RESEARCH ARTICLE

The Neutrophil to Lymphocyte Ratio has a High Negative Predictive Value for Pathologic Complete Response in Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) is a strong predictor of mortality in patients with pancreatic, colorectal, lung, gastric cancer and renal cell carcinoma. The aim of this study was to determine the relationship between pathological complete response (pCR) and pretreatment NLR values in locally advanced breast cancer (BC) patients receiving neoadjuvant chemotherapy (NACT). Materials and Methods: Datawere collected retrospectively from the Akdeniz University School of Medicine Database for locally advanced BC patients treated with NACT between January 2000- December 2013. Results: A total of 78 patients were analyzed. Sixteen (20%) patients achieved pCR. Estrogen receptor (ER) positivity was lower in pCR+ than pCR- cases (p=0.011). The median NLR values were similar in both arms. The optimum NLR cut-off point for BC patients with PCR+ was 2.33 (AUC:0.544, 95%CI [0.401- 0.688], p=0.586) with sensitivity, specificity, positive predictive value and negative predictive value (NPV) of 50%, 51,6%, 21,1%, and 80%, respectively. Conclusions: This study showed no relationship between the pCR and pretreatment NLR values. Because of a considerable high NPV, in the patients with higher NLR who had luminal type BC in which pCR is lower after NACT, such treatment may not be recommended.

Keywords: Breast cancer - neutrophil to lymphocyte ratio - pathologic complete response - neoadjuvant chemotherapy

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Introduction

Breast cancer (BC) is the most common cancer in women and approximately 20-25 % of the patients-diagnosed with BC is locally advanced (Sinacki et al., 2011). Locally advanced disease includes a subset of patients with clinical stage IIB disease (T3N0) and patients with stage IIIA to IIIC disease. Neoadjuvant chemotherapy (NACT) represents the standard of care for patients with locally advanced BC. The goal of NACT is to induce a tumor response before surgery and enable breast conservation. (Fisher et al., 1997; Kaufmann et al., 2012). Pathologic complete response (pCR) is the most commonly used endpoint in the neoadjuvant study. There is a strong correlation between pCR with improved event-free survival and overall survival (Rastogi et al., 2008; Cortazar et al., 2014).

The inflammatory response plays an important role in the development and progression of the cancer (Coussens et al., 2002). Pre-treatment increased number of peripheral blood neutrophils in patients with cancer is associated with poor surveillance (Schmidt et al., 2007). Unlikely the low lymphocyte count is a negative predictor of cancer survival (Ray-Coquard et al., 2009). Neutrophil to lymphocyte ratio (NLR) is a simple indicator of systemic inflammation. Elevated NLR in patients with BC is an independent factor of poor survival rates. Elevated NLR is associated with a poorer prognosis particularly in the luminal A subtype (ER positive and/ or PR positive and HER2 negative) (Azab et al., 2012; Noh et al., 2013).

In our study, we aimed to determine the relationship between the pCR and pre-treatment peripheral blood NLR in patients who had NACT for locally advanced BC.

Materials and Methods

In this study, we evaluated data's of 110 locally advanced BC patients who received NACT between January of 2000 and December of 2013 at Medical Oncology Department of Akdeniz University Hospital, retrospectively. Patients without pathology report and laboratory test results were excluded. The patients with

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stage IV or inflammatory (T4d) or pregnancy related BC was excluded. The patients who preoperatively diagnosed as any chronic disease such as chronic liver disease, end stage renal disease or any inflammatory disease such SLE were also excluded. Data's of 78 patients were analyzed. The age, menopausal status, pathologic results such as tumor size, histological type, lymph node status, grade, hormonal status, human epidermal growth factor receptor 2 (HER2) receptor status and laboratory data into the Statistical Package for the Social Sciences version 16.0 (SPSS 16.0) from the medical archives retrospectively. NLR was calculated by odds absolute neutrophil count to absolute lymphocyte count in blood sample received before NACT. Patients divided into two groups as pCR+ and pCR-.

To determine the properties of BC patients with pCR+ and pCR-, frequency analysis, two independent samples t test, and chi-square tests were performed. The capacity of NLR in predicting pCR to NACT in patients with BC was analyzed using receiver operating characteristic (ROC) curve analysis. Optimal cut-off values were determined. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were presented. While evaluating the area under the curve, a5% type-I error level was used to accept a statistically significant predictive value of the test variables. Statistical analysis was performed by using SPSS software version 16.0. A p value of < 0.05 was considered significant.

Results

After NACT, of 78 patients 16 (20%) had pCR. The mean age was 48,0±10,3 and 48,3±9,5 for groups with pCR+ and pCR-, respectively (p=0.919). The ratio of premenopausal patients was 58% and 68% for pCR+ and pCR- groups, respectively (p=0.436). There is no difference between groups regarding histological type, clinical T, clinical N stage and grade (p=0.713, p=0.459, p=0.936, p=0.659, respectively). It was significant difference regarding estrogen receptor (ER) positivity between groups and ER positivity was more frequent at pCR- than the pCR+ (p=0.011). The ratio of progesterone receptor (PR) positivity was 53% and 31% for pCR- and pCR+ groups, respectively (p=0.117). HER2 positivity is also more frequent in pCR+ but statistically not significant. (68% *vs* 45% for pCR+ and pCR- groups, respectively, p=0.092). Median NLR values were 2,89 *vs* 2,65 for pCR+ and pCR- groups, respectively, p=0.603). The characteristics of patients with pCR+ and pCR- are summarized Table 1.

Table 1. The Characteristics of Patients with Pathologic Complete Response (+) and (-).

	Patients with pathologic CR (+) (n:16)	Patients with pathologic CR (-) (n:62)	p value
Age(mean-years)	48.0±10.3	48.3±9.5	0.919
Menopausal Status			0.436
Premenopausal	58.10%	68.80%	
Postmenopausal	41.90%	31.20%	
Histologic type			0.713
Invazıv ductal Carcinom	81.20%	85.50%	
Invazıv Lobular Carcinom	0	1.60%	
Ductal+Lobular	6.20%	1.60%	
Other	12.50%	11.30%	
T stage (Clinic)			0.459
T0	0	1.60%	
T1	6.20%	3.20%	
T2	68.80%	50%	
T3	18.80%	19.40%	
T4	6.20%	25.80%	
N stage (Clinic)			0.936
N0	12.50%	19.40%	
N1	43.80%	40.30%	
N2	37.50%	33.90%	
N3	6.20%	6.50%	
Estrogen Positivity	31.20%	66.10%	0.011
Progesteron Positivity	31.20%	53.20%	0.117
CerbB2 receptor Positivity	68.80%	45.20%	0.092
Grade			0.659
Grade1	0	5%	
Grade2	62.50%	60%	
Grade3	37.50%	35%	
NLR (mean)	2.89±2.0	2.65±1.49	0.603

ROC analysis suggested that the optimum NLR cut-off point for BC patients with PCR (+) was 2.33 (AUC:0.544, 95%CI [0.401- 0.688], p=0.586) with sensitivity, specificity, PPV, and NPV of 50%, 51,6%, 21,1%, and 80%, respectively.

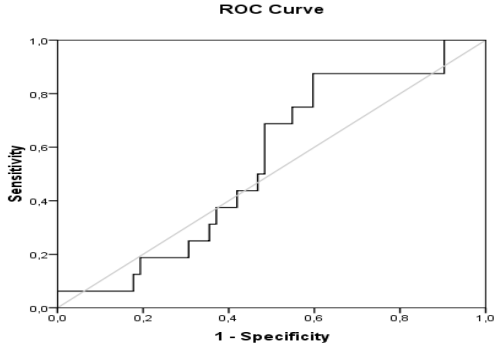

Figure 1. Receiver Operating Characteristic (ROC) Curves

Discussion

This study showed no relationship between the pCR and pretreatment NLR values. The optimum NLR cut-off point in ROC curve analysis was 2.33. The negative predictive value was a considerable high.

Neutrophils and lymphocytes have different roles inflammatory response to cancer. Neutrophils are main sources of circulating angiogenetic and growth factors, which helps the tumor progression whereas lymphocytes dominate host immune response via cytotoxic cell death and cytokines production that inhibit proliferation of tumor cells (Ownby et al., 1983; Strieter et al., 2006). Lymphopenia is an independent prognostic factor for overall and progression-free survival in many cancers (Fogar et al., 2006; Ray-Coquard et al., 2009; Dou X et al., 2013). Elevated NLR has been associated with poor prognosis in many cancers, such as in pancreatic

(Aliustaoglu et al., 2010), colorectal (Ozdemir et al., 2014), lung (Kaya et al., 2013; Unal et al., 2013), gastric (Jung et al., 2011) cancers and renal cell carcinoma (Fox et al., 2013). Elevated NLR at initial clinical presentation of BC was an independent factor for poor survival rate in breast cancer patients. A higher NLR was related with an advanced stage of BC (Azab et al., 2012). Also Luminal A subtype with higher NLR patients showed significantly poor prognosis (Noh et al., 2013). This study is the first to determine whether the pretreatment NLR values are predictive or not for the pCR. There was no significant difference between pCR+ and pCR- for pretreatment NLR values.

pCR was showed to improve the disease-free survival and overall survival compared to those with residual cancer (Hennessy et al., 2005). There were many previous studies demonstrated the predictive factors of pCR to NACT. The histological type was significantly associated with the pathologic response to chemotherapy. pCR to NACT was lower in invasive lobular carcinoma compared with invasive ductal carcinoma (Cocquyt et al., 2003, Cristofanilli et al., 2005). Higher Ki-67 expression is associated with higher pCR rates (Kim et al., 2014). Smaller size tumors were also significant predictors of pCR (Bonadonna et al., 1990). Furthermore, pCR are associated with absence of ER and PR expression, and grade 3 (Colleoni et al., 2004). Compared with luminal a tumors, HER2-overexpression and triple-negative subtypes are more sensitive to NACT (Lv et al., 2011). NACT agents are also important for the pCR. Taxan addition to an anthracycline-containing regimen (Bear et al., 2003) and trastuzumab addition in HER2 positive tumors have been shown to improve the pCR (Buzdar et al., 2005). The association between pCR and long-term outcomes was strongest in patients with triple-negative BC and in those with HER2-positive, hormone-receptor negative tumors who received trastuzumab (Cortazar et al., 2014).

The major limitations of our study were insufficient case quantity and nonstandardised therapies (some patients had antracycline-taxane based, some had hormonal based NACTs and trastuzumab treatment was not administered to all HER2+ patients).

In recently presented a meta-analysis, it was reported that a high NLR is associated with an adverse OS in many solid tumors (Templeton et al., 2014). This study showed no relationship between the pCR and pretreatment NLR values in locally advanced BC who received NACT. But the considerable high negative predictive value of 80% of NLR may be used in clinical decision making. Especially in the patients with higher NLR who had luminal type BC in which pCR is lower after NACT, NACT may be not preferred due to lower pCR. This decision is very important because radical surgery which is most important curative treatment will not delay. As a result, when the other predictive factors are evaluated with NLR, the decision of NACT may be more accurate in patients with locally advanced luminal type BC.

Further studies with greater number of patients should be designed in order to document the real relationship.

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