Original Article

Effect of Response to Neoadjuvant Chemotherapy and Change in Biomarker Status Post Neoadjuvant Chemotherapy on Prognosis of Locally Advanced Breast Cancer

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ABSTRACT

Objective: To explore the significance of pathological and biomarker changes in response to neoadjuvant chemotherapy in terms of disease free survival and overall survival in Pakistani population.

Study Design: Retrospective study

Place and Duration of Study: This study was conducted at the Department of Oncology, Liaquat National Hospital from January 2004 to January 2011.

Materials and Methods: A total of 104 patients with locally advanced breast carcinoma (inoperable) were included in the study retrospectively who had received neoadjuvant chemotherapy followed by surgery.

Results: Out of the 104 patients who completed chemotherapy and underwent surgery, 19 (14.4%) had complete pathological response (pCR), 47 (35.6%) had node negative residual disease (NNRD), and 38 (28.8%) had node positive residual disease (NPRD). Factors associated with better 2 year overall survival included pCR, NNRD, post-chemotherapy unchanged positive hormonal status and post chemotherapy changed from negative to positive hormonal status, prechemotherapy Ki-67 <20 % as well as Ki-67 score of >20% changed to less than 20% post chemotherapy. Factors associated with less chances of recurrence were NNRD, unchanged hormone positive and change from hormone negative to hormone positive. Prechemotherapy HER2Neu positive had higher chances of recurrence. Patients with more than 20% pre-chemotherapy Ki-67 had 8.3 times higher chances of recurrence than those with less than 20%.

Conclusion: We concluded that 2yrs overall survival in patients who received neoadjuvant chemotherapy were significantly associated with cPR, NNRD, unchanged positive hormonal status, and post chemo changed from –ve to +ve hormonal status, prechemo ki67 <20% as well as ki67 score of >20% changed to less than 20% post chemotherapy. Factors associated with less chances of recurrence were pCR, node negative residual disease, unchanged hormone +ve and change from hormone –ve to +ve disease.

Key Words: Neoadjuvant chemotherapy, Pathological complete response (PCR), Node Negative Residual Disease (NNRD), Node Positive Residual Disease (NPRD), Her2Neu Receptors, Ki-67, Estrogen Receptor, Progesterone Receptor.

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INTRODUCTION

Breast Cancer is next only to Lung Cancer as cause of cancer related deaths among women from all ethnicities.

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Locally advanced Breast Cancer (LABC) describes a subset of invasive breast cancer where initial clinical & radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes represented by Stage III T_{0-3} N_2, T_4 anyN or T_3 N_1 (AJCC) with no distant metastasis. These are the patients where an initial surgical approach is unlikely to successfully remove all these with adequate margins.

The incidence of locally advanced breast cancer is more common in third world countries with possibly more aggressive disease. This is partly attributable to deficiencies in mammographic screening and possibly lack of awareness regarding breast cancer and inadequate healthcare infrastructure.

The response of primary breast carcinoma to neoadjuvant chemotherapy co-relates with survival. Patients who achieve a complete pathological response are reported to have a significantly improved disease free and over-all survival.[1]

Several studies have reported change in biomarker status estrogen receptor (ER), progesterone receptor (PR), Human epidermal growth factor receptor 2 (Her2Neu) & Ki67 expression after neoadjuvant chemotherapy[2-5]**.** It has been reported that change in the hormone receptor status in the positive direction post neoadjuvant chemotherapy (ER -/+ or PR -/+ or both) has been associated with a statistically significant improvement in the overall survival.[6]

To explore, the significance of pathological and biomarker changes rin response to neoadjuvant chemotherapy in terms of Disease Free Survival and Overall Survival in Pakistani population, we evaluated the effect of neoadjuvant chemotherapy induced pathological and biomarker changes on survival outcome.

MATERIALS AND METHODS

This study was conducted at the Department of Oncology, Liaquat National Hospital from January 2004 to January 2011. Patients with locally advanced breast carcinoma (inoperable) were included in the study retrospectively who had received neoadjuvant chemotherapy followed by surgery. Patients who had progressed on neoadjuvant chemotherapy or had bilateral breast disease or metastatic disease were excluded from the study.

Chemotherapy regimens received included combination regimens AC followed by Taxanes & FAC regimen and Trastuzumab in case of Her2Neu positive tumors.

Hormone status (ER/PR), Her2Neu and Ki67 were performed on post chemotherapy surgical specimen on the residual disease (if any) on the available specimens by Envision method .Her2Neu positivity in specimens with 2+ (by IHC) was confirmed by FISH amplification.

Data of all patients with locally advanced breast cancer who completed their neoadjuvant chemotherapy followed by surgery was analyzed for Complete Pathological Response (CPR), Node negative Residual Disease (NNRD), Node Positive Residual Disease (NPRD), post treatment hormonal (ER/PR) Her2Neu & KI67 score, change in hormone status (change in either ER or PR or both from -/+ or +/- or unchanged), change in HER2neu from -/+ or +/- or unchanged and change in Ki67 status (from >20% to <20% or vice versa or unchanged) and was co-related with disease free survival and overall survival. Patients' 2 years follow-up was assessed retrospectively for disease recurrence and overall survival.

Statistical Analysis: Descriptive statistics were used and odds ratios were calculated by applying binary logistic regression. Inferential statistics were applied to check the association between various categorical variables. Overall survival and recurrence were checked by chi-square test. Data was entered and analyzed using SPSS 17.0, Chi-square/Fisher exact test. Likelihood ratio test were applied to check association between various categorical variables, overall survival and recurrence. P-value of less than 0.05 was considered as statistically significant. Binary Logistic regression was applied to compute odds ratio.

RESULTS

From Jan 2004 to Jan 2011, we registered 1306 breast cancer patients. Out of these, 327 patients were having locally advanced breast cancer, and advised for neoadjuvant treatment. Total 132 patients received neoadjuvant chemotherapy. Complete data (residual disease status, pre chemotherapy and post chemo hormone, Her2Neu and KI67 and 2 years follow-up), was available on 104 patients which was retrospectively analyzed. The remaining 28 patients either had progressed on treatment, or lost to follow or did not undergo surgery so their data could not be analyzed. Pathological response and molecular markers were correlated with 2 year survival and the significance of change in molecular biology after neoadjuvant chemotherapy was analyzed.

Baseline Characteristics: Out of the 132 patients, none belonged to Stage I and IV of Breast Cancer. 52 patients were Stage II-B, 40 patients were III-A and 39 were III-C. Only one patient was Stage III-C. Mean Age: Mean age is 46.37 years.

Out of 104 patients who completed neoadjuvant chemotherapy and underwent surgery, 19 had pathological complete response, 47 had node negative residual disease while 38 had node positive residual disease.

84% (N-16) patient who had pCR remained recurrence free at 2 yrs which is statistically significant as compared to the patients with residual disease. Similarly patients with Node Negative Residual Disease had a statistically significant Recurrence Free Survival as compared to Node Positive Residual Disease as shown in Table I.

Patients with pCR and Node Negative Residual Disease had statistically significant better Overall Survival as compared to Node Positive Residual Disease who had Inferior Overall Survival as shown in Table 1.

Both pre and post chemotherapy Hormone & Her2Neu status were available in 64 samples, while Ki67 score both pre chemo & post chemo were available in 41 patients. Change in status is represented in table 2.

As seen in the table 5 change in hormone status, Her 2 Neu and ki 67 expression before chemo and after chemo exposure was statistically significant (p-value <0.001).

Table No.1: Relationship of recurrence with residual tumor

Recurrence: Yes[b]					
Residual Disease	Odds Ratio	95% C.I. for OR		Sig.	N
		Lower	Upper		
Complete Pathological Response	Reference				19
Node Negative Residual Disease	2.844	0.72	11.242	0.136	46
Node Positive Residual Disease	3.556	0.871	14.511	0.077[a]	35

a. Shows significant results (P-Value < 0.1); Binary Logistic Regression
b. No recurrence is a Reference category

Overall Survival : Alive[b]					
		95% C.I. for OR			
Residual Disease	Odds Ratio	Lower	Upper	Sig.	N
Complete Pathological Response	3.06	0.587	15.956	0.184	19
Node negative residual disease	2.952	0.888	9.811	0.077[a]	46
Node positive residual disease	Reference				35

a. Shows significant results (P-Value <0.1); Binary Logistic Regression
b. Expired is a reference category

Table No.2: Change in Biomarker status after neoadjuvant chemotherapy

		Unchanged				
	N	**Pos**	**Neg**	**Pos → Neg**	**Neg → Pos**	**P-value**
Hormonal Status	64	32	22	1	9	*<0.001
HER2NU	64	23	27	13	1	*<0.001
KI67	41	9	18	13	1	*<0.001

It was also been observed that pre-chemo Her2neu +ve had a higher chance of recurrence (that is among 33 patients who had recurrence, 19 patients (57.3%) were her2neu +veprechemo).(OR: 1.63).

Unchanged hormone +ve (N-32) patients were seen to have lesser chance of recurrence (31% of the patients with no recurrence) as well as better overall survival (33% of the alive patients). This was also seen among the patients who changed from prechemo hormone –ve to post chemo hormone +ve (Table 3).

Table No.3: Change in Hormone receptor and Her2Neu receptor status and it's effect on recurrence

Recurrence: Yes[b]				
	Odds Ratio	**95% C.I. for OR**		
		Lower	Upper	Sig.
Post Surgery Hormonal Status				
Unchanged –ve	Reference			
Unchanged +ve	0.833	0.264	2.631	0.756
Change from –ve to +ve	0.583	0.094	3.603	0.562
Post Surgery HER2Neu Status				
Changed from +ve to –ve	Reference			
Unchanged +ve	0.544	0.133	2.235	0.399
Unchanged –ve	0.519	0.131	2.045	0.348

a. Shows significant results (P-value < 0.1); Binary logistic regression
b. No recurrence is a reference category

Overall Survival : Alive[b]			
		95% C.I. for OR	
	Odds Ratio	**Lower**	**Upper**
Post Surgery Hormonal Status			
Unchanged –ve **Reference**			
Unchanged +ve	2.196	0.437	11.027
Change from –ve to +ve	1.647	0.155	17.47
Post Surgery HER2Neu Status			
Changed from +ve to –ve	**Reference**		
Unchanged +ve	1.727	0.212	14.048
Unchanged –ve	1	0.158	6.33

a. Shows significant results (P-value<0.1); Binary Logistic Regression
b. Expired is a reference category

Patients with more than 20% prechemo Ki67% score were seen to have an 8.3 times higher chances of recurrence than those with a prechemo ki67 score of <20%. Patients with Ki-67 score <20% Pre-Chemo as well as unchanged Post-Chemo Ki-67 score of <20%

had better Overall Survival and Relapse Free Survival whereas patients with ki-67 score changed from >20% to <20% had statistically better OS. (Table 4).

Table No.4: Change in Ki 67 and Recurrence

Recurrence				
Post Chemoki67	No	Yes	Lost to follow up	P – Value
Changed from less than 20% to more than 20%	0	0	1 (25%)	*<0.001
Changed from more than 20% to less than 20%	9 (13.4%)	4 (12.1%)	0	0.427
Unchanged Negative	16 (23.9%)	1 (3%)	1 (25%)	*0.008
Unchanged Positive	5 (7.5%)	4 (12.1%)	0	0.317
Lost to Follow	27(40.3 %)	12(36.4%)	2 (50%)	0.560
	Overall Survival			
Post Chemoki67	Expired	Alive	Lost to follow up	P – Value
Changed from less than 20% to more than 20%	0	0	1 (20%)	*<0.001
Changed from more than 20% to less than 20%	2 (12.5%)	10 (12%)	1 (20%)	*0.002
Unchanged Negative	0	17 (20.5%)	1 (20%)	*0.046
Unchanged Positive	3 (18.8%)	6(7.2%)	0	0.097
Lost to follow	8 (50%)	31 (37.3%)	2 (40%)	0.342

DISCUSSION

Neoadjuvant chemotherapy is the recommended systemic treatment approach for locally advanced breast cancer. The major aims of primary systemic therapy in these patients are to eradicate possible distant micro-metastatic disease and to increase breast conserving therapy. Neoadjuvant chemotherapy also allows in vivo assessment of tumor sensitivity to systemic treatment. Pathologic Complete Response to NAC carries prognostic significance independent of other prognostic biological markers.[7]

Change in Estrogen receptor, progesterone receptor and Her2neu receptor and Ki 67 has also been reported in several reports[8]. What is still unclear is whether there is any prognostic significance of these changes in biomarkers in response to chemotherapy. The prognostic significance of change in Ki 67 has been reported previously.

In our study we studied the effect of residual tumor in terms of size and number of positive lymph nodes on relapse free survival and overall survival. We also tried to identify any relationship between change in biomarkers in response to chemotherapy with relapse free survival and overall survival.

Patients with pathologic complete response had better 2 year recurrence free survival and overall survival which was statistically significant. Furthermore it was also seen noted that node negative residual disease also had statistically significant better recurrence free survival and overall survival as compared to node positive residual disease. Whether there was any prognostic significance of size of residual tumor could not be analyzed because of small sample size.

We also found a significant change in hormone receptor status from negative to positive, Her2neu status from positive to negative and Ki 67 score from more than 20% to less than 20%.

Pre chemotherapy hormone positive patients as well as those who changed from negative to positive had better prognosis. Prechemotherpay Her2neu positive tumors had higher relapse rate but we didn't find any prognostic significance of change in her2neu status.

Prechemotherapy Ki 67 less than 20% and change in Ki 67 score from more than 20% to less than 20% had statistically significant effect on survival but significant effect on relapse free survival couldn't be appreciated probably because of small sample size.

The limitations of this study can be treatment limitations where some Her2neu positive patients did not receive Trastuzumab which could explain the lack of prognostic significance of change in Her2neu status. Another limitation is small sample size.

CONCLUSION

2yrs overall survival in patients who received neoadjuvant chemotherapy were significantly associated with cPR, NNRD, unchanged positive hormonal status, and post chemo changed from –ve to +ve hormonal status, prechemo ki67 <20% as well as ki67 score of >20% changed to less than 20% post chemotherapy.

Factors associated with less chances of recurrence were pCR, node negative residual disease, unchanged hormone +ve and change from hormone –ve to +ve disease.

We think that these factors can guide us in planning further postoperative treatment in patients receiving neoadjuvant chemotherapy for locally advanced breast

cancer and studies should be designed to analyze treatment planning according to these factors.

Patients with a High Ki67 score & significant residual nodal disease might benefit and should be given further chemotherapy to change the outcome. Further studies/trials in this regards are needed.

Author's Contribution:

Concept & Design of Study:	Naila Zahid
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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