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Research Article

In Which Luminal Breast Cancers Might Neoadjuvant Chemotherapy Be Appropriate to Achieve a Pathological Complete Response in Axillary Lymph Nodes?

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Abstract

Objectives: In this study, we aimed to evaluate in which luminal/human epidermal growth factor receptor 2 negative (her2-) breast cancers (BCs) would be achieved complete pathological response in axillary lymph nodes with neoadjuvant chemotherapy (ypN0).

Methods: We retrospectively analyzed 66 patients with luminal/her2- BC who were operated after neoadjuvant chemotherapy (NAC). We evaluated the predictive factors for ypN0 after NAC.

Results: We detected ypT0 in 15.2% of the patients and ypN0 in 31.8%. Univariate analysis indicated that grade, cN stage, and anatomical stage were significant predictors of ypN0. According to the multivariate analysis, grade was the only significant factor in predicting ypN0 independently of other factors (p=0.037). Considering the grades of cN1 patients, the ypN0 rate was 2/18 (11.1%) for grade 1-2 and 7/10 (70%) for grade 3 (p=0.01).

Conclusion: In the presence of cN1 axillary lymph nodes, the decision of NAC can be challenging for clinicians in luminal BC patients, especially with no clear indication for NAC. Nowadays, if ycN0 is provided after NAC in cN1 cases, methods such as sentinel lymph node dissection/targeted axillary dissection are more commonly used for axillary staging. Based on the findings of our study, we think it would be appropriate to use NAC in patients with luminal BC with the goal of reducing axillary surgery in the presence of cN1, grade 3 tumors.

Keywords: Axilla, breast cancer, chemotherapy, luminal

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Breast cancer (BC) is the most diagnosed cancer worldwide and the leading cause of cancer-related mortality in women.[1] Molecular subtypes of BC have been identified that differ in prognosis based on their gene expression profiles.[2] Luminal BCs often overlap with estrogen receptor-positive (ER+) BCs determined by clinical assays. Luminal/human epidermal growth factor receptor-negative (luminal/her2-) BC is the most frequent type.[3,4] Of all BC cases, 66.6% consist of luminal/her2-, 9.7% of luminal/her2 positive (luminal/her2+) cancers.[4]

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BC is treated with a multidisciplinary approach with combinations of surgery, radiotherapy, and systemic treatments. Neoadjuvant therapy (NAT) refers to systemic treatments used prior to definitive surgery. NAT is performed in most BC patients with locally advanced tumors.

It is known that the complete pathological response (pCR) obtained after NAT is associated with a good prognosis, more prominently in triple-negative (TN) and her2+ tumors.[5] The rates of obtaining pCR of luminal/her2- BCs with NAT are much lower than that of her2+ and TN tumors with more aggressive biology. The relationship between pCR and prognosis is weaker in luminal BCs.

In cases that do not provide post-NAT pCR, it is possible to provide a survival advantage with additional adjuvant treatments in stage I-II her2+ and TN tumors.[6,7] For this reason, NAT is often used in her2+ and TN tumors in the early stages. However, the location of NAT in early-stage luminal BCs is less precise.

In addition to reducing mortality in BC, improving the quality of life of its survivors are important global cancer goals. Methods such as axillary sentinel node biopsy (SNB) or targeted axillary biopsy (TAB) are important targets in terms of performing limited surgery, reducing the risk of lymphedema, and maintaining functionality. Today, in cases with clinical node-positive (cN+) at the beginning, less morbid surgeries such as SNB or TAB may be applied instead of axillary lymph node dissection (ALND) if clinical complete response is achieved in the axilla (ycN0) after NAT.[8,9]

We aimed in this study to evaluate which patients surgical targeting limited to the axilla would be a rational target by providing a complete pathological response in axillary lymph nodes with neoadjuvant chemotherapy (NAC) in luminal/her2- cases.

Methods

The files of BC patients scheduled for NAC in our clinic between March 2013 and March 2021 were reviewed retrospectively. It was planned to include those with ER+ (>10%) and her2- among these patients. ER+, her2- tumors were evaluated as luminal/her2-. Those younger than 18 years of age, those with her2+ and TN tumors were excluded from the study. Those who used endocrine therapy in NAT were excluded from the study. Written patient files of patients and data recorded in the hospital system were recorded. ER, progesterone receptor (PR), Her2, Ki-67 status, and histological grades were recorded. The scoring recommendation of the American Society of Clinical Oncology/College of American Pathologists was used to evaluate ER, PR, and Her2 status.[10,11] The cT and cN were defined as clinical stages in primary tumour and axillary lymph nodes at the diagnosis, respectively. The ypT0 and ypN0 were defined as the absence of residual invasive carcinoma in the breast tissue and absence of invasive carcinoma or presence of isolated tumour cells in axillary lymph nodes after NAC, respectively. The ypN+ was defined as presence of invasive carcinoma in axillary lymph nodes after NAC. The pCR was defined as absence of residual invasive carcinoma in the breast tissue, absence of invasive carcinoma or isolated tumour cells in axillary lymph nodes.

The primary objective was to assess the impact of predictive factors on ypN0 after NAC. The continuous variables were investigated by using visual tests (histograms, probability plots) and the Kolmogorov-Smirnov test to determine whether or not they are normally distributed. Whether there was a change in N stages, according to before and after NAC, was compared using the Wilcoxon test. Differences between groups were analyzed by chi-square or Fisher tests for categorical variables and non-normally distributed variables. The Kruskal-Wallis and The Mann-Whitney-U tests were used to compare ypN0 ratios between the groups. Bonferroni correction was done for multiple comparisons. All statistical tests were 2-sided with a significance level of $p<0.05$. Factors with $p<0.25$ in univariate analysis were included in the multivariate analysis. The data were analyzed using the Statistical Package for the Social Sciences, Statistics V.22 (IBM Corp, Armonk, NY).

Results

During the study period, NAT was administered to 184 BC patients at our center. 70 of these had luminal/her2- tumors. 4 of these patients had received endocrine therapy in NAT. A total of 66 patients were evaluated. The clinical characteristics are summarized in Table 1. In NAC, 65 (98.5%) patients received anthracycline and taxane-based therapy (anthracycline+cylophospahmide followed by paclitaxel or docetaxel). Paclitaxel was administered for 12 weeks without anthracycline in 1 patient. NAC was terminated early in 1 patient due to neuropathy during the paclitaxel period.

The pCR rate was 6/66 (9.1%) in all patients. While the pCR rate was 4/25 (16%) in grade 3 patients, no pCR was detected in grade 1-2 patients (p=0.018). After NAC, ypT0 was detected in 15.2% of patients and ypN0 in 31.8% of patients. Univariate analysis indicated that the histological grade, cN stage, and anatomical stage were significant predictors of ypN0 (Table 1). We looked at which subgroups caused the significant difference between ypN+, ypN0 rates for grade 1, 2, 3 after NAC. We found that the difference was because of the difference between grade 2 and grade 3 tumors (p=0.01). Multivariate analysis grade was the only significant factor in predicting ypN0 independently of other factors (p=0.037) (Table 2). For cN0, 1, 2, 3, we looked at which subgroups caused the difference in ypN0 ratios. Only the dis-

Table 1. Clinicopathological features of patients and, univariate analysis of predictive factors to ypN0

Clinicopathologic characteristics	Overall	ypN0	ypN+	p
Age (years), mean±SD	48.7±11	44±11.65	50.9±10.08	0.365
ER (%), median, IQR	90, 13	90.22	90.13	0.468
PR (%), median, IQR	65, 70	60.83	70.70	0.162
Ki67 (%), median,I QR	30, 23	30.35	25.25	0.248
Ki67 cuttoff: 14%, n (%)				
>14	55 (83.3)	19 (34.5)	36 (65.5)	0.291
≤14	11 (16.7)	2 (18.2)	9 (81.8)	
Ki67 cuttoff: 20%, n (%)				
>20	49 (74.2)	4 (23.5)	13 (76.5)	0.398
≤20	17 (25.8)	17 (34.7)	32 (65.3)	
Ki67 cuttoff: 30%, n (%)				
>30	34 (51.5)	9 (28.1)	23 (71.9)	0.535
≤30	32 (48.5)	12 (35.3)	22 (64.7)	
Grade, n (%)				
G1	6 (10.3)	2 (33.3)	4 (66.7)	0.045
G2	27 (46.6)	4 (14.8)	23 (85.2)	
G3	25 (43.1)	12 (48)	13(52)	
cT stage, n (%)				
cT1	10 (15.2)	2 (20)	8 (80)	0.547
cT2	38 (57.6)	13 (34.2)	25 (65.8)	
cT3	4 (6.1)	1 (25)	3 (75)	
cT4	14 (21.2)	5 (35.7)	9 (64.3)	
cN stage, n (%)				
cN0	6 (9.1)	6 (100)	0 (0)	0.001
cN1	33 (50)	11(33.3)	22 (66.7)	
cN2	14 (21.2)	3 (21.4)	11(78.6)	
cN3	13 (19.7)	1 (7.7)	12 (92.3)	
Anatomical stage, n (%)				
Stage 2	31 (47)	14 (45.2)	17 (54.8)	0.03
Stage 3	35 (53)	7 (20)	28 (80)	
Menopausal status, n (%)				
Pre	37 (56.1)	15 (40.5)	22 (59.5)	0.086
Post	29 (43.9)	6 (20.7)	23(79.3)	

ER: Estrogen receptor; PR: Progesteron receptor; Pre: premenopausal; Post: postmenopausal: G: Grade; n: number

tribution between cN0 and cN3 was significant (p<0.001). There was no significant difference in ypN0 ratios among cN+ patients compared to cN stage (p=0.072). The change was significant when compared the cN stage distributions with the ypN0 stage distributions (p=0.004). In terms of N stage distribution, downstaging was observed in 29/66 (43.9%) patients, while up-staging was detected in 8/66 (12.1%) patients. Stage distributions of patients with cN1 after NAT were 11/33 (33.3%), 16/33 (48.5%), 3/33 (9.1%), 3/33 (9.1%) for ypN0, ypN1, ypN2, ypN3, respectively. SNB/TAB was performed in 32 (48.5%) patients after NAC. Of these 32 patients, 17 (53.1%) ypN+ and 15(46.9%) ypN0 were detected. No additional axillary surgery was performed in patients with SNB/TAB and ypN0. According to grades of cN1 patients, ypN0 rates were 2/18(11.1%) and 7/10(70%) for grade1-2 and grade 3 patients, respectively (p=0.01).

Table 2. Multivariate analysis of predictive factors to ypN0

Predictive factor	OR	95% confidence interval	p
PR (%)	0.99	0.97-1.01	0.462
Ki67(%)	0.98	0.94-1.02	0.360
Grade 1-2 vs 3	8.40	1.13-61.9	0.037
cN stage	0.46	0.02-10.2	0.68
Anatomical Stage	0.71	0.04-10.8	0.806
Menapausal status	0.27	0.05-1.44	0.128

OR: Odds ratio; PR: Progesteron receptor

Discussion

Currently, it is widely preferred surgery after NAC unless there is a contraindicated condition in almost all locally advanced ER+, her2- BCs. However, a significant number of patients have earlier-stage tumors. In such patients, the choice of patients who will benefit most from chemotherapy and the decision to give chemotherapy in an adjuvant or neoadjuvant setting can be a challenge for clinicians.

The effectiveness of multigene molecular panel tests in determining patients who will benefit from adjuvant chemotherapy in early-stage ER+, her2- BC has been demonstrated by clinical studies.[12] With the use of these tests, it may be possible to protect patients from many toxicities, for whom chemotherapy cannot be obtained in addition to endocrine therapy without additional survival advantage.[12] Moreover, according to the preliminary results of the ongoing Southwest Oncology Group (SWOG) S1007 RxPONDER trial with cN1 patients, approximately 20% of cN1 hormone receptor positive, her2- BC patients had a risk score of 0-25.[13] It was reported in this study that adding chemotherapy to endocrine therapy did not contribute to additional survival in postmenopausal patients with low-risk scores. Data is accumulating on the guiding role of genomic testing in NAT as well.[14,15] A meta-analysis showed higher pCR rates in ER+, Her2- tumors with a high genomic risk score.[14] However, due to the high cost of genomic tests, in most cases, we do not benefit from these tests in everyday practice.

The results of the SENTINA and ACOSOG Z1071 studies in patients with cN1 and ypN0 have shown that SNB can be performed in selected cases. Thus, ALND and the risk of morbidity caused by it can be avoided.[16] Moreover, it was shown in a study evaluating the effectiveness of TAD after NAC that in cN+ patients, the FNR after NAC with SNB alone was around 10%, while this rate decreased to a reasonable 2% with TAD.[17] In daily practice, in almost all cN2/cN3 patients, it is preferable to administer chemotherapy in the neoadjuvant setting unless there is a contraindication. However, in the presence of cN1 luminal disease, the decision to apply chemotherapy in the neoadjuvant setting may be challenging for clinicians, as some patients may avoid chemotherapy by making a decision based on genomic tests in the adjuvant setting. Therefore, there is a need for clinical and pathological parameters that guide the NAT decision, especially cN1+, ER+, and Her2- BC.

ypN0 was detected in 7 (38.9%) of 33 patients who have cN1 in our study. In cN1, grade 3 cases, ypN0 was 70% (p=0.01). This is a very satisfactory result. These rates obtained in ypN0 seem to be higher than those reported in the literature. One reason for this may be that the majority of the patients studied in our study consisted of patients with high Ki67 and/or grade 3, that is, luminal -B BC. In cN1, Grade1/2 cases, the rate remained at 11%. We detected that grade 3 tumors had 8.4 times more ypN0 than grade 1/2. It was found in a study evaluating the risk-scores of patients who underwent NAC with the 21-gene real-time polymerase chain reaction assay that the presence of grade 3 tumor was significant in predicting a high-risk score (RS>25) (odds ratio: 3.83).[18] This supports the findings of our study. The nodal staging was completed with limited axillary surgery without ALND in all patients with cN1, ypN0. This is an important acquisition in order to protect patients from complications associated with ALND.

In 18.2% of patients with cN1, ypN2 or ypN3 were detected in postoperative pathology, although no progression was detected in the follow-up imaging or physical examinations performed during or after NAC. If these patients had been operated without receiving NAC, it was likely that ypN2 and ypN3 would have been detected in postoperative pathology in a larger number of patients. Accordingly, ALND would be performed in these patients. In other words, the N stages we evaluated initially may be up-stage in postoperative pathology, even if no progression was detected during NAC by radiological methods and physical examination. Moreover, the number of lymph nodes involved is taken into account in the pathological staging after NAC while cN evaluation is performed regardless of the number of lymph nodes involved. This may be causing a discordance.[19]

The pCR rate in all patients was 9.1% in our study. Our pCR rate was 16% in grade 3 ER+ Her2- tumors. This rate was similar to the 16.7% reported in a previous large pooled analysis.[20] In this study, pCR was reported as 7.5% in ER+her2- grade 1, 2 tumors.[20] In our study, there were patients whose grade was not evaluated in the initial tru-cut biopsy. In our study, none of the grade 1/2 tumors had pCR. This may be due to the small number of patients.

Ki67 is widely used as a proliferation marker in BC. However Ki67 is viewed with suspicion because of its known lack of reproducibility (especially between different laboratories).[21] Tumors with a high proliferation index would be expected to benefit more from NAC, hypothetically.[22] So far, many cut-offs such as 14%, 20%, 30% have been tested in different studies where Ki67 has been used as a predictive and prognostic marker. However, studies evaluating the role of Ki67 in predicting chemotherapy effectiveness have poor analytical validity, and inconsistent study designs have confounded studies of this issue.[22] And it is not recommended to be used alone to predict NAC response. What is accepted today is that <5% can be considered low, and >30% can be considered high.[22] Therefore, in our study, we

evaluated the role of different Ki67 cut-offs in predicting ypN0. There was no significant difference in Ki67 between ypN0 and ypN+ patients at any cut-off. However, due to the retrospective nature of our study, this may be since patients who were planned for NAC were generally selected from those with a high proliferation index.

Conclusion

The decision of NAC in the presence of cN1 axillary lymph nodes can be challenging for clinicians in luminal BC patients especially with no exact indications for NAC. Based on the findings of our study, we think that it would be appropriate to use neoadjuvant chemotherapy in patients who have luminal/her2- BC with the goal of reducing axillary surgery in the presence of cN1, grade 3 tumor. It may be reasonable to perform primary surgery on grade 1-2 tumors and make a chemotherapy plan using genomic tests if necessary, according to postoperative pathology. It would be appropriate to evaluate these findings in more comprehensive, prospective studies.

Disclosures

Ethics Committee Approval: The study was approved by The Haydarpasa Numune Training and Research Hospital Institutional Review Board (Date: 06/09/2021, No: 2021/215).

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