DOI: 10.7860/JCDR/2022/52512.15919

Original Article

Oncology Section

Evaluation of Clinical and Pathological Response in Breast Cancer Following Neoadjuvant Chemotherapy- A Single Institution Experience

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ABSTRACT

Introduction: In locally advanced breast cancer, Neoadjuvant Chemotherapy (NACT) is the mainstay of treatment. NACT is also considered as a potentially helpful treatment option in early-stage HER2 positive and triple-negative breast cancer.

Aim: To assess pathological Complete Response (pCR) in patients with breast cancer who received NACT and to evaluate the association with clinical and pathological factors.

Materials and Methods: The present retrospective analysis was conducted at Breast Oncology Division of Regional Cancer Centre, Thiruvananthapuram, Kerala, India, from January 2013 to December 2015. The data of patients with invasive breast cancer who received NACT were retrieved from medical records and analysed in August 2021. In the surgical pathology specimens, pCR was defined as ypT0 ypN0: no residual invasive cancer and/or in-situ cancer in the breast or axillary lymph nodes. All factors identified with univariate analyses were entered into multivariate analysis, and statistical analysis was done using logistic regression. The p-value <0.05 was considered significant.

Results: This study included 586 breast cancer patients who received NACT, with mean age of 50.7 years. The proportion of postmenopausal patients was higher than premenopausal patients (56.3% vs 43.7%). Overall, 21.3% patients (125/586) attained pCR (ypT0 ypN0). In univariate analysis, factors associated with pCR were higher histologic grade (grade III) of tumour {Odds Ratio (OR): 2.879, 95% Confidence Interval (CI): 1.615-5.129, p-value=0.001)}, lower composite clinical stage (OR: 2.236, 95% CI: 1.468-3.408, p-value=0.001), lack of Oestrogen Receptor (ER) expression (OR: 3.23,95% CI: 2.10-4.968, p-value=0.001) and lack of Progesterone Receptor (PR) expression (OR: 4.396, 95% CI: 2.714-7.121, p-value=0.001). Higher grade of tumour (OR: 2.211, 95% CI: 1.179-4.146, p-value=0.013), lower composite clinical stage (OR: 2.033, 95% CI: 1.262-3.276, p-value=0.004) and lack of PR expression (OR: 3.823, 95% CI: 2.301-6.350, p-value=0.001) remained predictive variables in multivariate analysis after correction for the other variables.

Conclusion: The lower composite clinical stage, lack of Progesterone Receptor (PR) expression and higher histologic grade of tumour are associated with good response to NACT in breast cancer patients.

Keywords: Lymphovascular invasion, Oestrogen receptor, Pathological complete response, Progesterone receptor, Tumour grade

INTRODUCTION

Neoadjuvant Chemotherapy (NACT) is the systemic treatment given prior to definitive surgical procedure [1]. In the treatment of breast cancer, NACT was introduced with the aim to downstage locally advanced or inflammatory (inoperable) disease and make it operable [2,3]. Because of the benefits such as higher rates of breast conserving surgery and the possibility to monitor early in-vivo response to systemic therapy, NACT is becoming more widely used in operable breast cancer [1,2].

The clinical response of the primary tumour to NACT can range from a minimal response to pathological Complete Response (pCR) [1]. The definition of pCR varies across studies [4]. Absence of invasive cancer and in-situ cancer in the breast and axillary nodes-ypT0 ypN0, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in-situ -ypT0/is ypN0 and absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement-ypT0/is are the three most commonly used definitions of pCR [4].

The aim of the present study was to assess pCR in patients with breast cancer who received NACT and to evaluate the association with clinical and pathological features i.e., age, clinical composite stage, tumour grade, Lymphovascular Invasion (LVI), Oestrogen Receptor (ER) and Progesterone Receptor (PR) expression status, Human Epidermal Growth Factor Receptor 2 (HER2) status, breast cancer subtype and the NACT received.

MATERIALS AND METHODS

The present retrospective analysis was conducted at Breast Oncology division of Regional Cancer Centre, Thiruvananthapuram, Kerala, India, from January 2013 to December 2015. After obtaining the approval of the Institutional Scientific Review Board (Approval No: 10/2017/07), the case files of these patients were retrieved from the hospital database and their details were documented in a structured proforma for analysis. Considering the retrospective nature of this study, patient consent was not obtained.

Inclusion criteria: Patients who received NACT prior to surgery for clinical stage II and stage III breast cancers were included in the study.

Exclusion criteria: Patients with metastatic disease at presentation, stage I disease, defaulting treatment during the planned chemotherapy or prior to surgery, patients receiving neoadjuvant endocrine therapy and male breast cancers were excluded from the study.

Chemotherapy regimens included:

1) Anthracycline-Taxane combination {AC (Doxorubicin and Cyclophosphamide)/EC (Epirubicin and Cyclophosphamide) for 4 cycles followed sequentially by Docetaxel×4 cycles/weekly Paclitaxel×12 cycles; FEC (5-Flurouracil, Epirubicin, Cyclophosphamide)/FAC

(5-Flurouracil, Doxorubicin, Cyclophosphamide) for 3 cycles followed sequentially by Docetaxel for 3 cycles; TAC (Docetaxel, Doxorubicin and Cyclophosphamide) for 6 cycles};

2) Taxane based protocols: {TC (Docetaxel and Cyclophosphamide) for 4-6 cycles};

3) Anthracycline based protocols {FAC(5- Flurouracil, Doxorubicin, Cyclophosphamide) for 6 cycles; FEC(5- Flurouracil, Epirubicin, Cyclophosphamide)×6 cycles}.

For patients with HER2 positive tumours, Trastuzumab was recommended in addition to chemotherapy and was given either as 1 year treatment (neoadjuvant and adjuvant) or as a shorter 9-week treatment protocol concomitantly with 3 cycles of Docetaxel followed by 3 cycles of FEC.

The following data was collected from the patient records: age, menopausal status, clinical tumour size, nodal status and composite clinical stage, histological type and grade of tumour, ER, PR status and Human Epidermal Growth Factor Receptor 2 (HER2) status, NACT regimen and pathological outcomes.

Age at diagnosis was stratified into <35 and ≥35 years. The diagnosis of invasive carcinoma was confirmed by core biopsy or excision biopsy. Histopathologic grading of the tumour was done in accordance with the Nottingham combined histologic grade (Elston-Ellis modification of the Scarff Bloom-Richardson grading system) [9-11].

The {Tumor (T), Node (N), Metastasis (M)} Staging Manual, 7th edition of the American Joint Committee on Cancer (AJCC) was used to define clinical staging; tumour size and nodal status were recorded by physical examination and/or radiological imaging prior to start of the treatment. The ER, PR and HER2 status was analysed by Immunohistochemistry (IHC) staining as per American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) histopathological consensus guidelines [12,13]. Tumours were termed as HER2 positive if they were 3+ by IHC or demonstrated gene amplification by in-situ hybridisation [13]. Lymphovascular space invasion (LVI) was evaluated in the peritumoural tissue on Haematoxylin and Eosin (H&E)-stained sections and was defined by the presence of cancer cells within a definite, endothelial-lined space (lymphatic and/or blood vessel) [14].

In the surgical pathology specimens, pCR was defined as ypT0ypN0: no residual invasive cancer and/or in-situ cancer in the breast or axillary lymph nodes [4].

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 11.0 software (SPSS, Inc., LEAD Technologies, Inc., USA) was used for all statistical analyses. Univariate analysis for estimating crude Odds Ratio (OR) was done using logistic regression analysis. pCR (ypT0 ypN0) with respect to age, composite clinical stage, tumour grade, LVI, ER, PR and HER2 status, breast cancer subtypes and chemotherapy protocol was studied. All factors identified with univariate analyses were entered into multivariate analysis, and statistical analysis was done using logistic regression. The p-value <0.05 was considered significant.

RESULTS

Of the total 5575 patients with histologically proven invasive carcinoma of breast during the study period (January 2013 to December 2015), 586 patients who received NACT for stage II and III disease were included in the analysis. Clinical and pathological characteristics of the patients are shown in [Table/Fig-1].The mean age of the patients in the study was 50.7 years (Range 23-70). The proportion of postmenopausal patients was higher than premenopausal patients (56.3% vs 43.7%).

Infiltrating ductal carcinoma was the predominant tumour type (98.6%), with lobular carcinoma accounting for only 1.0% of the

Variables	No. of patients n (%)
Age (in years)	
<35	32 (5.5)
≥35	554 (94.5)
Menopausal status	
Premenopausal	256 (43.7)
Postmenopausal	330 (56.3)
Clinical Tumour (T) stage	
T1	7 (1.2)
T2	149 (25.4)
T3	237 (40.4)
T4	190 (32.4)
Unknown	3 (0.5)
Clinical Nodal (N) stage	
N0	107 (18.3)
N1	293 (50)
N2	150 (25.6)
N3	35 (5.9)
Unknown	1 (0.2)
Composite clinical stage	
IIA	21 (3.6)
IIB	132 (22.5)
IIIA	224 (38.2)
IIIB	181 (30.9)
IIIC	26 (4.4)
Unknown	2 (0.3)
Histopathology	
Infiltrating ductal	578 (98.6)
Infiltrating lobular	6 (1)
Unknown	2 (0.3)
Grade of tumour	
I and II	147 (25.1)
III	426 (72.7)
Unknown	13 (2.2)
Lymphovascular Invasion (LVI)	
Present	64 (10.9)
Absent	522 (89.1)
Oestrogen Receptors (ER) status	
Negative	282 (48.1)
Positive	301 (51.4)
Unknown	3 (0.5)
Progesterone Receptor (PR) status	
Negative	320 (54.6)
Positive	263 (44.9)
Unknown	3 (0.5)
Human Epidermal Growth Factor Receptor 2 (HER2) status	
Negative	382 (65.2)
Equivocal (IHC score 2+, FISH not done)	31 (5.3)
Positive	170 (29)
Unknown	3 (0.5)
Composite receptor status/Breast cancer subtype	
ER-, PR-, HER2-	161 (27.5)
ER-, PR-, HER2 Equivocal	12 (2)
ER-, PR-, HER2+	98 (16.7)

ER+, PR+, HER2-	187 (31.9)
ER+, PR+, HER2 Equivocal	16 (2.7)
ER+, PR+, HER2+	49 (8.4)
ER/PR+, HER2+	23 (3.9)
ER/PR+, HER2-	34 (5.8)
ER/PR+/HER2 Equivocal	3 (0.5)
Unknown	3 (0.5)
Neoadjuvant chemotherapy	
Anthracycline based	99 (16.9)
Taxane based	7 (1.2)
Anthracyclie and Taxane combination	480 (81.9)

[Table/Fig-1]: Clinical and pathological characteristics of the patients (N=586).

tumours. The majority of patients presented with clinical stage IIIA (38.5%) and stage IIIB (30.8%) disease. Patients presenting with Grade III disease was found to be 72.7%. LVI was reported in 64 patients (10.9%). Most of the tumours were hormone receptor (ER and/or PR) positive (51.4%). HER2 over expression was detected in 170 patients (29.0%) by IHC score of 3+ or gene amplification {demonstrated by Fluorescent In-Situ Hybridisation (FISH) in patients with IHC score of 2+}. HER- 2 was negative (IHC score of 0 or 1+) in 382 patients (65.2%). Thirty one patients (5.3%) with an IHC score of 2+, who did not undergo further evaluation with FISH were termed 'equivocal' [Table/Fig-2].

Of the total 586 patients, 480 patients (81.9%) received regimens containing anthracycline and taxane combination, 99 patients (16.9%) received anthracycline based protocols and 7 patients (1.2%) received taxane based regime as NACT. Among 170 HER2 positive patients, only 55 of them (32.4%) received trastuzumab along with their chemotherapy protocol.

Overall, 21.3% patients (125/586) attained pCR (ypT0 ypN0) following NACT. [Table/Fig-2] summarises the characteristics of the patients who achieved pCR.

Variables	No. of patients n (%)
Age	
<35 years	7 (5.6)
≥35 years	118 (94.4)
Composite clinical stage	
IIA	9 (7.2)
IIB	40 (32)
IIIA	41 (32.8)
IIIB	29 (23.2)
IIIC	5 (4)
Unknown	1 (0.8)
Grade of tumour	
I and II	15 (12)
III	105 (84)
Unkown	5 (4)
Lymphovascular space invasion (LVI)	
Present	1(0.8)
Absent	124(99.2)
Oestrogen Receptors (ER) status	
Negative	86 (68.8)
Positive	36 (28.8)
Unknown	3 (2.4)
Progesterone Receptor (PR) status	
Negative	98 (78.4)
Positive	24 (19.2)
Unknown	3 (2.4)
Human Epidermal Growth Factor Receptor 2 (HER2) status	
Negative	75 (60)
Equivocal (IHC score 2+, FISH not done)	6 (4.8)
Positive	41(32.8)
Unknown	3 (2.4)
Composite receptorstatus/Breast cancer subtype	
ER-, PR-, HER2-	29 (23.2)
ER-, PR-, HER2 Equivocal	4 (3.2)
ER-, PR-, HER2+	21 (16.8)
ER+, PR+, HER2-	39 (31.2)
ER+, PR+, HER2 Equivocal	5 (4)
ER+, PR+, HER2+	12 (9.6)
ER/PR-, HER2+	4 (3.2)
ER/PR-, HER2-	8 (6.4)
ER/PR-/HER2 Equivocal	1 (0.8)
Unknown	2 (1.6)
Neoadjuvant chemotherapy	
Anthracycline based	20 (16)
Anthracycline-Taxane combination	105 (84)

[Table/Fig-2]: Characteristics of patients with ypT0 ypN0 -pCR (N=125).

In patients with HER2 positive breast cancer (170 patients), there was no significant difference in pCR (p-value=0.152) with the addition of Trastuzumab to the chemotherapy protocol [Table/Fig-3].

Cross-tabulation					
Trastuzumab		pCR (ypT0 ypN0) No	pCR (ypT0 ypN0) Yes	Total	p-value
Not received	No. of patients	91	24	115	0.152
	% of total	53.5%	14.1%	67.6%	
Received	No. of patients	38	17	55	
	% of total	22.4%	10.0%	32.4%	
Total	No. of patients	129	41	170	
	% of total	75.9%	24.1%	100.0%	

[Table/Fig-3]: pCR (ypT0ypN0) in HER2 positive patients who received Trastuzumab versus not received Trastuzumab.

Factors associated with pCR (ypT0 ypN0) in univariate analysis were: higher histologic grade (grade III) of tumour (OR: 2.879, 95% CI:1.615-5.129, p-value=0.001), lower composite clinical stage (OR: 2.236, 95% CI: 1.468-3.408, p-value=0.001), lack of ER expression (OR: 3.23, 95% CI:2.10-4.968, p-value=0.001) and lack of PR expression (OR: 4.396, 95% CI:2.714-7.121, p-value=0.001) [Table/Fig-4]. However, there was no association of pCR with age of patient, HER- 2 status, LVI, chemotherapy protocol and breast cancer subtype.

Variables	p-value	Odds Ratio (OR)	95% Confidence Interval (CI) for OR Lower	95% Confidence Interval (CI) for OR Upper
Age (≥35 vs <35 years)	0.938	0.967	0.408	2.290
Tumour grade (III vs II)	0.001	2.879	1.615	5.129
Composite stage (II vs III)	0.001	2.236	1.468	3.408
Lymphovascular Invasion (LVI) (Present vs Absent)	0.997	0.000	0.000	
Estrogen Receptors (ER) status (Negative vs Positive)	0.001	3.230	2.100	4.968
Progesterone Receptor (PR) status (Negative vs Positive)	0.001	4.396	2.714	7.121
Human Epidermal Growth Factor Receptor 2 (HER2) status (Negative vs Positive)	0.271	0.784	0.508	1.209
Drug schedule (Anthracyclines v/s Anthracyclines+Taxanes)	0.713	1.106	0.647	1.891

Breast cancer subtype (HR-, HER2+ vs TNBC)	0.500	1.241	0.662	2.326
Breast cancer subtype (HR+, HER2- vs TNBC)	0.432	1.229	0.735	2.058
Breast cancer subtype (HR+, HER2+ vs TNBC)	0.453	1.300	0.655	2.582

[Table/Fig-4]: Univariate analysis for pCR-ypT0ypN0.
Triple-negative breast cancer (TNBC); p-value <0.05 was considered as significant

Higher grade of tumour (OR: 2.211, 95% CI: 1.179-4.146, p-value=0.013), lower composite clinical stage (OR: 2.033, 95% CI: 1.262-3.276, p-value=0.004) and lack of PR expression (OR: 3.823, 95% CI: 2.301-6.350, p-value=0.001) remained predictive variables in multivariate analysis after correction for the other variables [Table/Fig-5].

Variables	p-value	OR	95% CI for OR	
			Lower	Upper
Tumour Grade (III v/s II)	0.013	2.211	1.179	4.146
Composite clinical stage (II vs III)	0.004	2.033	1.262	3.276
Progesterone Receptor (PR) status (Negative v/s Positive)	0.001	3.823	2.301	6.350

[Table/Fig-5]: Multivariate analysis for pCR-ypT0 ypN0.
p-value <0.05 was considered as significant

DISCUSSION

The most commonly used endpoint in neoadjuvant trials is pCR; however, various studies have defined it differently, making data reporting and interpretation challenging [4]. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) working group proposed pCR to be defined in future trials as either ypT0/is ypN0 or ypT0 ypN0 (ie, eradication of tumours from both breast and lymph nodes) [4]. The present study defined pCR as ypT0 ypN0. Out of the 586 patients in the study, 125 attained pCR (21.3%).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocols B-18 and B-27, surgical specimens with no invasive cancer in the breast were considered to be pCR [5]. A pCR of 13% was documented in patients receiving preoperative Adriamycin-Cyclophosphamide (AC) in the NSABP B-18 Protocol [5]. Compared with AC alone, Docetaxel(T) added sequentially to AC preoperatively significantly increased the proportion of patients having pCRs (13 % vs 26%, respectively; p-value <0.0001) in the NSABP B-27 study [5]. The GeparTrio trial defined pCR as a histopathological complete response of all invasive tumour cells removed during surgery from the breast and axillary tissue {ypT0, ypTis, ypN0=Regression Grade (RG) 3a and RG 5} [6]. The overall pCR rate in the GeparTrio trial was 20.5% [6]. One of the four key objectives of the CTNeoBC pooled analysis was to establish the definition of pCR that correlated best with long-term outcome, and it was observed that the frequency of pCR decreased with increasingly stringent definitions: 22% (95% CI 21-22) of patients achieved ypT0/is, 18% (17-19) achieved ypT0/Tis ypN0 and 13% (12–14) achieved ypT0ypN0 [4]. The pCR (pT0ypN0) of 21.3% in the present series was comparable to the existing literature [4-6].

The association of pCR with respect to age, composite clinical stage, histologic grade, hormone receptor (ER and PR) status, HER2 status, LVI, breast cancer subtype and chemotherapy protocol was analysed in the present study. In univariate analysis, higher grade of tumour, lack of ER and PR receptor expression and lower composite stage was found to have statistically significant association with achievement of pCR (ypT0 ypN0). In the multivariate analysis, lower composite clinical stage, lack of PR expression and higher histologic grade were independent predictive factors for achievement of pCR at surgery.

In breast cancer patients, studies have shown a negative relation between hormone receptor positivity and pCR [4,7,15]. Subtype specific pCR% (lowest to highest) was 8.3% in hormone receptor positive (HR+/HER2–) patients, 18.7% in HER2 positive/HR+ patients, 31.1% in triple negative and 38.9% in HER2 positive/HR- patients in a meta-analysis involving 11,695 patients [7]. The CTNeoBC analysis revealed that more aggressive subtypes- triple negative and HER2 positive tumours- had increased frequencies of pCR [4]. Within the HER2 positive group, pCR was more common for hormone receptor negative tumours than for hormone receptor-positive tumours, and with the addition of trastuzumab [4]. In a study by Haque W et al., 19% of the patients achieved pCR; however, luminal A tumours had the lowest pCR of 0.3% and HER2 positive tumours had the highest pCR of 38.7% [15].

In patients with HER2 over expression, though studies have shown that anti-HER2 directed therapy resulted in higher pCR, the present series could not find a relationship between pCR and treatment with Trastuzumab [4,7]. This could probably be owing to the fact that majority of patients (67.65%) in the present series did not receive Trastuzumab.

Studies have demonstrated a higher pCR rate with smaller clinical tumour size [8,16]. Lower clinical tumour stage (cT1-2 vs cT3-4) was a significant independent predictor of greater pCR rate (p<0.001, OR 3.15) in a study by Goorts B et al., [16]. In the present series, patients with lower composite clinical stage (stage II) had higher odds for achieving pCR compared to stage III disease and the findings were consistent with previous research.

A study by Liu YL et al., observed LVI to be an independent predictor of survival in women with breast cancer receiving NACT [17]. Other studies have supported this finding, however in the current series there was no association of pCR with LVI [17-20].

Limitation(s)

The main drawback of the present study was its retrospective nature. Moreover, among the HER2 positive patients, only 32.4% of them received trastuzumab along with their chemotherapy protocol.

CONCLUSION(S)

The present retrospective study which included patients from a single institution evaluated factors influencing pathological complete response following NACT in breast cancer patients and the results suggest that lower composite clinical stage, lack of progesterone receptor expression and higher histologic grade (grade III) are significantly associated with the achievement of pCR. Overall, 21.3% patients (1 in 5) attained pCR in the present series, which is comparable to those observed in previous studies. Considering the fact there is improvement in survival for individual patients who attain pCR, clinical trials are warranted to further evaluate the clinicopathological and treatment related parameters contributing to higher pCR in breast cancer patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 22, 2021
- Manual Googling: Oct 08, 2021
- iThenticate Software: Dec 08, 2021 (17%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 21, 2021**
Date of Peer Review: **Oct 11, 2021**
Date of Acceptance: **Nov 18, 2021**
Date of Publishing: **Jan 01, 2022**