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Research Article

Predictive Factors Involved in Determining Response to Neoadjuvant Chemotherapy in Breast Cancer and Impact of Response on 5 Years Disease Free Survival and Overall Survival

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ABSTRACT

Objective: To evaluate all the known factors that may play a role in predicting response to Neoadjuvant chemotherapy in breast cancer and to see impact of response on five years' disease free survival (DFS) and Overall survival (OS).

Material and Method: Data of 156 patients was reviewed retrospectively from January 2012 to December 2012 at Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore, Pakistan. All received neoadjuvant chemotherapy (NAC) and had no distant metastasis. The response was measured in term of percentage reduction from 1st radiological size on presentation to final size on histopathology (of resected specimen). Four groups were identified, complete responder (CR) (100% reduction), Responders (R) (>50% reduction), Partial responder (PR) (<50% reduction) and Non-responder (NR). Relationship of predictive factors with each response group was observed. Five year survival was noted for each response group.

Result: Median age of patients was 45 years (25-64 years). 67% of patients underwent breast conservation surgery, while the rest underwent mastectomy. Mortality for whole group was 22%, and recurrence was shown in 34% (Majority i.e. 26% were distant, while contralateral were 3%). Out of 156 patients, 25% of patients were CR, 13% were NR, 23% were PR and 37% were R. Progesterone receptor negative and Grade III tumors showed more complete responses. The Rest of the receptor types, including triple negative, initial T and N stage and other clinical factors showed no impact on chemo-response. Survival was significantly poor in NR group (45% OS, 40% DFS), while rest of three groups had comparable survival outcome, with CR group having best survival outcome (86% OS, 80% DFS).

Conclusion: Most of factors studied did not show impact on achieving good chemo response, however good chemo response did show better survival.

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Introduction

Breast cancer accounts for 23% of total cancer cases worldwide and 14% of all cancer deaths [1]. As per World Health Organization (WHO), breast cancer affects more than 1.2 million people every year [2]. According to GLOBOCAN 2018, breast cancer is the leading cause of cancer death among females [3]. In Pakistan, one in every nine women will develop cancer at some stage of life [4]. In the last few decades, neo-adjuvant chemotherapy (NAC) has become a standard treatment in the management of breast cancer. The United States National Cancer data database reported an increase in usage of NAC from 15.7% to 26% in 2015 [5, 6]. Potential benefits of NAC are killing systemic micro-metastasis right from beginning, achieving higher rates of breast conservative surgery (BCS), allowing in vivo evaluation of chemo sensitivity and subsequently changing chemo regimen accordingly [7].

Response of NAC is variable, and it is multi-factorial, as some patients can be either non-responders (NR), complete responders (CR) or partial responders (PR) [8]. Patients with highest sensitivity to NAC were expected to have more than five years disease-free survival; however, a subset of patients with hormone receptor positive tumors were resistant to chemotherapy however showed a good 5 years disease free survival ratio [9]. Chemo response variations have led to the researchers focusing on differences among patients that may have influence on achieving better responses; these are patient factors and tumor biomarkers, collectively referred to as "Predictive response factors". However, the value of the predictive response factors within the neo-adjuvant scenario is still uncertain, as there are some conflicting results in literature. The rationale of this study is to evaluate all the known factors that may play a role in predicting response to chemotherapy and to see impact of response on five years disease free survival (DFS) and overall survival (OS).

Methodology

I Patients

During 1st January 2012 to 31st December 2012, patients who underwent resections for invasive ductal breast cancer after NAC at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC), Pakistan were selected. It is a retrospective study with convenience sampling. Patients who underwent upfront surgery or had distant metastases were excluded from disease. The ethical approval was sought from Institutional Review Board (IRB) of SKMCH&RC.

II Variables

Data was collected through human information system (HIS), electronic database of SKMCH&RC. Variables (supposed predictive factors) recorded were age, parity, menopausal status, family history, pre surgery histopathology including immunohistochemistry, clinical staging, type of neo-adjuvant chemotherapy received and survival outcomes. Every patient had detailed history and examination in the walk-in clinic and referred to One Stop Breast Clinic (OSBC) for detailed assessment and investigation. Investigations included were baseline blood tests, mammogram, ultrasound breast, tru-cut biopsy of breast masses and fine needle aspiration (FNA) of axilla. Metastatic workup includes ultrasound abdomen and pelvis, chest radiograph (CXR) or Computed tomography scan (CT) where indicated and Bone scan. Every case was discussed in our Multi-Disciplinary Team (MDT) meeting comprising of trained breast surgeons, interventional radiologists, pathologists, medical and radiation oncologists. Ultrasound guided metal clips were parked in patients who were candidates of breast conserving surgery (BCS) before starting NAC.

As a routine, all cadres including doctors, nurses, allied health professionals, put all patient data real time into a computerised Hospital Information System (HIS). Therefore, information like patient demographics, investigations, Multi-Disciplinary Team discussions, Nursing assessments, outpatient, operative notes and post- operative outcomes were collected. As the data is collected in real time and stored, it allows for accurate retrospective review of the data.

Response to chemotherapy was calculated on histopathology of resected specimen. They were categorized into four groups i.e. CR- 100% reduction in tumour mass, R- more than 50% reduction in tumour mass, PR- less than 50% reduction in tumour mass and NR- No reduction seen. The response was measured in term of percentage reduction (final size on excision ÷ initial size on ultrasound × 100 -100).

III Statistical Analyses

Calculations were performed with Statistical Package for the Social Sciences (SPSS 20) for Windows version 20 statistical software. Data was described using median with minimum and maximum value for skewly distributed quantitative variables. For categorical variables, number of observations and percentages were reported. The study is complied with the SKMCH&RC guidelines on research involving human subjects.

Results

A total of 156 patients underwent breast surgery after NAC. Median age of patients was 45 years (25-64 years). 14% of the patients had positive family history of cancer. Majority of the patients (68%) were pre-menopausal. 90 patients (57%) had grade II disease, while 64 patients (41%) had grade III disease, while grade-I were 2 patients only (1.3%) T2 was the commonest size encountered (90%). Mean size of tumor before NAC therapy was 34.57±10.63mm and after NAC therapy it was 12.03±12.679mm. SLNB was performed at diagnosis before starting NAC in radiologically negative axilla or in those who were negative on FNA. 87 (56%) patients underwent SLNB (out of which 34 were positive), 69 patients were positive on FNA (44%) Therefore, at presentation lymph nodes were positive in 102 patients (66%) and all underwent axillary clearance after completion of chemotherapy. At axillary clearance, 56 patients out of 102 showed complete axillary response. 105 patients (67%) underwent breast conservation surgery (BCS), rest underwent mastectomy. Estrogen receptors was positive in 81% of patients, while progesterone receptors was positive in 56% of patients. 21% of the patients were positive for Her 2 Neu receptor. Triple negative subgroup was observed in only 11% of the patients. 34% of patients had recurrence either local or distant. 22% of patient died within five year after completion of treatment. Median disease free survival

and median overall survival after surgery for breast cancer was 58±22 months and 60±19.2 months respectively.

Table 1: Predictive factors distribution in each group.

Variables	CR	R	PR	NR	TOTAL	P-VALUE
Grade of tumor						**0.014**
1	0	2 (3%)	0	0	2 (1.2%)	
2	14 (35%)	38(65.5%)	25(67.7%)	13 (62%)	90 (57%)	
3	26 (65%)	18 (31%)	12 (32%)	8 (38%)	64 (41%)	
ER status						**0.002**
Negative	14(35%)	4 (7%)	5 (13.5%)	6 (29%)	29 (19%)	
Positive	26 (65%)	54 (93%)	32(86.5%)	15 (71%)	127 (81%)	
PR status						**0.002**
Negative	28 (70%)	20(43.5%)	12 (32%)	9 (43%)	69 (44%)	
Positive	12 (30%)	38(65.5%)	25(68%)	12(57%)	87 (56%)	
H2N						**0.524**
Negative	27(67.5%)	46 (79%)	29 (78%)	16 (76%)	118 (76%)	
Positive	11(27.5%)	9 (15%)	8 (21%)	5 (23%)	33 (21%) (Rest- H2N not done)	
Triple negative						**0.348**
Yes	7 (17.5%)	4 (7%)	3 (8%)	3 (14%)	17(11%)	
No	33(82.5%)	54 (93%)	34 (92%)	18(86%)	139 (89%)	
Age						**0.126**
≤ 35 years	6(15%)	13(22.4%)	2(5.4%)	2(9.5%)	23(14.7%)	
36-50 years	22(55%)	33(56.9%)	21(56.8%)	9(42.9%)	85(54.5%)	
≥ 51 years	12(30%)	12(20.7%)	14(37.8%)	10(47.6%)	48(30.8%)	
Family history						**0.478**
Yes	8 (20%)	7 (12%)	3 (8%)	3 (14%)	21 (14%)	
of cancer						
No	32 (80%)	51 (88%)	43 (92%)	18(86%)	135(86%)	
Menopausal						**0.251**
Yes	12 (30%)	14 (24%)	15 (40%)	9 (43%)	50 (32%)	
Status						
No	28 (70%)	44 (76%)	22 (60%)	12 (57%)	106 (68%)	
T stage						**0.674**
T1	3 (7.5%)	3 (5%)	0	2 (9.5%)	8 (5%)	
(At Presentation)						
T2	39 (90%)	52 (90%)	34 (92%)	19(90.5%)	144 (90%)	
T3	0	2 (3%)	2(5%)	0	4 (2.6%)	
T4	1(2.5%)	1 (1.7%)	1(2.7%)	0	3 (1.9%)	
LN Status						**0.711**
Negative	12 (30%)	18 (31%)	15(40.5%)	8 (38%)	53 (34%)	
(At presentation)						
Positive	28 (70%)	40 (69%)	22(59.5%)	13 (62%)	103 (66%)	

After NAC, 40 patients (25%) showed CR. 58 patients (37%) were in R, 37 patients (23%) showed PR, 21 patients (13%) showed no response (NR) at all. As the groups were categorized only on tumor response i.e. T stage after chemotherapy, so LNs response was not taken in account. In complete responders' 36 patients (out of 40) showed complete pathological response (T0N0), (12 were negative at diagnosis on SLNB). Out of all variables, only Grade of tumor, progesterone receptors (PR) showed relationship with the chemo response with significant P- values. ER negative tumors were comparatively more in CR group (Table 1).

Grade III tumors distribution was highest in complete responder group (40%- percentage within Grade III), which was not observed in rest of the groups. Similarly, PR negative distribution was highest in complete responder group (41%), but not seen in rest of the groups. Estrogen positivity was 81% in whole group, so it showed higher distribution in each group; however, among the 19% ER- tumors most were in CR group (48%). Her 2- Neu positivity was only 21% in whole group so its distribution was also not significant, also Herceptin / Targeted therapies were not used in 2012 in our set-up, so it can not truly represent any relationship with chemo response. Similarly, Triple Negative tumors were only 11 %, so its distribution among subgroups also was not significant. Menopausal status, multicentricity and family history and parity were also not related to chemo response. Majority i.e. 90% of tumors were stage-II, so its impact on chemo response was not significant. 66% of patients were LN positive and showed similar distribution in all sub-groups. Only 14 patients had multi centric tumors.

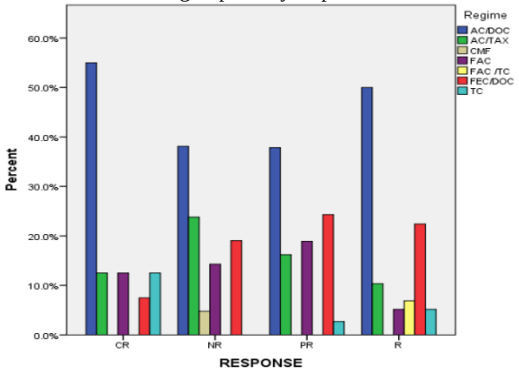

Figure 1: Different Chemo regimens distribution in each group; AC/DOC: Doxorubicin (Adriamycin), Cyclophosphamide, TAX: Taxol, CMF: Cyclophosphamide Methotrexate Fluorouracil, FAC: Fluorouracil Adriamycin Cyclophosphamide, TC: docetaxel (Taxotere) Cyclophosphamide, FEC: Fluorouracil (5-FU) Epirubicin Cyclophosphamide, DOC: Docetaxel.

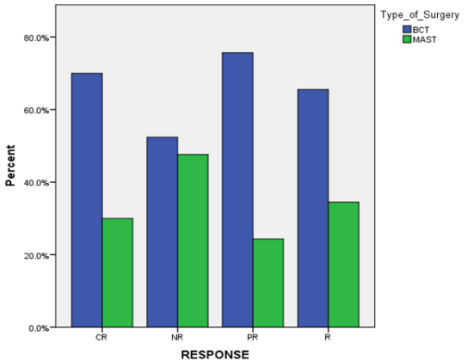

Figure 2: Distribution of Mastectomy vs BCS in each response group.

The Chemotherapy regimens were also studied. Most common regimen used was AC/DOC (in 46% of total), rest were used less frequently (AC/TAX, FAC, FAC/TC, TC, FEC/DOC). The distribution of various chemotherapy regimens among all four groups was not significantly different. Only one patient received CMF and did not respond (NR group) (Figure 1). Out of total 156, 105 patients underwent Breast Conserving Surgery (BCS) and 51 patients underwent Mastectomy. Non-responder group showed relatively higher rate of Mastectomy compared to rest of groups (Figure 2).

I Impact of Response of Survival (DFS & Overall Survival)

Prognosis was taken from date of end of active treatment (completion of either radiotherapy or Surgery). Five year OVS for whole study group was 78%, while DFS was 70%. While 80 months OVS was 75% and DFS was 52%. Two of the deaths were due to acute myeloid leukemia (within 2 years of primary diagnosis), and 2 died of worsening medical condition (one heart failure and one liver cirrhosis). Impact of chemo response on prognosis was very evident. The best survival was shown by complete responder group with 86% overall survival and 80% DFS (Table 2). The survival functioned declined proportionately according to decreasing response, the non-responder group showed least percentages as clearly shown in survival curves in (Figures 3 & 4). The highest recurrences were observed in Non-responder group (62%) and lowest in complete responder group (25%). Similarly, mortality was least in CR group and highest in NR group (Table5). The commonest recurrence in all groups was distant (Tables 3 & 4).

Table 2: Survival in each group.

Response	Overall survival	Disease free survival
CR (100% response)	**86%**	**80%**
R (>50% response)	**84%**	**70%**
PR (<50% response)	**78%**	**73%**
NR (No response at all)	**45%**	**40%**

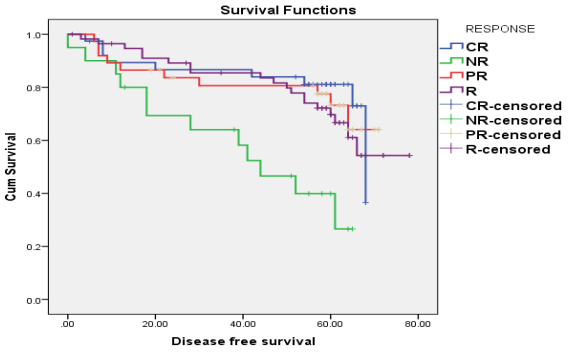

Figure 3: Disease Free Survival (For each group).

Table 3: Recurrence.

	CR	R	PR	NR	Total
Yes	25%	34%	27%	62%	34%
No	75%	66%	73%	38%	66%

Table 4: Type of recurrence.

	CR	R	PR	NR	Total
AML	0	0	1	1	2
Distant	6	14	5	8	33
Local	0	3	3	2	7
Distant + Local	2	1	1	2	7
Local + Contralateral	0	0	1	0	1
Contralateral	2	2	0	1	5
Total	10 (25%)	20 (34%)	11 (AML excluded) (30%)	13(AML excluded) (61%)	53 (AML excluded) (34%)

Table 5: Alive and Dead status.

	CR	R	PR	NR	Total
DEAD	5 (12.5%)	10 (17%)	8 (22%)	11 (52%)	34 (22%)
ALIVE	35(87.5%)	48 (83%)	29 (78%)	10 (48%)	122 (78%)

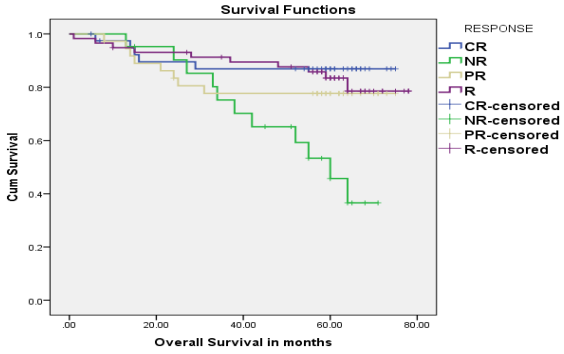

Figure 4: Overall Survival (For each group).

Discussion

This retrospective study studied few clinical and pathological factors that may act as predictive factors in determining response to NAC in breast cancer and then the impact of chemo response on survival. Researchers are trying to find a way by which chemo-response can be predicted before subjecting the patient to this potentially hazardous treatment mode. So, chemotherapy might be omitted in a subset of patients who may not respond well to chemotherapy, thus not delaying onset of other mode of treatment. The goal of chemotherapy in neo-adjuvant settings is to shrink the size of tumor and lymph nodes and if any micro metastasis. It would be a big breakthrough in the field of science if we know before starting chemotherapy that who will achieve this goal and who will not. Younger age and lesser BMI were shown to have better chemo response [9]. Among the pathological factors grade of tumor, receptor status, HER 2 neu expression, proliferation index (Ki-67), P53 mutation and other rarer genes are extensively studied in the past. Some patients despite having good predictive factors, show resistance to chemotherapy or have early recurrences, suggesting there might be certain cellular characteristics at the molecular level [10].

In one study, triple negative and HER 2 Neu (H2N) enriched tumor types are more likely to achieve pCR [11]. However, those who did not achieve pCR, the survival was the worst for H2N enriched type and triple negative compared to survival in hormone receptors positive tumor [12]. In other similar study, achieving pCR in triple negative breast cancer was associated with better disease free survival ($P < 0.001$) compared to luminal A type/ER positive ($P= 0.39$) [13]. Another study reported none of the factors was a predictive of response to NAC [14]. Ki-67 proliferation index is believed to be one very important predictive marker for better chemo response especially in ER negative and H2N positive tumors [15, 16].

In this study the degree of response was graded in 4 groups, however in most of the studies done previously, only pCR was studied in relation with predictive factors. Response meant tumor size reduction only, lymph node response was separately studied but it was not the main focus of study. The four grades were the complete responders and non-responders with 2 groups of variable responses in between (< and > 50% response). The distribution of each factor was observed across the 4 grades. None of the clinical factors like age, menopausal status, family history and parity showed any effect. BMI was not evaluated in this study. Among the pathological factors Ki-67 was not studied because in 2012 it was not routinely done in each patient. Another problem was lack of fluorescence in suit hybridization (FISH) testing for 2+ score on immunohistochemistry, due to which status of 12 patients could not be clear, subsequently, population of H2N+ tumor was low in study population (8 only). Five out of 8 H2N positive patients showed complete response. Another limitation with H2N was the use of targeted therapies, which was then used on 2 patients only. Currently, it is used on almost all H2N+ tumors in our setup. In one similar study H2N status was not linked to chemo-sensitivity [17].

In our study population, ER and PR positivity was high (81% ER+, 56% PR+). So, ER positive tumors was almost evenly distributed in all response groups, however ER- tumor were more clustered in complete responder group (14 out of 29 patients). In complete responder group 70% of patients were PR- tumors showing PR negativity may be favorable predictive factor towards chemo response (0.002). Grade III tumors showed more complete response ($P=0.014$) compared to grade II. Large majority, i.e. 92% of our population was T- II tumors (T1 are less frequent presentation in this part of world and T3 tumors usually does not fulfill hospital acceptance criteria), so T size also showed not impact on chemo response. 64% of study population was lymph node positive at presentation and showed no propensity towards better or worst response ($P= 0.711$). Although, a pCR does not mean a definitive cure, however it can predict a more favorable outcome with reduced relapse rates [18]. Patients with residual disease have significantly lesser survival especially in triple negative disease [19]. In one study, the 5-

year survival for patients achieving complete pathologic response was 96% compared with 75% in those with partial response [13].

In our study, 61% of the patients' responded partially after neo-adjuvant chemotherapy, 13.5 did not respond at all. 25.5% of patients had no residual tumor (T0) out of which pCR was shown in 22% of patients (pT0N0). Survival for each response group was measured separately; the worst survival was shown by non-responder group (OS 45%, DFS 40%). In rest of three groups, if survival is compared, it fell proportionately as the response decreased (0S= 86%CR, 84%R, 78%PR). The survival in complete responder group (which had 36 T0N0 out of 40) was not as good as in other published studies, perhaps because only 5% patients had T1 disease at presentation, almost all the rest were T2 disease, and because 28 patients out of 40 were LN+ at diagnosis [19].

Most common type of recurrence in the whole cohort as well as in each response group was distant (41 out of 53 patients) implying breast cancer is either a systemic disease or because NAC induces changes in microenvironment that may cause distant metastasis [20]. Rest (12 out of 53 patients) were local or contralateral only. Two patients developed acute myeloid leukemia within 2 years of completion of treatment. In Summary, the more a tumor responds to chemotherapy the better is survival. However, the goal should be to predict the response before starting chemotherapy. In this study, only PR + and Grade III tumors had better chemo response. More work is needed on molecular and genetic level to better understand variability of chemo-response.

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