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Predicting Pathologic Complete Response in Triple Negative Breast Cancer

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ABSTRACT

Pathologic complete response (pCR) has a strong correlation with improved survival in breast cancer. Peripheral blood values such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIV) have prognostic value in triple-negative breast cancer (TNBC). In this study, we aimed to investigate the prediction of pCR by using the peripheral blood values prior to neoadjuvant chemotherapy in triple negative breast cancer.

A total of 102 patients with locally and locally advanced TNBC treated with neoadjuvant chemotherapy (nChT) in four out-patients clinics of medical oncology were included. Hemogram parameters obtained within three weeks prior to neoadjuvant ChT were used. The relationship between pCR and these values was tested with Mann-Whitney U and Student's t test, which were appropriate. Categorical variables were tested by Chi-Squared test.

The median age was 42 years. One third of the patients received carboplatine along with their backbone chemotherapy. Patients who received carboplatine had a higher rate of pCR (65.7% vs. 31.3% of patients with or without carboplatine had pCR, respectively). The median values of NLR, PLR, and LMR were similar in the patients with and without pCR. Similarly, SII and PIV were not able to predict pCR in patients with TNBC who were treated with neoadjuvant ChT.

The addition of carboplatin to the neoadjuvant chemotherapy improved the pCR in TNBC. The pre-treatment peripheral blood values such as NLR, PLR, LMR, SII and PIV values could not predict the pCR.

Keywords: Breast cancer, neoadjuvant treatment, response evaluation, biomarkers

Introduction

Triple-negative breast cancer (TNBC), which accounts for approximately 15-20% of breast cancers, is a heterogeneous, aggressive disease with a high likelihood of early recurrence and distant metastasis(1). TNBC has unique and special characteristics; they tend to inherit gene mutations mainly BRCA 1 /2, most of the TNBC cases have TP53 mutations and, have higher level of tumor infiltrating lymphocytes (TIL) compared to other subtype(2-4). All of these factors contribute to genomic instability and high mutational burden, making TNBC more immunogenic than other subtypes. The tumor microenvironment, which includes immune cells, the extracellular matrix, blood vessels and connective tissue elements, plays a pivotal role in the immunogenicity of the tumor. TNBC has a higher level of neoantigens, leading to an increase in the number of immune cells, especially lymphocytes, which accumulate around the tumor. Higher levels of CD4, CD8 lymphocytes are associated with improved survival outcomes and are predictive of pathologic complete response (pCR) in the neoadjuvant setting.

Pathologic complete response, defined as no residual invasive disease in both breast and axilla after neoadjuvant chemotherapy, strongly correlates with improved breast cancer survival. This correlation has been shown to be greatest in TNBC(5).

Based on the assumption that peripheral blood values can predict intratumor immune status, peripheral blood-derived inflammatory factors such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), systemic inflammatory index (SII), and pan-immune-inflammatory value (PIV) have been extensively studied in various cancers including breast cancer. For example, a low NLR, a high LMR, a low

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PLR, a low SII and a low PIV value are associated with poorer prognosis in breast cancer (6-9).

Since TNBC is an immunogenic subtype and pCR after neoadjuvant chemotherapy predicts better survival, a novel and easily available tool for predicting pCR is imperative. We proposed to find a prediction tool from pre-treatment peripheral cell populations for pCR in TNBC.

Materails and Methods

Triple-negative breast cancer (TNBC) was defined as the lack of expression of the estrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 (HER-2). Medical records from Departments of Medical Oncology, Harran University, Sanliurfa Mehmet Akif Inan Training and Research Hospital, Mardin Training and Research Hospital, Batman Training and Research Hospital, Gaziantep University hospitals database were retrospectively reviewed. A total of 102 patients with locally and locally advanced TNBC who were treated with neoadjuvant chemotherapy (nChT) were included in the study. Clinical information including age at diagnosis, tumor size, lymph node status, grade, and Ki-67 were recorded. Eligible patients were women between 18 and 80 years of age, staged with either PET-CT or computed tomography and bone scintigraphy. Patients were excluded if they had infectious diseases, rheumatological diseases, and chronic liver and kidney diseases. Patients who used antibiotics and corticosteroids within three weeks before neoadjuvant ChT were excluded. The study has been approved by the Ethics Committee of Harran University (number: HRÜ/ 23.02.17, date: 23.01.2023)

Pathologic complete response (pCR) was defined as no invasive carcinoma in the breast and axillary lymph nodes in postoperative specimens. The neoadjuvant cytotoxic chemotherapy regimens that were administered to the patients were recorded. The patients were classified as those with and without pCR. The relationship between pretreatment NLR, LMR, PLR, SII, PIV values and pCR was investigated.

The parameters of the hemogram that were recorded within three weeks prior to neoadjuvant ChT were used. If more than one value was available, the value closest to ChT was selected. NLR was calculated as an absolute ratio of neutrophils to lymphocytes, LMR as a ratio of lymphocytes to monocytes, and PLR as a ratio of platelets to lymphocytes. The systemic immune-inflammation index (SII) was calculated using the formula SII: P x N/L, the pan-immune-inflammation value (PIV) was calculated using the formula PIV: PxNxM/L, where P is the absolute number of platelets, N is the absolute number of neutrophils, M is the absolute number of monocytes, and L is the absolute number of lymphocytes.

Statistical analysis was performed using SPSS version 25.0 statistical software package. Chi-square test was used to examine associations between categorical variables. All numeric variables were tested for distribution using the Kolmogorov-Smirnov test. Student's T-test was used to compare two groups for variables with normal distribution; Mann Whitney U test was used to compare two groups for variables with non-normal distribution. Univariate and multivariate logistic regression analysis was planned to be carried out for the statistically significant results of the Student T test and the Mann-Whitney U test. Normally distributed variables were reported as mean and standart deviation, non-normally distributed variables were reported as median and minimum maximum values. A p value of 0.05 was considered significant.

Results

A total of 102 patients were included in the study. The median age was 42 (23-72) years. Median tumor diameter was 3 cm (1.4-12) cm, and 87.3% (n:86) of patients had clinically positive axillary lymph nodes at the time of diagnosis. As a neoadjuvant chemotherapy, 34.3 % (n:35) of the patients received carboplatin in addition to their backbone chemotherapy regimen. Pathologic complete response (pCR) was seen in 65.7% (n:23) and 31.3% (n:20) of patients with and without carboplatin, respectively (p= 0.001). Patient characteristics are summarized in Table -1.

The median NLR was 2.16 (1.35-20.6) in pCR patients and 2.13 (0.78-20.50) in non-pCR patients (p = 0.3). The median PLR was 138.4 (81-1731) in pCR patients and 138.5 (45.6-2510) in non-pCR patients (p=0.24).

The median LMR was 3.696 (0.2-7.91) in patients with pCR and 4.16 (0.4-20) in patients without pCR (p = 0.11). Median SII values were 643 (283-5818) versus 679 (242-5145) in pCR and non-pCR patients, respectively (p = 0.304). The median PIV value was 365 (133-4247) in patients with pCR and 317 (54-3640) in patients without pCR (p=0.158). All results are presented in Table 2.

Discussions

Pathologic complete response rate is one of the most important primary endpoints in the neoadjuvant

Table 1: Patients Characteristics

Age		
(median-years)	42	(23-72)
Ki-67		
median(min-max)	60	(5-95)
Tumor diameter		
Median (min-max)	3 cm	(1.4-12)
Clinical lymph node	%	n
Positive	83.3 %	(86)
Negative	12.7 %	(13)
Pathological complete response	%	n
Yes	44.1%	(45)
No	55.9%	(57)
Chemotherapy		
AC*+ paclitaxel	52.9 %	(54)
AC*+paclitaxel+carboplatin	31.4 %	(32)
AC*+docetaxel	6.9 %	(7)
Others	8.8 %	(9)

Table 2: Peripheral blood values in pCR and non-pCR patients

	pCR median(min-max)	non-pCR median(min-max)	P
NLR	2.16 (1.35-20.6)	2.13 (0.78-20.50)	p = 0.3
PLR	138.4 (81-1731)	138.5 (45.6-2510)	p=0.24
LMR	3.696 (0.2-7.91)	4.16 (0.4-20)	p = 0.11
SII	643 (283-5818)	679 (242-5145)	p = 0.304
PIV	365 (133-4247)	317 (54-3640)	p=0.158

treatment of breast cancer in clinical trials. Achievement of pCR after neoadjuvant treatment suggests a significant reduction in the risk of recurrence (10) and, death compared to patients without pCR (5). This correlation is greatest in triple negative breast cancer compared to other subtypes (11). TNBC is a heterogeneous and aggressive breast cancer subtype. TNBC consists of more than one subtype, including basal-like, mesenchymal, immunomodulatory, and luminal subtypes. TNBC is more immunogenic than other subtypes. Higher stromal tumor infiltrating lymphocytes (TIL), specific immune activation signatures, higher immunosuppressive genes contribute to TNBC immunogenicity (12). Because of this immunogenicity, immunotherapies have shown benefit in both the neoadjuvant and metastatic settings in patients with TNBC.

Inflammation is part of the tumor microenvironment, inflammatory cells have a role in proliferation, invasion and metastasis. Peripheral blood cells may reflect the microenvironment of the tumor (13). In this study, we investigated the prediction of pathologic complete response using formulas derived from peripheral blood values in patients with TNBC treated with neoadjuvant chemotherapy.

All patients were female and the median age was 42 years. Our patients were younger than in previous studies; for example, the median age in one study was 56 years, and in another study the median age in patients with TNBC was 54 years (14). In our study, carboplatin was used in combination with the ChT backbone in 31.7% of the patients. Patients who received carboplatin had more pCR than patients who did not receive carboplatin (65.7% versus 31.3%, respectively). In one study, the addition of carboplatin increased pCR from 41.5% to 55.2%; in another study, the addition of carboplatin increased pCR from 46% to 60% (15). In our study, the addition of carboplatin nearly doubled the pCR, which is higher than the literature. BRCA wild-type benefit more from carboplatin than BRCA mutants. For example, in the BrighTNess trial, the addition of carboplatin increased the pCR from 29% to 59% in BRCA wild-

type patients, while the increase in BRCA mutant patients was from 41% to 50%. We did not know the BRCA mutation status of our patients; the higher rate of pCR in our patients may be due to BRCA mutation status.

NLR is a prognostic factor in TNBC patients. In a meta-analysis, TNBC patients with higher NLR had poor prognosis (16), in another study and systemic review, patients with TNBC who had higher NLR had bad prognosis. Prediction of pCR after neoadjuvant chemotherapy with NLR is controversial. While some studies have suggested that a low NLR correlates with pCR(10), others found no correlation between NLR and pCR (17). In a systemic review, the authors conclude that NLR was found to be an independent prognostic factor, while no significant correlation was found between pCR and NLR (18). Similar to this systemic analysis, in our study, we found no correlation between pCR and NLR. Patients with or without pCR had similar median NLR values.

PLR has been suggested to reflect the overall immune status of the patient; for example, a positive correlation between PLR and tumor infiltrating lymphocytes has been reported in patients with TNBC. In a meta-analysis that included 3741 patients with breast cancer, a high PLR value was found to be associated with a poor survival outcome (19). There is also evidence that high PLR may be associated with lymph node involvement and distant metastasis. In one study, no significant association was found between pCR and PLR in patients with TNBC,(20) in another study, the lower PLR group had higher pCR than the higher PLR group in TNBC patients (21). In our study, we found that the median value of PLR was similar in both pCR and non-pCR TNBC patients treated with neoadjuvant chemotherapy. TNBC is a heterogeneous disease with distinct subtypes. Each subtype has unique characteristics and immunogenicity. We did not know which subtype was prominent in our sample and the discordance with the literature may be due to the different dominant subtype in our study.

LMR is another peripheral blood-derived formula; in one study, increased LMR was associated with better prognosis in TNBC (7), in a meta-analysis, low LMR was found to be associated with poor prognosis in solid tumors consisting of breast cancer. For predicting pCR, in one study, low LMR had worse prognosis, but no correlation was found between LMR and pCR in patients with breast cancer. In another study, even low LMR was not associated with pCR in the breast, the axillary pCR was found in 44.9% of the low LMR group while in the high LMR group 29.9% of patients had pCR (p = 0.003) (22). In our study, we found that patients with or without pCR had a similar median LMR value (3.96 versus 4.16 p = 0.11) In our study, we did not measure prognosis. However, although low LMR may reflect poor prognosis in breast cancer, in TNBC, LMR did not reflect pCR.

The SII may be a better reflection of the balance of the host's immunity and inflammatory status because it includes the neutrophil, platelet, and lymphocyte counts. High SII is associated with poor overall survival in patients with TNBC (44.2 months vs. 82.4 months of OS in the high SII group vs. the low SII group, respectively) (23). In a meta-analysis consisting of 2642 patients with breast cancer showed that patients with a high SII level had worse survival.(9) In a study of patients with TNBC treated with neoadjuvant ChT, 15.7% of patients with low SII and 6% of patients with high SII had a pCR (p= 0.019) (24). In our study, the median SII value is similar in both pCR and non-pCR patients. Generally, about 40-50% of all TNBC patients achieve pCR after neoadjuvant ChT, in our study 44% of patients achieved pCR, while in the above study small number of patients achieve pCR. This could result from heterogenity of disease as well as drugs used in neoadjuvant setting. Even though, according to the above study, it can be suggested that the low SII may be related to the pCR, the low rate of pCR raise suspicious about the result.

Pan-immune inflammation value (PIV) is a novel, easily accessible and comprehensive biomarker calculated from neutrophils, lymphocytes, monocytes and platelets. PIV is prognostic in breast cancer, in patients with metastatic triple negative breast cancer, higher PIV value is associated with worse survival outcome (25). In a study of 743 patients with breast cancer, a low level of PIV was found to be associated with pCR (8). In our study we found no correlation with PIV and pCR in triple negative cancer. This difference may result from two study population, in former study all subtypes of breast cancer patients were included , in our study we just included triple negative breast cancer. The number of patients in that study was higher than in our study, which may also contribute to the difference.

Our study has some limitations, the retrospective design may have caused unanticipated bias. A total of 102 patients included in the study, although all patients have triple negative breast cancer, perhaps large prospective study may be more conclusive. We only measure peripheral blood values before the start of treatment. Tumor microenvironment should be examined along with peripheral blood values to find out the relationship.

In conclusion, triple-negative breast cancer is a heterogeneous and immunogenic subtype of breast

cancer. Pathologic complete response is a surrogate endpoint in the neoadjuvant setting that predicts survival. Peripheral blood derivatives are easily accessible and may reflect the tumor microenvironment. In this study, we found that NLR, PLR, LMR, SII and PIV levels did not predict pCR in patients with TNBC.

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