Original Article

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Inflammatory Markers Predicting Pathological Complete Response in Cases with Breast Cancer Treated by Neoadjuvant Chemotherapy

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ABSTRACT

Objective: Response to neoadjuvant chemotherapy (NAC) is predictive for survival times in some patients with breast cancer (BC). The aim of this study is to explore the predictive value of some inflammatory markers including neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), monocyte-to-high density lipoprotein ratio (MHR) and prognostic nutritional index (PNI) in cases with BC treated with NAC.

Materials and Methods: One hundred and ten patients with BC treated with NAC were included in the study. Measurements for NLR, dNLR, MHR and PNI were calculated with available formulas. The value of NLR, dNLR, MHR and PNI in predicting pCR to NAC in BC was analyzed using receiver operating characteristic (ROC) curve analysis. All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0).

Results: Mean NLR values were 2.2±0.8 vs. 2.6±1.3 for pCR (+) and pCR (-) groups (p=0.603). Mean dNLR values were 1.5±0.5 vs. 1.9±0.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.022). Mean MHR values were 15.4±17.2 vs. 13.2±10.1 for pCR (+) and pCR (-) groups (p=0.406). Mean PNI values were 52±5.1 vs. 49±5.8 for pCR (+) and pCR (-) groups, and this was statistically significant (p=0.015). In multiple logistic regression analysis PNI was found to be independent factor for pCR.

Conclusion: In this study pre-treatment dNLR and PNI were found to be predictive for pCR while NLR and MHR were not found to be associated with pCR. PNI and dNLR are simple but useful biomarkers predicting response to NAC.

Keywords: Breast cancer, dNLR, MHR, NLR, PNI

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Introduction

Breast cancer (BC) is the second leading cause of death among the woman cancers. Systemic chemotherapy increases the progression free survival (PFS) and overall survival (OS) in high risk patients and may be performed before or after surgery. Chemotherapy given before surgery is named as neoadjuvant chemotherapy (NAC) (1). Response to NAC is predictive for survival times in some subgroups of BC especially in triple negative cases. Pathological complete response (pCR) is defined as the absence of invasive cancer in breast and lymph nodes (2). Tumor relapse is higher in cases with residual cancer after NAC as compared with patients achieving pCR (3). Cancer development is multifactorial and inflammatory response besides genetic basis has important role in carcinogenesis and progression of the disease (4). Neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR) and monocyte-to-high density lipoprotein ratio (MHR) are blood based inflammatory markers defined and used in recent years (5). Although the relationship between NLR and pCR is the most studied among these inflammatory markers, the results are confusing. Prognostic nutritional index (PNI) is calculated with multiplying the albumin and lymphocyte and is an important score reflecting inflammatory and nutritional status of the patient (6). Although this score has been proposed as predictive factor for the risks of gastrointestinal surgery, it has been shown prognostic in various cancer cases including colorectal cancer, malignant pleural mesothelioma and hepatocellular cancer (7-9). Prognostic role of PNI in cases treated by NAC is not clear. The aim of this study to determine the predictive value of NLR, dNLR, MHR and PNI for pCR in cases with BC treated by NAC.

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Materials and Methods

Patients

Between March 2006 and January 2019, 206 patients who received NAC for BC at the Medical Oncology Department of Cukurova University were evaluated for the study. The fact that all patients' biopsies and post-NAC surgeries were in our center at the time of diagnosis was accepted as the key inclusion criterion in the study. Biopsy and surgical materials were evaluated by our experienced pathologists. Twenty-six patients who underwent biopsy at the external center and 23 patients who underwent NAC in our center but operated at the external center were excluded from the study. Three patients who voluntarily abandoned the operation after NAC and 5 patients who could not be operated due to metastasis during NAC were excluded from the study. Twenty-one patients with invasive lobular carcinoma, 4 patients with metaplastic carcinoma and 4 patients with mixed type carcinoma were excluded from the study. And also, the patients with chronic diseases such as end stage renal disease, chronic heart failure, systemic lupus erythematosus, liver cirrhosis, or any myeloproliferative neoplasms such chronic myeloid leukemia were excluded. 110 patients with BC treated with NAC were included in the study. Neoadjuvant therapy was given to patients with at least one lymph node involvement. Tumors with T1, T2, T3 and T4 were included in the study. All patients were female, age was between 18 and 70, stage II or III patients with non-inflammatory invasive ductal carcinoma. All patients underwent surgery such as breast-conserving surgery or modified radical mastectomy after NAC. NAC regimens were AC+P (doxorubicin 60 mg/m^2, cyclophosphamid 600 mg/m^2 every 21 days and paclitaxel 80 mg/m^2 weekly) or TC (docetaxel: 75 mg/m^2, cyclophosphamide: 600 mg/m^2 every 21 days). In HER2 positive cases; trastuzumab added to AC+P regimen or TCH (docetaxel: 75 mg/m^2, carboplatin: AUC=5, trastuzumab: 8 mg/kg followed by 6 mg/kg every 21 days) regimen was used for NAC. Estrogen (ER) and progesterone (PR) receptor status were evaluated by immunohistochemistry and considered positive if there is >1% positive tumor nuclei (10). Tumor grading was performed according to the Scarff-Bloom-Richardson scheme (11). HER2 status was evaluated by immunohistochemistry and/or fluorescent in situ hybridization (FISH). It was considered positive if the score was +++ with immunohistochemistry or there were at least 2.2 times as many HER2 signals as CEP 17 signals in the tumor cells (12). The tumor size (T stage), lymph node status (N stage), presence of metastasis (M stage) and the American Joint Committee on Cancer (AJCC) stage for each patient were obtained by reviewing the cancer registry data. Patients were staged before NAC according to AJCC (13). pCR was defined as the absence of invasive disease in breast and in axillary lymph nodes (14). The age, pathologic findings including histological type, tumor size, grade, lymph node status, hormonal status, Ki-67 level, HER2 receptor status were obtained from the patients archive files. At the time of diagnosis, fasting blood tests; leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, albumin and HDL (high-density lipoprotein) were recorded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval and written informed consent could not be taken due to retrospective nature of this study.

Key Points

- In breast cancer, neoadjuvant chemotherapy is being used more and more frequently; therefore, there is a need for markers to predict the response to be obtained.
- We aimed to explore the predictive value of neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), monocyte-to-high density lipoprotein ratio (MHR) and prognostic nutritional index (PNI) in cases with breast cancer treated with neoadjuvant chemotherapy.
- In this study, NLR and MHR were not found to be associated with pathological complete response (pCR).
- Pretreatment dNLR and PNI were found to be predictive for pCR and PNI was found to be independent factor for pCR.
- As a result, PNI and dNLR are simple but useful biomarkers predicting response to NAC.

Statistical analysis

NLR was calculated dividing the neutrophil counts by lymphocyte counts. The dNLR was calculated using the following ratio: neutrophil count/(WBC-neutrophil count). MHR was calculated by dividing the absolute count of the monocytes by the HDL (mg/dL). PNI was calculated with the formula '(10 × albumin (g/L) + (0.005 × total lymphocyte count)'. Patients divided into two groups according to the response to NAC: pCR(+) and pCR(-). The descriptive statistics was done using mean with standard deviation (SD) and percent (%). To determine the properties of BC patients with pCR+ and pCR-; frequency analysis, two independent samples t test, and chi-square tests or Fisher's exact test were performed. The value of NLR, dNLR, MHR and PNI in predicting pCR to NAC in BC was analyzed using receiver operating characteristic (ROC) curve analysis. The most sensitive and specific cut-off values were determined. While evaluating the area under the curve, 5% type-I error level was used to accept a statistically significant predictive value of the test variables. Multiple logistic regression analysis was used to calculate the independent prognostic value of variables with a $p<0.05$ in univariate analysis. All analyses were performed using the IBM Statistical Package for the Social Sciences version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). Statistical significance was calculated at the 95% confidence interval ($p<0.05$).

Results

One hundred and ten patients were enrolled in this study, and the characteristics of patients with pCR and without pCR have been summarized in Table 1. Pathological complete response was achieved in 43 (39.1%) of 110 patients who received NAC. The mean age was 51.7±10.8 and 51.8±9.8 for groups with pCR (+) and pCR (-), respectively (p=0.966). The ratio of premenopausal patients was 44.18% and 55.82% for pCR (+) and pCR (-) groups, respectively (p=0.845). There was no difference between groups regarding clinical T, clinical N stage and grade (p=0.140, p=0.990, p=0.239, respectively). Pathologic complete response was achieved more frequently in cases with hormone receptor negative and HER2 positive disease ($p<0.001$, p=0.028, respectively). Also, pCR was detected more frequently in cases treated by trastuzumab and chemotherapy (Cht) compared with not treated with trastuzumab (p=0.005). The mean Ki-67 level (37%) was higher in the cases with pCR (+) than pCR (-) group and this was statistically significant ($p<0.001$).

The association between pretreatment NLR, dNLR, MHR, PNI and pCR is shown in Table 2. Mean NLR values were 2.2±0.8 vs. 2.6±1.3

Table 1. The association between clinicopathological factors and pCR

	Patients with pCR (n=43)	Patients without pCR (n=67)	p
Age (mean-years)	51.7±10.8	51.8±9.8	0.966
Grade			0.239
II	20	40	
III	23	27	
Menopausal status			0.845
Premenopausal	19 (44.18%)	28 (41.80%)	
Postmenopausal	24 (55.82%)	39 (58.20%)	
Estrogen receptor status			<0.001
Positive	21	62	
Negative	22	5	
Estrogen receptor level (% mean)	32±40.2	69±35.5	<0.001
Progesterone receptor status			<0.001
Positive	10	52	
Negative	33	15	
Progesterone receptor level (% mean)	13±28.4	43±38.1	<0.001
Ki-67 level (mean)	51±23.5	28±19	<0.001
HER2 status			0.028
0	11	20	
I	1	1	
II	7 (1 FISH positive)	26 (0 FISH positive)	
III	24	20	
T stage			0.140
1	5	5	
2	22	22	
3	2	7	
4	14	33	
N stage			0.990
1	6	10	
2	28	43	
3	9	14	
Treatment			0.005
Cht	18	47	
Cht+trastuzumab	25	20	

Cht: chemotherapy; pCR: pathological complete response

for pCR (+) and pCR (-) groups, respectively (p=0.603). ROC curve analysis suggested that the optimal NLR cut-off point for BC patients with PCR (+) was 2.1 (AUC: 0.430, 95% CI [0.321-0.539], p=0.219), with sensitivity and specificity of 51%, 42%, respectively. Mean dNLR values were 1.5±0.5 vs. 1.9±0.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.022). Optimal dNLR cut-off point for BC patients with PCR (+) was 1.6 (AUC: 0.395, 95%CI [0.288-0.501], p=0.033), with sensitivity and specificity of 71%, 61%, respectively. Mean MHR values were 15.4±17.2 vs. 13.2±10.1 for pCR (+) and pCR (-) groups, respectively (p=0,406). Optimal MHR cut-off point for BC patients with PCR (+) was 11.5 (AUC: 0.527, 95% CI [0.412-0.643], p=0.628), with sensitivity and specificity of 58%, 50%, respectively. Mean PNI values were 52±5.1 vs. 49±5.8 for pCR (+) and pCR (-) groups, respectively and this was statistically significant (p=0.015). Optimal PNI cut-off point for BC patients with pCR (+) was 50 (AUC: 0.598, 95% CI [0.488-0.709], p=0.01), with sensitivity and specificity of 75%, 60%, respectively (Figure 1). Multiple logistic regression analysis showed that ER, PR receptor status; HER2 status; Ki-67 level and PNI were independent prognostic markers for pCR (Table 3).

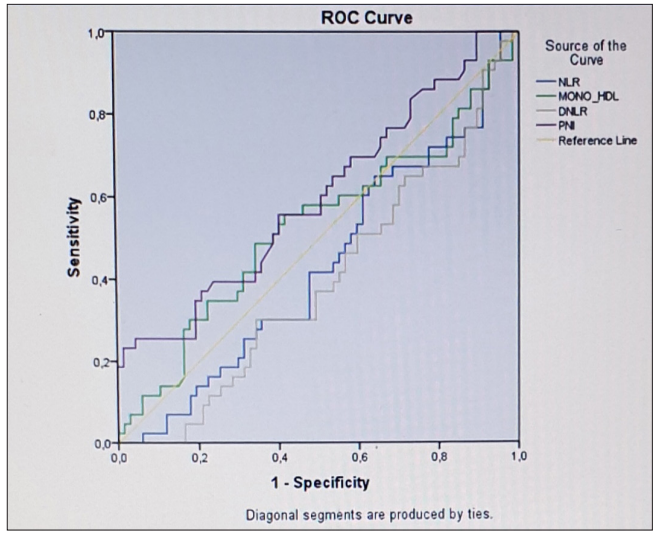

Figure 1. Receiver operating characteristic (ROC) analysis and AUC for sensitivity and specificity of parameters

NLR: neutrophil-to-lymphocyte ratio; DNLR: derived neutrophil-to-lymphocyte ratio; MONO_HDL: monocyte-to-high density lipoprotein ratio; PNI: Prognostic Nutritional Index

Table 2. The association between pretreatment NLR, dNLR, MHR, PNI and pCR

	Patients with pCR (n=43)	Patients without pCR (n=67)	p
NLR (mean)	2.2±0.8	2.6±1.3	0.125
dNLR (mean)	1.5±0.5	1.9±0.8	0.022
MHR (mean)	15.4±17.2	13.2±10.1	0.406
PNI (mean)	52±5.1	49±5.8	0.015

NLR: neutrophil-to-lymphocyte ratio; dNLR: derived neutrophil-to-lymphocyte ratio; MHR: monocyte-to-HDL ratio; PNI: Prognostic Nutritional Index; pCR: Pathological complete response

Table 3. Univariate and multiple logistic regression analysis of potential prognostic factors for pCR

		Univariate		Multivariate	
Parameters	**Categories**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Estrogen receptor status	Positive vs. negative	0.254 (0.214-0.385)	<0.001	0.346 (0.302-0.413)	<0.001
Progesterone receptor status	Positive vs. negative	0.324 (0.256-0.438)	<0.001	0.416 (0.332-0.534)	<0.001
HER2 status	Positive vs. negative	2.342 (1.135-3.876)	0.028	1.654 (0.896-1.853)	0.065
Ki-67 level (mean: 37%)	High>37% vs. low≤37%	3.568 (3.128-5.678)	<0.001	3.136 (2.873-4.564)	0.026
dNLR cut off value	Low≤1.6 vs. high>1.6	1.936 (1.237-2.652)	0.033	1.216 (0.784-1.442)	0.256
PNI cut off value	High>50 vs. low≤50	3.427 (1.452-5.368)	0.01	2.165 (1.256-3.875)	0.044

dNLR: derived neutrophil-to-lymphocyte ratio; PNI: Prognostic Nutritional Index; CI: confidence interval; pCR: Pathological complete response

Discussion and Conclusion

Nowadays, NAC has been used increasingly in the treatment of locally advanced breast cancer and to increase the chance of breast-conserving surgery by decreasing tumor size in operable breast cancer patients. Historically, new agents for breast cancer treatment have been approved primarily in the metastatic process; the agents for the treatment of early-stage breast cancer have been introduced with long-term follow-up of adjuvant studies. The rapid assessment of drug efficacy and the possibility of approval for use increases the importance of NAC. It is very well known that cases achieved pCR with NAC show longer PFS and OS compared with residual cancer after NAC. For this reason primary end point in recent NAC studies is pCR to predict the PFS and OS (15, 16). It is very important to predict the response to NAC and to select the patients benefiting from NAC. However, NAC is not without risk and the danger of progression of the disease while patient receiving Cht and so delay of the surgery are important disadvantages of NAC so some predictive biomarkers have been looked for to determine the response to NAC (17). In this study, we investigated the predictive role of some inflammatory markers on pCR in cases with breast cancer treated by NAC and pre-treatment low dNLR values and high PNI values were found to be predictive for pCR and also we found that PNI was independent factor for pCR while NLR and MHR were not found to be associated with pCR. Recent studies have shown that systemic inflammation plays an important role in tumorigenesis and disease progression and that inflammation can be used as a prognostic marker. Tumor-associated inflammatory determinants contain hematologic and biochemical markers such as leukocytes, neutrophils, lymphocytes, and CA125. Although neutrophils in circulating blood are known to contribute tumor growth and metastasis with tumor inflammatory mediators (arginine, nitric oxide), lymphocytes inhibit tumor progression through immune surveillance (18, 19). NLR and dNLR in recent years are frequently used inflammatory markers used to determine the biology and clinical outcomes in cases with malignant tumors including BC. It has been detected the prognostic value of preoperative NLR and dNLR in cases with BC in a meta-analysis. Preoperative elevated NLR and dNLR has been associated poor prognosis in patients with breast cancer (20). And also NLR and dNLR have similar prognostic importance and have been shown to predict the survival in unselected cancer patient cohorts (21). There are controversial results about the association between NLR and pCR. In one study, NLR was found to be associated with pCR (22), while another study reported that NLR was not associated with pCR (23). While increased dNLR was found to be associated with poor survival in BC patients receiving neoadjuvant chemotherapy (24), its relationship with pCR is uncertain. In our study there was association between dNLR and pCR but no association between NLR and pCR. We do not know the cause of this association but our result may suggest the more predictive role of dNLR than NLR which has been shown in some tumors (25, 26). Circulating monocytes are a source of various inflammatory cytokines. They interact with endothelial cells and platelets and contribute to an increase in inflammation. Monocyte activation is an important step for atherosclerosis. HDL inhibits monocyte activation and migration and prevents its differentiation into macrophages. The combination of monocyte and HDL is a predictive factor for cardiovascular events (27, 28). ApoA1 is a dominant protein component of HDL and carries cholesterol from peripheral tissues to the liver. It has anti-inflammatory, anti-apoptotic and antioxidant functions as well as important immune missions such as regulation of regulatory T cells. Decreased serum levels of this important component of HDL have been associated with poor outcomes in colorectal cancer (29). Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by hyperandrogenism, menstrual cycle disorders, and polycystic ovarian morphology. Inflammation and insulin resistance play an important role, although pathogenesis is not fully elucidated. PCOS is also associated with increased long-term risks for diseases such as type 2 diabetes, atherosclerotic heart disease, and especially endometrial cancer. The role of MHR in the development of metabolic syndrome has been demonstrated in patients with PCOS (30). We wanted to investigate the relationship between MHR and pathological complete response in breast cancer patients receiving neoadjuvant chemotherapy based on the its predictive effect on hormonal disorders such as PCOS and insufficiency of MHR and cancer-related data but we did not find an association between MHR and pCR. This point needs to validate with further studies. PNI is a new prognostic index which is calculated by multiplication of albumin and lymphocyte counts reflecting chronic inflammation and nutritional status in patients with cancer (31). Previously, although it was used to determine the nutritional and immunogenic status of the patients before gastrointestinal surgery, it may be associated with the prognosis of many solid tumors. High PNI has been found to be associated with longer survival in cases with gastrointestinal cancer including stomach, pancreas, esophagus, colorectal, hepatocellular cancer and malignant pleural mesothelioma in a meta-analysis covering 14 studies and 3414 cases (32). PNI is important due to its capacity to reflect the nutritional status of the patient which is very important in cancer patients. The relationship between PNI and NAC has not been investigated so we wanted to see the predictive value of PNI in BC patients treated by NAC and we found that there

was an association between high PNI values and higher rate of pCR. This is the first report about this association and important due to its easy applicability in clinical practice so this finding must be confirmed with other studies. BC is considered a heterogeneous disease classified into molecular subtypes according to their prognostic significance. These subtypes can be classified as luminal A, luminal B, HER2 positive, and triple-negative. We know that BC subtypes show different sensitivities to NAC. It has been shown many times that patients with triple negative and HER2 positive disease have more sensitive to NAC compared with luminal A tumors (33). Higher Ki-67 (34) and hormone receptor negativity have been found to be associated with higher rate of pCR (35). pCR rate in cases treated by anthracycline based chemotherapy is between 20-40% (36) and this rate was 39% in our study group. On the other hand, chemotherapy agents used for NAC have been found to be important for pCR; addition of taxane to anthracycline-containing regimen (37) and addition of trastuzumab to HER2 positive tumors increased pCR rates (38). And also chemotherapy with a dual blockade of trastuzumab and another anti-HER2 agent pertuzumab increased pCR rates in HER2 positive tumors (39). We found higher pCR in cases with HER2 positive tumors, higher Ki67 index and hormone receptor negative tumors and in multiple logistic regression analysis these were independent prognostic factors for pCR. There are some limitations of our study. First, this study was a single-center retrospective study with a relatively small number of 110 patients, which can affect the accuracy of statistical tests. We wanted to separate the subgroups of the BC and to see the prognostic value of these inflammatory markers according to the biology of BC. However we did not make analyses with subgroups due to the relatively limited number of our cases.

The use of NAC in BC, which is the most common cancer in women, is increasing due to its advantages such as increasing the rates of breast-conserving surgery and short-time monitoring of the effectiveness of new drugs. In addition, the fact that the pCR obtained after NAC is associated with long survival increases the interest in markers predicting pCR before NAC. In this study we found that; dNLR and PNI can be useful markers in predicting response to NAC in cases with BC. Simple and easy accessibility is an advantage for their use. However our results need to confirm with larger and other studies.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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