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Research Article

Impact of Neutrophil to Lymphocyte Ratio on Pathological Response to Neoadjuvant Chemotherapy in Nonmetastatic Breast Cancer

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Abstract

Objectives: Recent reports showed an association between tumor progression and systemic inflammatory response. It was suggested that increased neutrophil lymphocyte ratio were associated with reduced pathological complete response rates after neoadjuvant chemotherapy. We aimed to investigate the relationship between pretreatment NLR and pathological response rates in nonmetastatic breast cancer patients who received neoadjuvant chemotherapy.

Methods: We retrospectively reviewed 67 patients who were diagnosed with breast cancer and received neoadjuvant chemotherapy at Kayseri City Hospital. NLR was calculated before neoadjuvant chemotherapy and we determined a cut off value. Low and high NLR were compared according to general characteristics. And the factors that predict complete response analysed using logistic regression analysis.

Results: There were no statistically significant difference among NLR low and high groups according to general characteristics. Both the univariate and multivariate analyses revealed that histological subtype, grade, hormone receptor status, HER2 status were correlated with complete response.

Conclusion: In this study there were no relationship between NLR and pathological complete response rate. As expected we showed that the histological subtype, grade, hormone receptor status, HER2 status were independent markers to predict complete response.

Keywords: Breast cancer, neutrophil-lymphocyte ratio, neoadjuvant chemotherapy

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Breast cancer is the mostly seen cancer in women[1] Neoadjuvant chemotherapy (NAC) is the widely accepted treatment strategy for locally advanced and some early stage breast cancer.[2] Neoadjuvant chemotherapy provides some advantages. Firstly it could led to breast conserving therapy who was unsuitable at diagnosis, secondly decreasing amount of tissue resection so it could give cosmetic advantages.[3] Also neoadjuvant chemotherapy provides positive effects on probability of pathological complete response. Pathological complete response is associated with increased survival.[4]

Recent reports showed an association between cancer progression and systemic inflammatory response.[5-7] Elevated levels of neutrophils is a marker of systemic in-

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flammation. Decreased levels of lymphocyte count is related with inadequate cell mediated immune response.[8] Neutrophil lymphocyte ratio (NLR) is a simple marker of systemic inflammation.[9,10] Recent studies revealed that increased neutrophil lymphocyte ratio leads to reduced pathological complete response rates after neoadjuvant chemotherapy.[11]

In present study we aimed to investigate the relationship between pretreatment NLR with pathological response rates in nonmetastatic breast cancer patients who received neoadjuvant chemotherapy.

Methods

We retrospectively reviewed patients who were diagnosed with breast cancer and received NAC at Kayseri City Hospital. The patients who were stage 4 and who had inflamattory breast cancer were excluded. The patients who had story of chronic disease like chronic cirrhosis and end stage renal disease, chronic inflamattory diseases like systemic lupus eritemtaosis and steroid use were also excluded. We retrospectively reviewed the age, gender, menopausal status, tumor size, histological type, grade, hormonal status, lymph node status, human epidermal growth factor receptor 2 (HER2) status and pretreatment neutrophil lymphocyte counts from the hospital archives. NLR was defined as ratio of absolute neutrophil and lymphocyte count before neoadjuvant chemotherapy.

Estrogen receptor, progesteron receptor and HER2 status studied by immunohistochemical method. If the hormon receptor staining level >1 % in the tumor cells we were categorised as hormon receptor positive. HER2 status were considired positive if the immunochemistry staining of the tumor cells were +3. Also if the HER2 staining was +2 on immunohistochemical testing, flourescence in situ hybridization positivity was regarded as HER2 positive disease.

We evaluated postoperative pathological response rates with Miller-Payne grading system[12] as grade 1 to 5. No invasive tumor on tumor bed and no axillary lymph node were regarded as a complete pathological response.

Neutrophil and lymphocyte count was perfomed before inititaion of neoadjuvant chemotherapy.

NLR was calculated as the ratio of absolute neutrophil and lymphocyte count before initiation of chemotherapy.

NLR was divided into two groups based on the cutoff points 3.64 as NLR high and low (area under the curve: 0.485 (0.336-0.635), sensitivity: 18.20% spesificity: 91.3 %, p=0.843). The cut off value of NLR were performed using ROC curve analysis.

Statistical Analysis

Median, min, max and frequencies were defined for the general characteristics. Chi-square and Fisher's exact test were used for comparision of categorical variables. Mann-Whitney U test were used for comparision of noncategorical variables. We performed univariate and multivariate analysis with the use of logistic regression to determine association of some variables with pathological complete response rate. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses. A p valueof <0.05 was considered statistically significant.

Results

Sixty seven patients were included in our study. All of them were female. Median age was 49 years (32-73) The median age was 30 in NLR low group, 50 in NLR high group. There were no statistically significant difference among NLR low and high groups. All of characteristics were showed in Table 1.

The univariate analysis revealed that histological subtype (95% CI 3.709 p= 0.017), grade (95 CI 4.044, p=0.004), hormone receptor status (95% CI 0.154 p=0.002), HER2 status (95% CI 4.625 p=0.008) were correlated with complete response. We incorporated into multivariate analysis that the statistically significant parameters in univariate analysis. The histological subtype (95% CI 8.613 p= 0.007), grade (95 CI 5.461, p=0.015), hormone receptor status (95% CI 0.188 p=0.031), HER2 status (95% CI 17.622 p=0.002) were correlated with complete response (Table 2).

Discussion

The prognostic value of NLR was studied in numerous cancers previously.[10,13] Previously the NLR was found associated with poor prognosis.[14] In this study we demonstrated that NLR was not a predictive marker to estimate complete response in patents received neoadjuvant chemotherapy. We demonstrated an associaton between histological subtype, grade, hormone receptor status, HER2 status and complate response rate.

Previously reported that the disease stage, axillary lymph node involvement, HER2 status associated with high recurrence rates in breast cancer patients received neoadjuvant chemotherapy.[15] Also residual disease is associated with worse prognosis than the complete response in breast cancer patients received neoadjuvant chemotherapy.[16] There were conflicting reports on the association with NLR and pathological complete response rates in breast cancer patients received neoadjuvant chemotherapy. Eryilmaz et al. reported that there were no association between pretreatment NLR and complete response in breast cancer

Table 1. General Characteristics

	All patients	NLR low group (N,%)	NLR high group (N,%)	P
Age, years (median, min-max)	49 (32-73)	30 (5-90)	50 (32-73)	0.396
Menopausal status				
Premenopause	36 (54)	30 (53)	6 (60)	0.742
Postmenopause	31 (46)	27 (47)	4 (40)	
Histological subtype				
Invazive ductal carcinoma	44 (66)	37 (65)	7 (70)	1
Others	23 (34)	20 (35)	3 (30)	
Stage				
2	45 (67)	39 (68)	6 (60)	0.718
3	22 (33)	18 (32)	4 (40)	0.718
Grade				
1	9 (13)	8 (14)	1 (10)	1
2	28 (42)	23 (40)	5 (50)	0.731
3	30 (45)	26 (46)	4 (40)	1
Surgery				
Breast Conserving	26 (39)	22 (39)	4 (40)	0.086
Mastectomy	41 (61)	35 (61)	6 (60)	
Lymph node status				
N0	6 (9)	5 (9)	1 (10)	1
N1	39 (60)	35 (63)	6 (60)	1
≥N2	20 (31)	17 (28)	3 (30)	1
Hormon receptor positive				
Yes	50 (75)	42 (74)	8 (80)	1
No	17 (25)	15 (26)	2 (20)	
HER2 enrich	19 (28)	16 (28)	3 (30)	1
Pathological response (Miller classification)				
1	7 (10)	7 (12)	0 (0)	
2	13 (20)	12 (22)	1 (10)	
3	16 (24)	11 (19)	5 (50)	
4	10 (15)	7 (12)	2 (20)	
5	21 (31)	20 (35)	2 (20)	
Complete response				
No	45 (67)	36 (63)	8 (80)	0.478
Yes	22 (34)	21 (37)	2 (20)	

patients received NAC.[9] In their study the cut off value of the NLR was 2.33. ROC curve analysis suggested the best NLR cut off value was 3.64 in our study. In another study they demonstrated that the NLR value is not an independent predictive marker for complete response like our study.[17] On the contrary in another study they found an independent association between low NLR and complete response.[18] Quian et al. reported that the high lymphocyte value and low NLR were significantly related with patological complete response rate but in the multivariate analysis NLR didn't remain a predictive marker.[19] In their study they also found that estrogen status, molecular subtype, ki67 proliferation are independent factors to predict complete response. In our study we demonstrated that histological subtype, grade, hormone receptor status, HER2 status were correlated with complete response in both univariate and multivariate analyses Battisti et al. showed a significant relationship between estrogen receptor negativity and pathological response rate.[20] In our study we demonstrated that hormone receptor negativity were correlated approximately 10-fold complete response rates compared with hormone positivity.

Our study had some limitations. Firstly retrospective nature and small number of patients due to single center experience. Due to small sample size the correlation analyses couldn't perform accurately across molecular subgroups

Table 2. Univariate and multivariate analysis

Characteristics	pCR+/N (%)	Univariate analysis	p	Multivariate analyses	p
Age		1.022 (0.978-1.068)	0.933		
Menopausal Status		1.642 (0.588-4.585)	0.344		
Premenopause	10/36 (28)				
Postmenopause	12/31 (39)				
Histological Subtype		3.709 (1.260-10.922)	0.017	8.613 (1.791-41.414)	0.007
Invasive ductal carcinoma	10/44 (23)				
Others	12/23 (52)				
Stage		1.979 (0.371-10.546)	0.424		
2	9/45 (20)				
3	13/22 (59)				
Grade		4.044 (1.550-10.553)	0.004	5.461 (1.390-21.462)	0.015
1	1/9 (11)				
2	5/28 (18)				
3	16/30 (53)				
Lymph node status		3.373 (0.78-14.55)	0.103		
0	1/6 (17)				
1	8/42 (19)				
2-3	13/20 (65)				
Hormon receptor status		0.154 (0.046-0.510)	0.002	0.188 (0.041-0.857)	0.031
Negatif	11/17 (65)				
Positive	11/50 (22)				
HER2 Status		4.625 (1.490-14.353)	0.008	17.622 (2.826-109.894)	0.002
No	11/48 (23)				
Yes	11/19 (58)				
NLR		0.463 (0.09-2.39)	0.357		
Low	20/57 (35)				
High	2/10 (20)				

and NLR low and high groups. Also there was heterogenity in study population according to the molecular subgrups and neoadjuvant chemotherapy regimens.

These results should be performed prospectively in large homogen populations.

Conclusion

In this study we didn't show a relationship between NLR and pathological complete response rate in nonmetastatic breast cancer patients received NAC. As expected we showed that the histological subtype, grade, hormone receptor status, HER2 status were independent markers to predict complete.

Disclosures

Ethics Committee Approval: Kayseri City Clinical Research Ethics Committee granted approval for this study (Date: 22.08.2023, Number: 880).

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Conflict of Interest: None declared.

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