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Prognostic importance of peripheral blood parameters in HER-2 positive metastatic breast cancer treated by pertuzumab, trastuzumab and docetaxel

Tolga Köşeci[1]*, Polat Olgun[2], Serdar Ata[1], Ertuğrul Bayram[3], Mehmet Ali Sungur[4], Kadir Eser[1], Berna Bozkurt Duman[1], Timuçin Çil[1]

1 Dept of Medical Oncology, University of Health Science, Adana City Teaching and Research Hospital, Adana,TR
2 Dept of Medical Oncology, University of Near East ,Cyprus
3 Dept of Medical Oncology, Çukurova University Hospital, Adana, TR
4 Dept of Biostatistics and Medical Informatics, Faculty of Medicine, Düzce University, Düzce, TR

*** Corresponding Author:** Tolga Köşeci **E-mail:** drtolgakoseci@gmail.com

ABSTRACT

Objective: There are some studies about the significance of the peripheral blood parameters in breast cancer. However, there is very few studies about prognostic importance of peripheral blood parameters in human epidermal growth factor-2 receptor (Her-2) positive breast cancer. We aimed to evaluate whether prognostic significance of peripheral blood parameters in patients Her-2 positive metastatic breast cancer with treated Pertuzumab, Trastuzumab, Docetaxel (PTD)

Material and Methods: We included 56 patients with Her-2 positive metastatic breast cancer patients who were treated with PTD. We recorded patients' clinical,demographic features and we obtained peripheral blood parameters such as neutrophil-lymphocyte ratio (NLR), red blood cell distribution (RDW), mean platelet volume (MPV), lymphocyte, neutrophil after the sixth cycle of the treatment and before the treatment. We separated the patients into two groups depending on the progression status. Progression-free survival was analyzed by Kaplan-Meier statistical analysis.

Results: Patients mean age was 50.7. Progression was detected in 34 patients. When we explored and compared hemogram parameters in the groups before the treatment, there wasn't statistically any significant difference between these parameters such as neutrophil, lymphocyte, neutrophil to lymphocyte ratio, mean platelet volume, red blood cell width. In the progressive group;,while pretreatment NLR was 3.83, it was detected 2.72 after six cycle treatment and difference was meaningful (p: 0.043). The pretreamtent MPV was 8.63, and It was 8.15 after six cycle treatment, and difference between these counts was statistically important (p: 0.006). PFS was 18.0 months in the study group.

Conclusion: Peripheral blood parameters were not statistically significant in both group comparisons. In the progression group, the difference between NLR and MPV count was statistically significant after the sixth cycle of the treatment and before the treatment.

Keywords: Breast cancer, Her-2, Pertuzumab, progression

INTRODUCTION

Breast cancer is heterogenous disease, and human epidermal growth factor-2 receptor (Her-2) overexpression approximately occurs in ratio 15-20% in metastatic breast cancer. That survival of patients was longer were detected as a result of development in the treatment of Her-2 positive metastatic breast cancer (1). Pertuzumab and Trastuzumab are anti-Her-2 monoclonal antibody. In the CLEOPATRA study, Pertuzumab,Trastuzumab were applied to patients with Docetaxel, and that this combination treatment was effective was demonstrated in this trial (2). These two drugs prevent Her-2 dimerization with other epidermal growth factor family receptors such as Her-3, Her-4, and these drugs demonstrate activity via hamper the signaling. In addition to, Anti-Her 2 antibodies are thought to mediate tumor regression not only by interrupting oncogenic signaling, but also by inducing antibody-dependent cell-mediated cytotoxicity (ADCC) (3).

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That inflammation is important in cancer progression is known. That many cancer may develop as a result of inflammation and chronic irritation due to infection is known. We may easily obtain some inflammatory markers from the peripheral blood samples. These markers have been shown to have prognostic significance in various solid tumors. (4,5). However, there are insufficient studies about inflammatory markers in patients using dual anti-Her-2 blockage treatment.

The aim of the present study was to investigate whether there was any prognostic significance of hemogram parameters in patients with Her-2 positive metastatic breast cancer receiving Trastuzumab, Pertuzumab and Docetaxel.

MATERIAL and METHODS

Fifty-six patients who got diagnosed Her-2 positive metastatic breast cancer were enrolled to this study. Data of the patients were collected retrospectively. Neutrophil lymphocyte ratio, red blood cell distribution, mean platelet volume, lymphocyte, neutrophil were recorded than the patients blood sample after the sixth cycle of the treatment and before the treatment. The neutrophil lymphocyte ratio was calculated by subdividing neutrophil to lymphocyte. Patient age, tumor location and tumor histology were determined from the patients file. Metastasis sides, SUV max value of metastatic lesion and primary tumor SUV max value in the PET-CT which was used for staging of the disease, were recorded. Moreover, tumor grade, Ki-67 proliferation index and hormon receptor status were obtained. The histopathological diagnosis to patients was made with a biopsy taken from the mass formed in the breast. Her-2 status was confirmed with an immunohistochemical score (IHC) of 3 (positive), and in situ hybridization test was used for those with a score of 2 according to the guidelines of the American Society of Clinical Oncology/College of American Pathologists for Her-2 testing in breast cancer (6). If there were at least 1% positive tumor cell nuclei in the sample that was evaluated by IHC, we accepted hormone receptor-positive. Patients who had kidney and liver disease got treatment for meastatic disease before the study, had a chronic infection or active infection disease, got immunosuppressive therapy and under 18 age were not included to this study. Progression-free survival (PFS) was defined as the time from pertuzumab treatment to either first disease progression or death. All patients were fully informed and approved by the ethics committee of date of 06.05.2020 and 848 decision no from Adana City Training and Research Hospital

Statistical analysis: Continuous variables were summarized in mean and standard deviation, while categorical data were summarized as frequency and percentage. Chi-square test was used to evaluate bivariate associations between categorical variables. Independent samples t test was used to compare two groups while Repeated Measures ANOVA was used to analyze the interaction effect of progression and treatment periods. Continuous variables obtained before and after treatment were compared with Paired samples t test, in each group. Life table and Kaplan-Meier curve were used to evaluate progression free survival. Statistical significance level was considered as 0.05, and statistical analyses were done by SPSS v.20 statistical package.

RESULTS

The mean age of the patients was 50.7. While estrogen receptor status was positive in 35 patients, ıt was negative in 21 patients. Progesterone receptor status was positive in the 26 patients. Her-2 results of 40 patients were detected positive by immunohistochemical method. Her-2 score was 2(+) in 16 patients and that Her-2 positivity was detected by the FISH method. The number of the patients who had grade II and III tumors was equal the each other. While the primary tumor SUV value was 10.2, metastasis SUV value was 9.9. The progression was detected in the 34 patients. The visceral metastasis ratio was 66 %. The most common visceral metastasis sides were lung and liver. There was no progression in the 22 patients. Demographic and clinical features were summarised in the **Table-1**.

We separated the patients into two groups depending on progression status. The mean age was 48.2 in patients having progression, It was 54.8 in patients not having progression (p:0.085). While estrogen receptor positivity was 50 % in the progressive group, It was 63.6% in the non-progressive group. The 18 patients' tumor grade was grade 2 , 16 patients were grade 3 in the progressive group. In the non-progressive group, tumor grade was only grade 2 in 10 patients and grade 3 in 12 patients, respectively. Ki-67 proliferation index was similar in the both group. Primary tumor SUV max value was alike in the both group(SUV max:10.3, in the progressing group, SUV max: 9,6 in non-progressive group, respectively). When we explored and compared hemogram parameters in the groups before the treatment, there wasn't statistically any significant difference between these parameters such as neutrophil, lymphocyte, neutrophil to lymphocyte ratio, mean platelet volume, red blood cell width. These results are summarized in the **Table 2**.

Patients' hemogram parameters before treatment and after six cycle treatment were compared. In the progressive group; while pre-treatment NLR was 3.83, ıt was detected 2.72 after six cycle treatment, and the difference was meaningful (p: 0.043). The pre-treatment MPV was 8.63, and It was 8.15 after six cycle treatment and difference between these count was statistically meaningful (p: 0.006). The pre-treatment RDW was 15.04 , it was determined 17.61 after treatment and the difference was meaningful (p: <0.001). Patients without progression, while pre-treatment NLR was 3.35, ıt was detected 2.71 after six cycle treatment and the difference wasn't meaningful (p: 0.163). The pre-treatment MPV was 8.54, and It was 8.28 after six cycle treatment and the difference between these counts wasn' t meaningful (p: 0.164). The pre-treatment RDW was 15.08, It was determined 17.29 after treatment and the difference was meaningful (p: 0.014). These results were summarized in **Table 3**.

Progression-free survival was detected 18.0 months and it was shown in **Figure-1.**

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Table 1: Demographics and baseline characteristics of patients

Charecteristics	n:56
Age	50.7
Estrogen receptor	
Pozitif	31(.% 55.3)
Negatif	25 (% 44.7)
Progesterone receptor	
Pozitif	26 (% 46.4)
Negatif	30 (%53.6)
Her-2 IHC status	
2(+) with FISH pozitif	16 (%28.5)
3(+)	40 (%71.5)
Grade	
II	28 (% 50)
III	28 (% 50)
Metastasis side	
Visceral	37 (%66)
Non visceral	19 (%34)
Primary SUV	10.2
Metastasis SUV	9.95
Progression	
Present	34 (% 60.7)
Absent	22 (% 39.3)

Table 2: Patients features depending on progression status

	Progression present (n=34)	Progression absent (n=22)	p
Age	48,26±12,87	54,81±14,34	0,085
Estrogen receptor			
Positive	17 (%50,0)	14 (%63,6)	0,316
Negative	17 (%50,0)	8 (%36,4)	
Progesterone receptor			
Positive	16 (%47,1)	10 (%45,5)	0,906
Negative	18 (%52,9)	12 (%54,5)	
Her-2 IHC status			
2(+) with FISH pozitif	9 (%26,5)	7 (%31,8)	0,665
3(+)	25 (%73,5)	15 (%68,2)	
GRADE			
II	18 (%52,9)	10 (%45,5)	0,584
III	16 (%47,1)	12 (%54,5)	
Ki-67 proliferation index	35,12±23,02	34,41±20,89	0,908
Primary SUV	10,34±4,07	9,60±4,87	0,563
Metastasis SUV	10,67±5,22	8,86±5,26	0,212
Pretreatment neutrophil	5638,24±2237,43	5609,09±2805,42	0,966
Pretreatment lymphocyte	1843,53±826,10	1881,82±770,68	0,863
Pretreatment NLR	3,84±2,55	3,35±1,82	0,438
Pretreatment MPV	8,66±1,39	8,54±0,98	0,727
Pretreatment RDW	15,12±3,11	15,08±3,02	0,966

NLR; neutrophil to lymphocyte ratio, MPV; mean platelet volüme, RDW; red blood cell distributio**n**

Table 3: Hemogram parameters

	Progression present (n=34)	p value	Progression absent (n=22)	p value
Pretreatment neutrophil	5557,58±2221,35	0.083	5609,09±2805,42	0.486
[a]Posttreatment neutrophil	4762,12±1942,89		5168,18±1911,22	
Pretreatment lymphocyte	1838,79±838,44	0.234	1881,82±770,68	0.399
Posttreatment lymphocyte	2011,82±662,44		2031,82±523,16	
Pretreatment NLR	3,83±2,59	**0.043**	3,35±1,82	0.163
Posttreatment NLR	2,72±2,03		2,71±1,35	
Pretreatment MPV	8,63±1,40	**0.006**	8,54±0,98	0.164
Posttreatment MPV	8,15±0,95		8,28±0,92	
Pretreatment RDW	15,04±3,10	**<0,001**	15,08±3,02	**0,014**
Posttreatment RDW	17,61±2,70		17,29±3,24	

NLR; neutrophil to lymphocyte ratio, MPV; mean platelet volüme, RDW; red blood cell distribution

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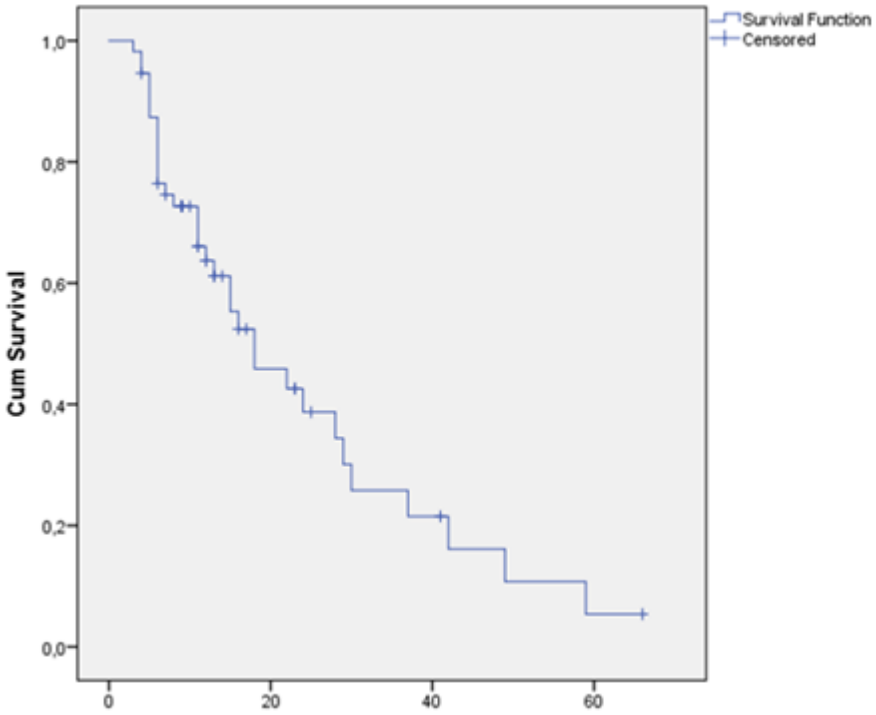

Figure 1: Progression-free survival (18.0 months)

DISCUSSION

Her-2 overexpression approximately occurs 15-20 % in the breast cancer. The breast cancer with overexpression HER-2 has a poor prognosis (7). However, better results were obtained, in study which is called CLEOPATRA, in Her-2 positive metastatic breast cancer via dual blockage with Pertuzumab and Trastuzumab which target the Her-2 (8). Median PFS was detected 18.5 months in the CLEOPATRA study. PFS was 18 months in the our study.

Hormone receptor positivity may accompany in Her-2 positive breast cancer. Hormone receptor positivity was 47 % in patients who were included to CLEOPATRA study (8). In another study which was performed by Esin et al, they published Pertuzumab real real life practice in metastatic patients with Her-2 positivity and they have detected 58.7 % hormon receptor positivity (9). The study was done by Araki et al, hormone receptor positivity was 45 % in Her-2 positive metastatic breast cancer (10). Hormon receptor positivity was ascertained 65.1 % in the study which was performed by Trıpathy et al (11). It was 55.3 % in our study. These results show that these ratios may change from center to center.

Her-2 positive status was confirmed centrally, by means of immunohistochemistry (with 3+ indicating positive status) or fluorescence in situ hybridization (with an amplification ratio ⩾2.0 indicating positive status) (12). Her-2 receptor positivity ratio with immunohistochemistry was 78 % in the study which was performed Araki et al (10). This ratio was detected 87.1 % in the CLEOPATRA study (8). Her-2 receptor positivity ratio with immunohistochemistry was 71.4% in the our study.

The different PFS ratio were seen in distinct studies in patients using Pertuzumab, Trastuzumab because of de novo Her-2 positive metastatic breast cancer.

While the median PFS was 18.5 months in the CLEOPATRA study (8), It was determined 28.5 months in the study which was performed by Esin et al. (9). PFS was 17.7 months in the study which was performed by Trıpathy et al (11). It was 18 months in the our study.

Advanced breast cancer comprises inoperable locally advanced breast cancer, which has not spread to distant organs, and metastatic (stage IV) breast cancer; common sites of spread are bone, the lungs and the liver (13). The most common metastasis sides were lung and liver in our study. Currently, it is a treatable but virtually incurable disease, with metastases being the cause of death in almost all patients, and a median overall survival of 2–3 years. Patients with metastatic breast cancer receive treatments that aim to relieve their symptoms and to prolong quality-adjusted life expectancy . The visceral metastasis more commonly observe in Her-2 positive breast cancer compared to luminal subtypes breast cancer. While Visceral metastasis ratio was 37 % in study that Araki et al were performed (10), It was determined 78.1 % in the CLEOPATRA study (8). Visceral metastasis ratio was 66 % in the our study .

The association between cancer and inflammation are shown distinct studies. Inflammation facilitates tumor development and metastasis (14). That some inflammatory markers are related the poor prognosis was shown in breast cancer (15).There are some studies about peripheral blood parameters for predictive the progression Her-2 positive breast cancer. In the study, including fifty-one patients with Her-2 positive metastatic breast cancer, patients were treated with Pertuzumab, Trastuzumab and systemic chemotherapy. They seperated patients two group according to lymphocyte count.

Patients with high lymphocyte count had longer PFS compared to with low lymphocyte count (10). Another study was performed by Ulas et al in the early stage Her-2 positive breast cancer. This study included 187 patients and median disease free survival was shorter in the high NLR than in the low NLR group, the difference was not statistically significant. In our study, we separated the patients depending on the progression status, and there wasn't a statistically significant difference between two groups peripheral blood parameters such as neutrophil, lymphocyte, neutrophil to lymphocyte ratio, mean platelet volum and red blood cell distribution.

CONCLUSION

Our PFS result was similar with CLEOPATRA study. However, we didn't detect differences in hemogram parameters between groups. Nevertheless, to affirm the prognostic importance of hemogram parameters in these patient populations, large-scale, multi-center, and prospective studies are warranted in the future

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

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