Efficacy of Neoadjuvant Chemotherapy in Lobular and Rare Subtypes of Breast Cancer

Erdogan Selcuk Seber[1], Yakup Iriagac[1,11], Eyyup Cavdar[1], Kubilay Karaboyun[1], Okan Avci[1], Ahmet Yolcu[2], Sibel Ozkan Gurdal[3], Meltem Oznur[4], Ferhat Ekinci[5], Ali Aytac[6], Ilkay Gulturk[7], Mesut Yilmaz[7], Nadiye Sever[8], Tanju Kapagan[9], Ferhat Ferhatoglu[9], Fatma Akdag Kahvecioglu[10] and Ilhan Hacibekiroglu[10]

[1]*Department of Medical Oncology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkiye*
[2]*Department of Radiation Oncology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkiye*
[3]*Department of Surgical Oncology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkiye*
[4]*Department of Pathology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkiye*
[5]*Department of Medical Oncology, Sirnak State Hospital, Sirnak, Turkiye*
[6]*Department of Medical Oncology, Aydin Adnan Menderes University, Aydin, Turkiye*
[7]*Department of Medical Oncology, Bakirkoy Sadi Konuk Training and Research Hospital, Istanbul, Turkiye*
[8]*Department of Medical Oncology, Marmara University, Istanbul, Turkiye*
[9]*Department of Medical Oncology, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkiye*
[10]*Department of Medical Oncology, Faculty of Medicine, Sakarya University, Sakarya, Turkiye*
[11]*Department of Medical Oncology, Balikesir Ataturk City Hospital, Balikesir, Turkiye*

ABSTRACT

Objective: To determine the predictive factors for the pathological complete response (pCR) in patients with non-ductal invasive breast cancer (ND-BC) receiving neoadjuvant chemotherapy.

Study Design: Observational study.

Place and Duration of the Study: Departments of Medical Oncology, Tekirdag Namik Kemal University, Sirnak State Hospital, Aydin Adnan Menderes University, Marmara University, Bakirkoy Sadi Konuk Hospital, Basaksehir Cam and Sakura Hospital, Sakarya University, Balıkesir Ataturk Hospital, Turkiye, from April 2016 to December 2022.

Methodology: A total of 222 non-metastatic breast cancer patients who received neoadjuvant chemotherapy were included in this retrospective multicentric study. The clinicopathologic data were obtained from the hospitals' electronic-record-system. The logistic regression models were used to identify predictive factors for pCR.

Results: One hundred and twenty-six patients (56.8%) had invasive lobular carcinoma and 28 patients (12.6%) had signet ring cell/mucinous carcinoma. A total of 45 patients (20.3%) achieved pCR. The pCR rate was 14.3% for lobular carcinoma and 17.9% for signet ring cell/-mucinous carcinoma. The univariate analysis showed that estrogen receptor-negative tumours ($p = 0.017$), high Ki-67 ($p = 0.008$), high histologic grade ($p<0.001$), HER2+ expression ($p<0.001$), and non-lobular histologic type ($p = 0.012$) were predictive factors for pCR. The multivariate model revealed that HER2 expression ($p<0.001$) and Ki-67 ($p = 0.005$) were independent predictors.

Conclusion: Neoadjuvant chemotherapy demonstrated effectiveness in ND-BC patients, leading to favourable pCR rates and enabling breast-conserving surgery. Predictive markers for pCR varied depending on histologic types, with HER2 expression, ER status, Ki-67, and histologic grade showing significance in non-ductal subtypes, while HER2 status alone was predictive in lobular carcinoma.

Key Words: *Neoadjuvant chemotherapy, Non-ductal breast cancer, Lobular carcinoma.*

How to cite this article: Seber ES, Iriagac Y, Cavdar E, Karaboyun K, Avci O, Yolcu A, *et al.* Efficacy of Neoadjuvant Chemotherapy in Lobular and Rare Subtypes of Breast Cancer. *J Coll Physicians Surg Pak* 2024; **34(01)**:37-41.

INTRODUCTION

According to the current knowledge, breast cancer is the most common cancer, excluding skin cancer.[1]

Correspondence to: Dr. Erdogan Selcuk Seber, Department of Medical Oncology, Faculty of Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkiye
E-mail: yakupiriagac@hotmail.com

Received: July 12, 2023; Revised: July 23, 2023;
Accepted: November 01, 2023
DOI: https://doi.org/10.29271/jcpsp.2024.01.37

Neoadjuvant chemo-therapy (NACT) is an accepted treatment modality in selected breast cancer patients since it provides axillary downstaging and increases the likelihood of breast conserving surgery.[2-4]

Moreover, pathologic complete response (pCR) after NACT is considered a valuable prognostic factor and pCR is considered to be a reliable endpoint for breast cancer patients receiving NACT by the United States Food and Drug Administration.[5,6] However, breast cancer includes different histologic/molecular subtypes, and these subtypes may respond differently to treatment. A better selection of patients who will benefit from NACT saves the patients from toxicities of ineffective treatments and the risk of disease progression due to delayed surgery.

Previous studies investigating factors predicting the NACT response have focused mostly on patients with ductal-type breast cancer histology. For ductal breast cancer patients, the international guidelines help clinicians in selecting patients who are suitable for NACT.[2-4] However, for non-ductal histologic types (ND-BC), it is challenging to select patients who would benefit from NACT and controversial to suggest a patient for NACT.[7,8] For ND-BC, invasive lobular carcinoma (ILC), and other less common histologic types, markers are still required that could predict pCR and identify tumours that may respond to chemotherapy.

In this study, the aim was to determine the pCR response rates of histologic subtypes and the ideal predictive markers for pCR in breast cancer patients with ND-BC histology receiving NACT, thus guiding the clinicians in NACT treatment decisions.

METHODOLOGY

This study was designed as a multicentre observation in accordance with the Declaration of Helsinki. Each researcher at the centres provided signed informed consent before registering the study. The Ethics Committee of Tekirdag Namik Kemal University, Turkiye approved this multicentric study. The data of patients who had received outpatient chemotherapy in the participating 7 medical oncology clinics throughout Turkiye between April 2016 and December 2022 were used. Patients aged ≥18 years, who received NACT and underwent the surgery were included in the study. The exclusion criteria were metastases concurrent or prior history of malignancy, ductal histologic subtype, those receiving neoadjuvant hormono-therapy, and the failure to complete the planned NACT. All included patients received either docetaxel every 3 weeks for 4 cycles or paclitaxel every 12 cycles after 4 cycles of cyclophosphamide and anthracycline (epirubicin or doxorubicin) combination. Patients with human epidermal growth factor receptor-2 expression positive(HER2+) received trastuzumab (±pertuzumab; patients receiving pertuzumab received only 4 cycles during the NAC period) in the neoadjuvant period.

Demographic and clinicopathologic characteristics of the patient were recorded. pCR was considered as the absence of histopathological evidence of residual cancer cells in the breast and axillary lymph nodes.[5] Patients with estrogen receptor (ER) and progesterone receptor (PgR) above 1% were considered positive.[9] Those with immunohistochemistry (IHC) HER2 scores +3 or IHC HER2 scores +2 /fluorescence *in situ* hybridisation (FISH) positive were considered HER2 positive. Tumour pathological staging was performed according to the AJCC TNM classification.[10] On the basis of previous studies, the subtype groups were defined as hormone receptor-positive (ER and/or PgR positive) and HER2 negative, HER2 positive regardless of hormonal status, and triple-negative (ER, PgR, and HER2 negative).[5]

Statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, Ill.). The categorical variables were presented as numbers and percentages. The univariate and multivariate analysis was performed using a logistic regression model to find predictors for pCR. Odds Ratio (OR) was reported with corresponding 95% confidence intervals (95% CI) and $p < 0.05$ was considered statistically significant. Binary logistic regression using the "Forward: LR" method for the multivariate analyses was used to predict pCR.

RESULTS

A total of 222 female patients who met the study criteria were included in the study. The median age was 49 (range 25-81) years. Of the patients, 83 (65.9%) were HR+/HER2-, 29 were HER2+, and 14 (11.1%) had triple-negative molecular subgroups. Out of the total patients, 108 (48.6%) were postmenopausal, while the remaining patients had menstrual cycles. The most common histologic types were lobular carcinoma (56.8%) and signet cell carcinoma /mucinous carcinoma (12.6%). Before NACT, 207 (93.2%) patients had axillary lymph node positivity. One hundred and eighty-six (83.8%) patients underwent breast-conserving surgery (BCS) and 144 (64.9%) underwent axillary lymph node dissection (ALND).

A total of 45 patients (20.3%) achieved pCR. The pCR rate of lobular histologic type was 14.3%, signet ring cell/mucinous 17.9%, micropapillary 25%, apocrine 50%, metaplastic 50%, medullary 25%, and other subtypes were 28.9%. The pCR rate of lobular histologic type was 14.3%, stony/mucinous 17.9%, micropapillary 25%, apocrine 50%, metaplastic 50%, medullary 25%, and other subtypes were 28.9%. Molecular subtype grouping and pCR results are shown in Table I.

A logistic regression model was established to detect the predictive factors of pCR. In a univariate analysis including all histologic types, ER-negative tumours ($p = 0.017$), high Ki-67 ($p = 0.008$), high histologic grade ($p<0.001$), HER2 expression ($p<0.001$), and non-lobular histologic type ($p = 0.012$) were found to be the predictive factors for pCR (Table II).

Table I: Distribution of molecular subtypes according to histological subtypes of breast cancer and pathological complete response (pCR) results.

Histological type	n	%	pCR (n)	pCR (%)	Molecular subgroups					
					HR+HER2-	%	HER2+	%	Triple -	%
Lobular	126	56.8	18	14.3	83	65.9	29	23.0	14	11.1
Signet ring cell/Mucinous	28	12.6	5	17.9	19	67.9	4	14.3	5	17.9
Micropapillary	8	3.6	2	25.0	3	37.5	3	37.5	2	25.0
Apocrine	8	3.6	4	50.0	3	37.5	5	62.5	0	0.0
Medullary	8	3.6	2	25.0	3	37.5	1	12.5	4	50.0
Metaplastic	6	2.7	3	50.0	1	16.7	1	16.7	4	66.7
Other	38	17.1	11	28.9	14	36.8	14	36.8	10	26.3

pCR: Pathological complete response.

Table II: Univariate and multivariate logistic regression analysis of clinical and pathologic markers for pCR in invasive non-ductal subtypes of breast cancer (n=222).

Variables	Category	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p	OR (95% CI)	p
Age	≤40 / >40	0.74 (0.41-1.60)	0.437		
Menopausal status	Prem/ postm.	0.57(0.29-1.12)	0.105		
ER	Negative/positive	0.44 (0.22-0.86)	0.017		
PgR	Negative/positive	0.66 (0.34-1.28)	0.223		
Ki-67	Continuous	1.02 (1.01-1.04)	0.008	1.03(1.01-1.04)	0.005
HER2	Negative/positive	9.65 (4.64-20.05)	<0.001	10.57(4.92-22.73)	<0.001
Grade	1/2/3	1.87 (1.01-3.46)	0.045		
Histological type	Non-Lobular/Lobular	0.43 (0.22-0.83)	0.012		

Prem/Postm: Premenopausal/postmenopausal, ER: Estrogen receptor, PgR: Progesterone receptor.

Table III: Factors affecting response in lobular cancer.

Variables	Category	Univariate analysis	
		OR (95% CI)	p
Age	40/40	0.65 (0.19-2.23)	0.497
Menopausal status	Prem/postm.	0.59 (0.21-1.64)	0.312
ER	Negative/positive	1.14 (0.30-4.30)	0.851
PgR	Negative/positive	1.04 (0.36-3.00)	0.939
Ki-67	Continuous	1.02 (0.99-1.04)	0.226
HER2	Negative/positive	10.71 (3.53-32.43)	<0.001
Grade	1/2/3	1.50 (0.59-3.75)	0.389

Prem/Postm: Premenopausal/postmenopausal, ER: Estrogen receptor, PgR: Progesterone receptor.

The multivariate analysis was performed to compare the effect of factors that were found to be predictive in univariate analysis. In the established model, HER2 expression (OR=10.57, 95% CI: 4.92-22.73, p<0.001) and Ki-67 (OR=1.03, 95% CI: 1.01-1.04, p=0.005) found independent predictive markers.

In the regression model established to determine the pCR predictors for Invasive Lobular Carcinoma subtype, HER2 expression alone (OR = 10.71, 95% CI: 3.53-32.43, p<0.001) was found to be predictive (Table III).

DISCUSSION

This study investigated the response rates of ND-BC patients to neoadjuvant chemotherapy and the predictors related to pCR. In this analysis, the rate of achieving pCR in the entire patient population was found to be 20.3%, while the highest pCR rates were attained in apocrine and metaplastic subtypes, both at 50%, the lowest pCR rate was found in lobular breast cancer subtype at 14.3%. For non-ductal histologic types, patients with ER-negative, high Ki-67, high histologic grade, and HER2 expression were more likely to have pCR, whereas only HER2 status was predictive for pCR in the ILC subtype analysis.

Apocrine and metaplastic breast cancers often have triple negative molecular features, enabling these patients to be more favourable for achieving pCR.[11,12] On the other hand, invasive lobular breast cancer (ILC) typically presents with hormone receptor-positive (HR+)/HER2-negative (HER2-) molecular characteristics, resulting in a limited response to neoadjuvant chemotherapy (NACT), in line with the existing literature.

In breast cancer patients having received NACT, achieving pCR provides a survival advantage and also affects the type of breast and axillary surgery to be performed. However, the lack of studies for ND-BC renders it challenging for clinicians to identify patients who could benefit from NACT. In this distinct group of patients, powerful pCR predictors might be insightful. In this study, ER-negative, high grade, high Ki-67, high grade, and HER2 expression were found to be predictive for pCR for non-ductal breast cancer. These factors are consistent with previous studies including patients with both ductal and non-ductal breast cancer.[13-15] High Ki-67 and high grade reflect the tumour's ability to proliferate and its aggressiveness. Since ER is a receptor primarily related to hormonal response rather than chemotherapy, it is an accepted predictive factor for breast cancer subtypes in accordance with the literature.[16,17]

In this study, it was discovered that among the histologic types of non-ductal breast cancer (ND-BC), HER2 over-expression was a positive predictive factor, specifically lobular carcinoma, in terms of pCR rate. This finding is distinct from the predictive factors identified in the analysis encompassing all other non-ductal types. The absence of statistical significance in factors such as hormone receptor status, Ki-67, and grade in lobular subtypes can be attributed to the immunohistochemical-phenotypic differences characteristic of ILC. ILC typically presents with a lower histologic grade and a lower mitotic index. Additionally, it frequently exhibits a high rate of hormone receptor positivity.[18] In this study, while the rate of hormone receptor positivity was 70% in the entire group, it reached 91% in ILC patients. Despite these differences, it is worth noting that current guidelines do not emphasise the role of histologic types in the decision making process for NACT. This underscores the need for distinct

neoadjuvant treatment strategies based on molecular subtypes and further research focused on molecular-targeted approaches.

The surgical procedures for breast cancer, including mastectomy and axillary lymph node dissection (ALND), come with inherent risks that may have a potential impact on a patient's quality of life. Furthermore, studies have reported both survival and better quality of life associated with breast conserving surgery when compared to mastectomy.[19,20] NACT is a pivotal treatment strategy as it enhances the feasibility of breast-conserving surgery and facilitates downstaging of the axilla, thus enabling axilla-sparing surgical procedures. It is widely recognised that surgery remains a viable option after NACT, even in cases with limited treatment response.[8] Notably, in this study, despite variations in treatment responses, a remarkable 83.8% of patients underwent breast-conserving surgery, and 35.1% did not require axillary dissection. These findings highlighted the effectiveness of NACT as a treatment choice, not only for ductal breast cancer but also for other histologic subtypes including ILC.

There were some limitations in this study. This study was retrospectively designed. Certain statements could not be used because of the relatively small sample size of some histologic types. Although the included pathology departments belonged to long-serving centres, the rate of patients whose histological subtypes could not be determined may affect the results. However, the strength of this study was that it was multicentric and included a large patient population for rare subtypes. More prospective clinical trials involving larger numbers of patients are needed.

CONCLUSION

NACT can be considered to be a preferable treatment modality for non-ductal breast cancer patients as it may provide an advantage for surgery with acceptable pCR response rates. The high BCS rates suggested that the treatment response may be high in non-ductal carcinoma subtypes, and NACT can be used as a treatment modality to spare patients from the morbidity of axillary lymph node dissection in these patients. Various factors, including HER2 expression, ER status, Ki-67, and histologic grade, were found to be predictive markers for pCR in non-ductal breast cancer subtypes receiving NACT. For lobular histologic types, HER2 expression emerged as a predictive marker for pCR.

ETHICAL APPROVAL:
An approval was granted by 2 Non-Interventional Ethics Committee of Tekirdag Namik Kemal University, Turkiye (Approval no. 2023.76.04.1).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were obtained from the electronic medical record system after approval of the Ethics Committee.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
ESS, YI, EC, KK, OA, AY, SOG, MO, FE, AA, IG, MY, NS, TK, FF, FAK, IH: Data acquisition.
ESS, YI, EC, KK, IH: Drafting of the manuscript.
ESS, YI, EC, KK: Critical revision of the manuscript.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023; **73(1)**:17-48. doi: 10.3322/caac.21763.
2. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, *et al*. Breast cancer, Version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022; **20(6)**:691-722. doi: 10.6004/jnccn.2022.0030.
3. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hang ES, *et al.* Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. *J Clin Oncol* 2021; **39(13)**:1485-505. doi: 10.1200/JCO.20.03399.
4. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio I, *et al*. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; **30**:1194-220. doi: 10.1093/annonc/mdz17373.
5. Cavdar E, Iriagac Y, Karaboyun K, Avci O, Oznur M, Seber ES. Prognostic role of lymphovascular invasion and perineural invasion in breast cancer treated with neoadjuvant chemotherapy. *UHOD* 2022; **32**:141-9.
6. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm305501.pdf (Accessed on 31/11/2021).
7. Makower D, Qin J, Lin J, Xue X, Sparano JA. The 21-gene recurrence score in early non-ductal breast cancer: A National Cancer Database analysis. *NPJ Breast Cancer* 2022; **8(1)**:4. doi: 10.1038/s41523-021-00368-9.
8. O'Connor DJ, Davey MG, Barkley LR, Kerin MJ. Differences in sensitivity to neoadjuvant chemotherapy among invasive lobular and ductal carcinoma of the breast and implications on surgery-A systematic review and meta-analysis. *Breast* 2022; **61**:1-10. doi: 10.1016/j.breast.2021.11.017.
9. Hammond MEH, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, *et al.* American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med* 2010; **134(7)**:e48-72. doi: 10.5858/134.7.e48.

10. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. *Ann Surg Oncol* 2018; **25**:1783-5. doi: 10.1245/s10434-018-6486-6.
11. Lips EH, Mukhtar RA, Yau C, Ronde JJ, Livasy C, Carey LA, *et al*. Lobular histology and response to neoadjuvant chemotherapy in invasive breast cancer. *Breast Cancer Res Treat* 2012; **136(1)**:35-43. doi: 10.1007/s10549-012-2233-z.
12. Reddy TP, Rosato RR, Li X, Moulder S, Piwnica-Worms H, Chang JC. A comprehensive overview of metaplastic breast cancer: Clinical features and molecular aberrations. *Breast Cancer Res* 2020; **22(1)**:121. doi: 10.1186/s13058-020-01353-z.
13. Riba LA, Russell T, Alapati A, Davis RB, James TA. Characterizing response to neoadjuvant chemotherapy in invasive lobular breast carcinoma. *J Surg Res* 2019; **233**:436-443. doi: 10.1016/j.jss.2018.08.011.
14. Nwaogu IY, Fayanju OM, Jeffe DB, Margenthaler JA. Predictors of pathological complete response to neoadjuvant chemotherapy in Stage II and III breast cancer: The impact of chemotherapeutic regimen. *Mol Clin Oncol* 2015; **3(5)**: 1117-22. doi: 10.3892/mco.2015.579.
15. Derouane F, van Marcke C, Berlière M, Gerday A, Fellah L, Leconte I, *et al*. Predictive biomarkers of response to neoadjuvant cChemotherapy in breast cancer: Current and future perspectives for precision medicine. *Cancers (Basel)* 2022; **14(16)**:3876. doi: 10.3390/cancers14163876.
16. Liang Q, Ma D, Gao RF, Yu KD. Effect of Ki-67 expression levels and histological grade on breast cancer early relapse in patients with different immunohistochemical-based subtypes. *Sci Rep* 2020; **10(1)**:7648. doi: 10.1038/s41598-020-64523-1.
17. Del Prete S, Caraglia M, Luce A, Montella L, Galizia G, Sperlongano P, *et al*. Clinical and pathological factors predictive of response to neoadjuvant chemotherapy in breast cancer: A single center experience. *Oncol Lett* 2019; **18(4)**:3873-9. doi: 10.3892/ol.2019.10729.
18. McCart Reed AE, Kutasovic JR, Lakhani SR, Simpson PT. Invasive lobular carcinoma of the breast: Morphology, biomarkers and 'omics. *Breast Cancer Res* 2015; **17(1)**:12. doi: 10.1186/s13058-015-0519-x.
19. Ji J, Yuan S, He J, Liu H, Yang L, He X. Breast-conserving therapy is associated with better survival than mastectomy in Early-stage breast cancer: A propensity score analysis. *Cancer Med* 2022; **11(7)**:1646-58. doi: 10.1002/cam4.4510.
20. Sun GY, Wen G, Zhang YJ, Tang Y, Jing H, Wang JY, *et al.* Radiotherapy plays an important role in improving the survival outcome in patients with T1-2N1M0 breast cancer - A joint analysis of 4262 real world cases from two institutions. *BMC Cancer* 2020; **20(1)**:1155. doi: 10.1186/s12885-020-07646-y.