Clinicopathologic predictors of pathologic complete response after neoadjuvant systemic therapy and impact on surgical management

Abstract

Neoadjuvant systemic therapy previously given for inoperable breast cancer is increasingly being administered in early breast cancer especially in triple negative and HER2 positive molecular subtypes. It is associated with an increased rate of complete pathologic response (PCR) which is a surrogate marker for good survival outcomes and has role in de escalation of surgical management. We conduct this study to identify clinical and pathologic factors and systemic treatment regimens that predict PCR among Pakistan's breast cancer patients and its impact on surgical management.

Materials and methods

Patients with clinical stage I-III who received Neoadjuvant systemic therapy (NST) and underwent surgical intervention at Liaquat national hospital were included. The clinicopathologic factors included age, menopausal status, clinical tumor size, nodal status, stage, pathologic type, grade, molecular subtype, PR status, pathologic response, and treatment in terms of systemic therapy. The surgery underwent and pathologic stage(ypTN) were recorded. The association between these factors and PCR was analyzed with the chi-square test. Univariate analysis was performed to evaluate the influence of clinicopathologic factors on PCR.

Results

PCR was achieved in 174(19.6%) out of the 889 patients. There was a significant association (P-value <0.001) with molecular subtype as follows PCR percentage for HER 2 enriched-39% and luminal B HER 2 positive-31%, triple negative-25% ,Luminal A-6.5% and Luminal B-9.6%, progesterone receptors negative tumors (PCR-26.9%) and chemotherapy regime-Anthracycline and taxane PCR-28%. The predictive value of the three factors remains significant on univariate analysis. The breast conservative surgery rate was 34%, sentinel node biopsy was 60% and axillary PCR is seen in 20% of the patients (cN+ 60% to ypN+ 40%).

Conclusion

NST has a good overall impact in terms of achieving PCR and downsizing for breast-conserving surgery with better cosmetic outcome and de-escalation of axillary surgery. The positive predictive factors include molecular subtype, Her2 positive tumors being the most sensitive, progesterone receptor-negative tumors, and anthracycline and taxane-based chemotherapy.

Keywords: Pathologic complete response, Molecular subtype, progesterone receptor status, predictive factors

Introduction

Neoadjuvant chemotherapy was introduced in the 1970s (1) for inoperable, locally advanced cases to downsize (2). However, further studies showed its benefit in eradicating micro metastasis not detectable at time of presentation(3) and acheiving pathological complete response (PCR). These findings led to its use in early breast cancer especially in triple-negative and HER2 enriched molecular subtypes(4).

The interest in detecting pathological response to neoadjuvant chemotherapy has rapidly grown as it provides information about the chemosensitivity of the tumor which can be implied to the recurrent or disseminated disease, help in subsequent chemotherapy selection, and is also a marker of overall survival (5). This has also lead to an ongoing debate on whether surgery can be omitted if PCR has been identified on imaging and pathologic assessment with core biopsy (6). The results of a meta-analysis investigating the prognostic impact of PCR showed that it is associated with improved outcomes, reduced disease recurrence (HR 0.31, 95% PI: 0.24-0.39), and overall survival (HR 0.22, 95% PI: 0.15-0.30), most significantly in triple-negative breast cancer (7). Many studies have been carried out to find the patient and tumor characteristics that achieve the PCR and identified positive relation with hormone receptor, Her 2 neu status, pathology type, grade of tumor and lympho-vascular invasion. Zhu et al. investigated these factors in triple-negative breast cancer (8) and absence of hormone receptors expression was found to be an independent predictor of PCR while high histological grade, low Ki-67 index, and incomplete NAC were independent predictors of disease progression. Disease-free survival and overall survival are reported to be significantly worse in presence of residual disease(RD) - 15.7, 21.3 vs. 52.4, 56.3 months (9).

Although many studies have investigated the predictive factors for PCR in breast cancer, such studies have not been carried on large scale in Pakistan. The knowledge of pathological and clinical predictive factors can guide personalized treatment regimes that will improve pathological response and downstaging. It can increase breast-conserving surgery rates, de-escalate axillary surgery, and improve long-term outcomes (10). The racial disparity has been reported in many previous studies, but whether these differences are due to the difference in clinicopathologic factors or molecular subtypes or related to poor socioeconomic status, incomplete NAC regimen and non-availability of dual anti HER2neu therapy is unclear. A US study reported Black women to have fewer PCR rates for triple-negative and HER2-positive breast cancer subtypes. It was reported that these patients have low income and lack of medical insurance leading to nonavailability of NST that might explain the lower PCR rather than biologic features (11). We did this retrospective review to identify the impact of NST on the pathologic response and surgical management. We also reviewed the factors predictive of PCR in Pakistan's and how they differ from other regions of the world.

Materials and methods

The study is conducted at the breast surgery clinic, Liaquat national hospital (LNH), and data was collected from the record of the patient's files from January 2016 till June 2021. All breast cancer patients with stage I-III (American Joint Committee on Cancer,

AJCC classification cT1-4, N0-3, M0) that received NST in the form of chemotherapy or combined chemotherapy and anti HER2 targeted therapy at our institute or outside(patient having complete record available in form of CHT regime card or medical report from oncologist) and underwent surgical intervention at LNH were included in the study. The clinical features recorded for the analysis included age, menopausal status (defined as the absence of menstrual cycle more than a year, history of oophorectomy), clinical tumor size T1-4 (T1 <2cm, T2 2-5cm, T3 >5cm, and T4 involvement of skin-A, pectoralis muscles-B or both-C, inflammatory-D), nodal status N0-3 assessed on clinical exam and ultrasound with or without cytology or histopathology (N0 no palpable ipsilateral axillary nodes, N1 palpable but moveable ipsilateral axillary nodes, N2 palpable fixed matted ipsilateral axillary nodes or enlarged internal mammary lymph nodes, N3 supraclavicular palpable nodes with above) and clinical stage as per the TNM classification of NCCN version 6.2020. The pathologic factors included tumor type, grade, molecular subtype (*Luminal A*-ER/PR positive/HER2 NEU negative /KI67 <16%, *Luminal B*-ER/PR positive/HER2 NEU negative/KI67 >16%, *luminal B*- ER/PR positive/HER2 NEU P*ositive, Triple negative*-ER/PR negative/HER2 NEU negative, *HER2 enriched*-ER/PR negative/HER2 NEU positive*),* proliferative index Ki 67%. The systemic treatment is given included chemotherapy regimens i.e., anthracycline with taxanes (ACT) versus others such as Taxotere and cyclophosphamide (TC), taxanes(T) alone, and epirubicin and taxanes (EC) and the anti-HER 2 neu therapy whether trastuzumab alone or dual in combination with pertuzumab. The other findings recorded include surgical intervention in terms of mastectomy versus breast-conserving surgery and axillary clearance versus sentinel lymph node biopsy alone and the pathologic tumor size (yPT similar to cT) and nodal status (yPN0 no nodal metastasis, N1 1-3 nodes with metastasis, N2 4-9 nodes and N3 more than 10 nodes). The pathologic response was recorded as PCR and non-PCR and pathological complete response defined as no residual invasive disease in the breast and axillary lymph nodes-yPT0, N0.

SPSS 22 version (SPSS Inc., Chicago, IL) is used to perform the analysis. Mean is calculated for the age and Ki67% and frequency and the percentage calculated for the rest of the categorical variables and also for the age groups (<35years and >35 years) and Ki67% (<10% and >10%). The association of baseline characteristics with the pathological response (PCR/non-PCR) was analyzed using the chi-square test (and Fischer test when required). Binary logistic regression analysis is performed for all predictive factors to evaluate the influence on the PCR. Factors achieving $p<0.05$ were considered statistically significant

Results

The study population included 889 patients and the demographic and clinical characteristics of the study population are given in table 1. The mean age at the time of diagnosis was 46.9 years (22 -78 years) and 12.7% were less than 35 years of age. Postmenopausal patients were slightly higher in number than the premenopausal

(48.7% vs 51.3). Invasive ductal carcinoma was the most predominant pathological type 96.4%, rest 3.6% included lobular (1.9%) and metaplastic (1.1%) etc., and grade 2 was the most common (52.2%). Tumor size at presentation was T2 in 37.4% of the patients followed by T4 (33%) and node positivity (N1-3) was documented in 60% and the majority had stage III (51.7%). The molecular subtypes were as follows Luminal A 14.2%, luminal B 34.9%, triple-negative 25%, HER2 enriched 11.8%, and luminal B HER2 positive 14.1%. Mean Ki 67% proliferative index was 37.3 and 84.7% had a high proliferative index (10%). As for the treatment modality, 84% of the patient received anthracycline and taxane. In the HER2 positive subtype (HER2 enriched and Luminal B) patients, 40% received trastuzumab and 11.6% received dual anti-HER2 therapy 48% of patients didn't receive any targeted therapy due to financial restrains. The surgical procedure post systemic therapy was mastectomy in 65% and axillary clearance for 40% while breast conservation was done for 34% and only sentinel node biopsy among 60% (ypN0-60%). The most common tumor size after surgery is reported yPT2 in 41%. PCR to systemic therapy is reported in 174(19.6%). Association was analyzed between the pathological response and the clinical and pathological factors using the chi-square test. Among the statistically significant associations($p<0.001$) , PCR was highest among the HER2 positive group (Estrogen receptor-negative 39.2% and Her2-positive luminal B 31.1%) and triple-negative (25%) and lowest rate of PCR seen among the luminal A (6.5%) and luminal B (9.6%). Secondly ($p<0.001$), progesterone receptor (PR) negative tumors showed 26.9% PCR which is higher than the PR positive group. The last significant association (p0.02) was with chemotherapy regime and complete response being highest among the anthracycline and taxane group (28%) as shown in table 2. The PCR for the rest of the subgroups was higher among postmenopausal 21%, invasive ductal carcinoma 19.7%, clinical stage I 31.3%, node-negative N0-21.6%, grade 3 tumors 22.8%, ki 67% above 10%, and the patient who received dual anti-HER 2 therapy 73%, however, these results were not statistically significant. The PCR was equal for both age groups and clinical tumor size.

In the univariate analysis (table 3), molecular subtype luminal A and B showed less likelihood of PCR as compared to the HER2 enriched tumors (Odds ratio-OR 0.154 and 0.235, p-value <0.001). The progesterone receptors (PR) positive tumors are less likely to show PCR as compared to PR negative tumors (OR 0.335 p-value <0.001). Patients who received anthracycline and taxanes had more chances of PCR than other chemotherapy regimens (OR 1.873 p-value 0.02). Clinical tumor size T1, T2, node-negative, and clinical-stage I had better chances of PCR than T3 and T4, node-positive, and higher clinical stages but these associations are not clinically significant.

Discussion

The outcome of this study showed that in breast cancer patients after receiving neoadjuvant systemic therapy a rate of pathological complete response was 19.6% that is comparable to PCR rates documented in international studies of 24% (12). However, the PCR rate reported in another study from Pakistan on smaller patient number reported a PCR rate of 7% and 3 % which was attributed to the high clinical stage at presentation and incomplete chemotherapy (13) (14). In our results, we found that

patients who recieved a complete chemotherapy regime and anti HER2 therapy had comparable PCR to international studies. The response can be even higher as 48% of the HER2 positive tumors did not receive anti HER 2 targeted therapy along with chemotherapy due to financial issues.

The PCR in axillary nodes (ypN0-60%) was higher than the overall complete pathologic response, the clinically positive nodes were cN+ 60% at the time of presentation and were downstaged to ypN+ 40% on surgical pathology. In a study to find a correlation of breast PCR and axillary node PCR found the conversion of 45% of cN1 disease to ypN0(12). In our results, the higher node negativity at the time of the surgical intervention resulted in de-escalation of axillary surgery to sentinel node biopsy in 60% of the patients. So, systemic therapy resulted in axillary downstaging in 20% of the patients and was able to forgo axillary clearance and avoid the associated morbidity and potential for lymphedema.

We observed a significant association of PCR with the molecular subtypes and was high for the triple-negative subtype and HER 2 positive subtype as was also observed in the results of the meta-analysis by Laura M Spring et al PCR of 32.6% for triple-negative and 36% for HER2 positive tumors (15). The luminal subtypes showed the least percentage for pathologic complete response. Hence, we can say that estrogen receptor-negative tumors and HER2 positive tumors have positive correlation with the pathologic response while estrogen-positive receptors show a poor response to chemotherapy. A meta-analysis result shows a similar response to NAS, the results showed PCR of 8.3% in HR+/HER2– 18.7% in HER2+/HR+ (OR 2.6), 38.9% in HER2+/HR– (OR 7.1), and 31.1% in triple-negative (OR 5.0) (16). Another study found a higher probability of PCR in ER-negative, LVI-negative tumors and patients treated with taxane based chemotherapy (17). Assessment of almost 14,000 women from a United States database to examine the relationship between response to NAC and molecular subtype showed luminal A disease is the least likely to have PCR and the highest PCR seen in Her2 disease (18).

The second significant relation is found with negative progesterone receptor achieving higher PCR. In previous studies, PR has been shown to have prognostic implications independent of ER receptors. The patient who had absent PR expression had increased rates of PCR and had better survival outcomes however who had incomplete response was poor survival outcomes and disease-free survival (19).

Chemotherapy regimens that included anthracycline and taxanes showed a higher percentage of pathologic complete response as compared to other regimes. A Turkish study reported higher PCR rates with dose-dense anthracycline followed by 12 cycles of paclitaxel and triple-negative patients were the most chemo sensitive subtype which correlates with our data (20).

It was observed that patients who had early breast cancer i.e., stage I and node-negative disease at presentation had better chances of achieving PCR as compared to

presentation with tumor size above 5cm and node-positive disease but was not statistically significant. None of the patients presenting with N3 disease achieved PCR, so PCR is negatively associated with the high tumor load. A study investigating the possibility of de-escalation of axillary surgery in patient achieving breast PCR showed pathologic responses had significant positive association with ypN0 disease. Patients with cN1 disease at presentation were 80% less likely to have ypN0 disease, with odds ratios (OR) ranging from 0.16 to 0.18 (P <0.0001) (21)

Although pathologic high grade and high Ki67% are poor prognostic markers but have shown a positive association with PCR similar to results of our study but did not reach statistical significance. (22, 23)

Downsizing of tumor size was observed in the majority of the cases. The patients in this study had a advanced clinical stage at presentation (T3 and T4 were 57%). The pathologic size at the time of surgery documented breast PCR in 20.8% and T1,2 and 3 in 23, 41, and 15% cases. The breast-conserving surgery rate was 34% and this would not have been possible if the patients underwent upfront surgery considering the clinical tumor size T3 and T4(57%).

The impact of neoadjuvant therapy in achieving PCR and downstaging of the disease is observed in our data. The predictive factors proved in our study are similar to the international data that is the molecular subtypes, progesterone receptor, and neoadjuvant chemotherapy regime. This impact was not observed in previous studies done in Pakistan due to lack of chemotherapy data and uniformity of regime and also the patient number in this study is very large as compared to these studies. We intend to do follow up of the patients who achieved PCR for 5 years to also investigate the prognostic impact of the PCR for locoregional and distant recurrence and survival.

Conclusion

Neoadjuvant chemotherapy has a good overall impact in terms of achieving PCR and downstaging making breast-conserving surgery and de-escalation of axillary surgery possible. The positive predictive factors include molecular subtype, HER2 enriched tumors being the most sensitive, progesterone receptor-negative, and anthracycline and taxane-based chemotherapy.

Ethical considerations:

All patient's confidentiality was maintained and Approval from the Hospital research and ethical committee was taken.

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

Tables

Table 1: Characteristics of population

Characteristics	Frequency(Percentage)
Age	
≤35 years	113(12.7)
>35 years	776(87.3)
Menstrual status	
Pre-menopausal	433(48.7)
Post-menopausal	456(51.3)
Pathologic type	
IDC	857(96.4)
Non-IDC	32(3.6)
Tumor size(T)	
T1	47(5.5)
T2	317(37.4)
T3	200(23.6)
T4	283(33.4)
Nodal status(N)	
N0	334(39.4)
N1	422(49.8)
N2	83(9.8)
N3	8(0.9)
Clinical stage	
I	32(3.8)
II	377(44.5)
III	438(51.7)
Grade(G)	
I	162(18.2)
II	464(52.2)
III	263(29.6)
Molecular subtype	
Luminal A	123(14.2)
Luminal B	302(34.9)
Triple negative	216(25)
Her2neu positive	102(11.8)
Luminal B(HER2+)	122(14.1)
Ki67%	
<10	136(15.3)
>10	753(84.7)
Chemotherapy regime	
Anthrcycline+taxanes	751(84.1)
Taxanes	75(8.4)
EC	63(7.1)
Anti Her2 Targeted Therapy	
Transtuzumab	91(40.6)
T+Pertuzumab	26(11.6)
No therapy	107(48)
Breast Surgery	

Breast Conservation	298(33.5)
Mastectomy	591(66.5)
Axilla Surgery	
Sentinel Node Biopsy	530(59.6)
Axillary Clearance	359(40.4)
Pathologic Tumor Size(yPT)	
0	185(20.8)
1	202(22.7)
2	365(41.1)
3	137(15.4)
Pathologic Node Status(yPN)	
0	536(60.3)
1	160(18)
2	116(13)
3	77(8.7)

Table 2: Association between clinicopathologic factors and PCR

CHARACTERISTICS	PCR (%)	NO PCR (%)	P VALUE
AGE			0.976
<35 YEARS	19.5	80.5	
>35 YEARS	19.6	80.4	
MENSTRUAL STATUS			0.254
PRE	18	82	
POST	21.1	78.9	
PATHOLOGIC TYPE			0.566
IDC	19.7	80.3	
NON-IDC	15.6	84.4	
TUMOR SIZE			0.460
T1, T2	20.9	79.1	
T3, T4	18.8	81.2	
CLINICAL NODE STATUS			0.277
N0	21.6	78.4	
N+	18.5	82	
CLINICAL STAGE			0.246
I	31.3	68.8	
II	19.1	80.9	
III	19.4	80.6	
GRADE			0.244
I	19.8	80.2	
II	17.7	82.3	
III	22.8	77.2	
MOLECULAR SUBTYPE			**<0.001**

LUMINAL A	6.5	93.5	
LUMINAL B	9.6	90.4	
TRIPPLE NEG	25	75	
HER 2 NEU POSITIVE	39.2%	60.8	
Luminal B(HER2+)	31.1%	68.9	
PROGESTERONE RECEPTOR			**<0.001**
POSITIVE	11.1	88.9	
NEGATIVE	26.9	73.1	
KI 67%			0.539
<10%	17.6	82.4	
>10%	19.9	80.1	
CHEMOTHERAPY REGIME			**0.02**
ACT	28	74	
OTHERS	16	84	
ANT HER2NEU TARGETED THERAPY			0.41
TRASTUZUMAB	39	61	
T+PERTUZUMAB	73	27	

Table 3: Univariate logistic regression model

PARAMETERS	RISK/REFRENCE	ODDS RATIO	CONFIDENCE INTERVAL 95%	P VALUE
AGE	<35/>35	0.992	0.603-1.633	.976
MENSTRUAL STATUS	Pre/post	0.824	0.591-1.149	0.254
PATHOLOGIC TYPE	IDC/non-IDC	1.326	0.503-3.945	0.568
TUMOR SIZE	T1, T2/T3, T4	1.137	0.809-1.598	0.461
NODAL STATUS	N0/N+	1.209	0.858-1.704	0.278
CLINICAL STAGE	I, II/III	1.888	0.862-4.135	0.112
		0.980	0.691-1.390	2.552
GRADE	I, II/III	0.833	0.514-1.349	0.457
		0.726	0.500-1.056	0.094
MOLECULAR SUBTYPE	Luminal A,	0.154	0.697-0.347	**<0.001**
	luminal B, triple	0.235	0.137-0.404	**<0.001**
	negative,	0.737	0.451-1.205	0.223
	Her2neu positive/ LUMINAL B(HER2+)	1.426	0.821-2.477	0.208
PROGESTERONE	Positive/negative	0.339	0.234-0.493	**<0.001**

RECEPTOR CHEMOTHERAPY REGIMEN	ACT/others	1.873	1.096-3.283	**0.02**

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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