage	
T1, n (%)	21(7.3)
T2, n (%)	143(49.8)
T3/T4, n (%)	123(42.9)
Response to neo-adjuvant therapy	
Partial response, n (%)	222(77.4)
Complete response, n (%)	65(22.6)

SD, standard deviation; DCIS, ductal carcinoma in situ; T, tumor; N, nodal; ER, estrogen receptor; PR, progesterone receptor; HER2/neu, human epidermal growth factor receptor 2; BCS, breast conservation therapy; MRM, modified radical mastectomy; T, tumor

Table 2. Association of clinicopathological parameters with response to neo-adjuvant therapy

Clinicopathological parameters	Pathological response to neo-adjuvant therapy		p-value
	Partial response	Complete response	
Age (years), mean±SD	47.31±10.65	47.41±9.99	0.946
Age groups			
≤35 years, n (%)	27(12.2)	5(7.7)	0.600
36-50 years, n (%)	119(53.6)	37(58.9)	
>50 years, n (%)	76(34.2)	23(35.4)	
Tumor size (cm), mean±SD	5.30±2.61	5.37±2.54	0.839
Tumor size groups			
≤5 cm, n (%)	98(58.3)	29(52.7)	0.466
>5 cm, n (%)	70(41.7)	26(47.3)	
Ki67 (%), mean±SD (n=244)	34.91±22.76	44.31±21.09	0.005*
Ki67 groups (n=244)			
≤25%, n (%)	81(44.3)	13(21.3)	0.001*
>25%, n (%)	102(55.7)	48(78.7)	
Histological subtype			
Invasive ductal carcinoma, n (%)	200(90.1)	57(87.7)	0.578
Others, n (%)	22(9.9)	8(12.3)	
ER			
Positive, n (%)	136 (61.3)	26 (40)	0.002*
Negative, n (%)	86 (38.7)	39 (60)	
PR			
Positive, n (%)	101 (45.5)	16 (24.6)	0.003*
Negative, n (%)	121 (54.5)	49 (75.4)	
HER2/neu			
Positive, n (%)	34 (15.3)	32 (49.2)	<0.001*
Negative, n (%)	188 (84.7)	33 (50.8)	
Nodal status (n=273)			
Positive, n (%)	126(60)	35(55.6)	0.529
Negative, n (%)	84(40)	28(44.4)	
Presence of metastasis(n=273)			
Present, n (%)	2(1)	2(3.2)	0.229
Absent, n (%)	208(99)	61(96.8)	

Clinicopathological parameters	Pathological response to neo-adjuvant therapy		p-value
	Partial response	Complete response	
Pathological stage(n=273)			
Stage I, II, n (%)	122(58.1)	39(61.9)	0.590
Stage III, IV, n (%)	88(41.9)	24(38.1)	
Tumor grade			
Grade I, n (%)	40(18)	11(16.9)	0.821
Grade II, n (%)	106(47.7)	29(44.6)	
Grade III, n (%)	76(34.2)	25(38.5)	

*SD, standard deviation; HER2/neu, human epidermal growth factor receptor 2; *p-value significant as <0.05*

Table 3. Odds ratio by Univariate binary logistic regression for pathological complete response to neo-adjuvant therapy

	Un-Adjusted		Adjusted	
Clinicopathological parameters	**p-value**	**Values**	**p-value**	**Values**
Age				
≤35 years, Odds Ratio (95% CI)	0.365	0.612(0.212-1.770)		
36-50 years, Odds Ratio (95% CI)	0.929	1.027(0.567-1.862)		
>50 years *		1		
Tumor size				
≤5 cm, Odds Ratio (95% CI)	0.467	0.979(0.432-1.469)		
>5 cm *		1		
Ki67 index (%)				
≤25%, Odds Ratio (95% CI)	0.002**	0.341(0.173-0.672)	0.006**	0.340(0.157-0.738)
>25% *		1		1
Histological subtype				
Invasive ductal carcinoma, Odds Ratio (95% CI)	0.579	0.784(0.331-1.854)		
Others *		1		
ER				
Positive, Odds Ratio (95% CI)	0.003**	0.422(0.240-0.742)	0.304	0.630(0.261-1.520)
Negative *		1		1
PR				
Positive, , Odds Ratio (95% CI)	0.003**	0.391(0.210-0.729)	0.331	0.622(0.238-1.621)
Negative *		1		1
HER2/neu				
Positive, , Odds Ratio (95% CI)	0.000**	5.362(2.919-9.850)	0.000**	7.852(3.852-16.006)
Negative *		1		1
Nodal status				
Positive, Odds Ratio (95% CI)	0.530	0.833(0.472-1.471)		
Negative *		1		
Presence of metastasis				
Present, Odds Ratio (95% CI)	0.225	3.410(0.470-24.712)		
Absent, Odds Ratio *		1		
Pathological stage				
Stage I, II, Odds Ratio (95% CI)	0.590	1.172(0.658-2.089)		
Stage III, IV *		1		
Tumor grade				
Grade I, Odds Ratio (95% CI)	0.663	0.836(0.373-1.872)		
Grade II, Odds Ratio (95% CI)	0.554	0.832(0.452-1.532)		
Grade III *		1		

*CI, confidence interval; HER2/neu, human epidermal growth factor receptor 2; *Reference group, **p-value significant as <0.05*

4. DISCUSSION

In this study, we found that hormone receptor negativity and HER2/neu positivity are strong predictors of response after neoadjuvant therapy in breast cancer. Moreover, high Ki67 index was also associated with better chemotherapeutic response.

Various international studies have assessed pathological predictors of response after post-neoadjuvant chemotherapy in breast cancer. A study was conducted in the United Kingdom, including 500 breast cancer patients with HER2/neu positivity. They concluded that ER negativity, strong HER2/neu positivity by immunohistochemistry (3+), and grade III were

independent predictors of response in breast cancer patients [8]. Although we didn't find any significant association of pCR with tumor grade, however, Ki67 index, which is a more reliable indicator of tumor proliferative activity, was significantly associated with pCR in our study. Del Prete S et al in a study involving 117 breast cancer patients found a significant association of pCR with menopausal status, T-stage and hormone receptor status [9]. However, we didn't find any significant association between pCR with tumor size or T-stage. Tan MC demonstrated that pCR was associated with four factors; tumor grade (II, III), hormone receptors (-ve), HER2/neu over expression and negative nodal status [10]. Although, concordant with their results, we found a significant association of pCR with biomarker status, no significant association was noted with nodal negativity in our study.

5. CONCLUSION

Therefore, in conclusion, we evaluated various clinical and pathological parameters associated with pCR. While, no significant association was noted with tumor grade, T and N-stage, a significant association was found with hormone receptor negativity, HER2/neu positivity and high proliferative index. These pathological predictors can help develop post-neoadjuvant chemotherapy protocols and guide patients regarding their likely chemotherapy response and prognosis.

6. LIMITATIONS

Major limitations of the study included a lack of follow-up and survival status of the patients, however, our aim was to evaluate the predictors of pCR. Moreover, as it was a single center study, therefore, the results cannot be extrapolated to the entire population. However, we comprehensively determined the clinical pathological predictors of chemotherapy response in this study, which is one of the most potent predictors of survival in these groups of patients.

ETHICAL APPROVAL AND CONSENT

Ethical review committee of Liaquat National Hospital, Karachi, Pakistan approved the study (0555-2020 LNH-ERC). Written informed consent was obtained from the patients for the participation.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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