

Factors affecting disease-free survival in patients with human epidermal growth factor receptor 2-positive breast cancer who receive adjuvant trastuzumab

SEYDA GÜNDÜZ¹, SEMA SEZGIN GÖKSU¹, DENİZ ARSLAN¹, ALI MURAT TATLI¹,
MÜKREMIN UYSAL¹, UMUT RIZA GÜNDÜZ², MERT MAHSUNI SEVINÇ³,
HASAN SENOL COŞKUN¹, HAKAN BOZCUK¹, HASAN MUTLU¹ and BURHAN SAVAS¹

¹Department of Medical Oncology, Akdeniz University Faculty of Medicine, Antalya 67070;

²Department of Surgery, Antalya Research and Training Hospital, Antalya 07070;

³Department of Surgery, Istanbul Research and Training Hospital, Istanbul 34000, Turkey

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Abstract. Breast cancer is the most frequently diagnosed cancer in women worldwide and the second cause of cancer-related mortality. A total of 20-30% of patients with early-stage breast cancer develop recurrence within the first 5 years following diagnosis. Trastuzumab significantly improves overall survival and disease-free survival (DFS) in women with human epidermal growth factor receptor 2 (HER2)-positive early and locally advanced breast cancer. This study aimed to determine the factors that affect DFS following adjuvant trastuzumab therapy. A total of 62 patients treated with trastuzumab for early and locally advanced breast cancer were included in our study. Data, including pathology, treatment and treatment outcome, rate of recurrence and laboratory tests, were retrospectively collected. There was no significant association between DFS and age, menopausal status, disease stage and hormone receptor status. The median follow-up was 48.4 months. The median DFS of patients treated with adjuvant trastuzumab was 64.1 months. In addition, the median DFS was 44.3 vs. 66.8 months in patients with platelet-lymphocyte ratio (PLR) ≤ 200 vs. >200 , respectively (log-rank test; $P=0.001$), and 70 vs. 45 months in patients with eosinophil count ≤ 70 vs. $>70 \times 10^3/\text{mm}^3$ (log-rank test; $P=0.001$). Our data revealed the prognostic relevance of a decrease in the peripheral blood eosinophil count and PLR value following trastuzumab therapy in breast cancer. PLR and eosinophil count measurements are cost-effective, readily available worldwide, non-invasive and safe. Combined with other markers, such as patient age, tumor stage and tumor histology, may be effectively used for patients with breast cancer.

Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide and the second leading cause of cancer-related mortality, accounting for 23% of the total new cases of cancer (1.38 million) and 14% of the total cancer deaths (458,400) (1).

Breast cancer recurrence usually occurs within the first 5 years following diagnosis, with the majority of these recurrences being hormone receptor-negative or human epidermal growth factor receptor 2 (HER2)-positive. In certain cases, relapse may occur after 5 years, which is more common in cases of hormone receptor-positive cancer with indolent disease and HER2-negative cancer. A retrospective study evaluating 2,838 cases reported that the 5-year recurrence risk for patients with stage I, II and III breast cancer receiving adjuvant therapy was 7, 11 and 13%, respectively (2,3).

T cells are known to play a critical role in tumor immune surveillance. Although the role of immune response in breast cancer has yet to be fully elucidated, certain studies reported that chemotherapy contributes to overall treatment response by stimulating the immune response. Antibody-dependent cellular cytotoxicity plays an important role in the mechanism of action of trastuzumab and peritumoral lymphocyte infiltration has been found to be associated with improved response and survival rates in antineoplastic and trastuzumab therapy (4-7).

Platelets play a balancing role in health and disease and are the origin of active metabolites and proteins. Platelets release growth factors, such as platelet-derived growth factor, platelet factor 4, transforming growth factor β and vascular endothelial growth factor, which may stimulate tumor growth and angiogenesis. The association of poor prognosis and the increase in white blood cells, platelets, or their ratio may be explained through an inflammatory process evoked by cancer cells (8,9).

The aim of this study was to retrospectively examine the survival data of breast cancer patients who received adjuvant trastuzumab and determine the prognostic value of different peripheral blood parameters in association with disease-free survival (DFS).

Correspondence to: Dr Seyda Gündüz, Department of Medical Oncology, Akdeniz University Faculty of Medicine, Antalya 07070, Turkey

E-mail: drsgunduz@gmail.com

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Patients and methods

Patients. A total of 62 patients treated at the Akdeniz University Hospital between January, 2008 and August, 2010, who received adjuvant trastuzumab for early and locally advanced breast cancer, were retrospectively reviewed.

The study was approved by the Akdeniz University Clinical Research Ethics Committee.

Statistical analysis. Statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). DFS was defined as the time period between initial diagnosis and detection of the first tumor recurrence based on radiological criteria. Survival was analyzed by the Kaplan-Meier method and the univariate Cox regression analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. A descriptive analysis was presented using means and standard deviations for normally distributed variables [platelet-lymphocyte ratio (PLR) measurements]. Variables with a P-value of <0.10 in the univariate analysis were also evaluated by multivariate analysis. A P-value of <0.05 was considered to indicate statistically significant differences.

PLR. Prior to treatment, PLR was calculated as the platelet count divided by the lymphocyte count. Using a number of different cut-off points, a PLR of 200 was found to represent the optimum stratification point at which the survival difference between two groups was maximized.

Results

Patient, disease and treatment characteristics. In this study, we evaluated the data of 62 patients diagnosed with breast cancer. The study group consisted of all patients diagnosed with breast cancer between January, 2008 and August, 2010. The median follow-up period was 48.4 months. The median age of the patients was 52 years (range, 24-73 years).

As regards menopausal status, 26 (41.9%) of the patients were premenopausal and 36 postmenopausal (58.1%). A total of 75.8% of the patients underwent modified radical mastectomy. The majority of the tumors were invasive ductal carcinomas (77.4%). At the time of diagnosis, 11.1% of the patients had stage I, 53.2% had stage II and 33.9% had stage III disease. Adjuvant chemotherapy included anthracyclines and taxanes in 96.8% of the cases (Table I).

A total of 22 patients (35.5%) developed metastasis after diagnosis, with 18 (29%) of the patients developing distant and 4 (6.5%) local metastasis, whereas 3 (4.8%) patients developed brain metastasis (data not shown).

Survival analysis. The median follow-up period was 48.4 months and the patients had a median DFS of 64.1 months.

There were no significant associations between DFS and age, menopausal status, stage or hormone receptor status. The univariate analysis revealed that DFS was significantly affected by tumor grade [P=0.086 (95% CI for HR: 0.96-1.62)], PLR [P=0.021 (95% CI for HR: 1.33-4.16)] and eosinophil count [P=0.029 (95% CI for HR: 1.03-1.91)]. However, eosinophil

Table I. Baseline characteristics of breast cancer patients.

| Characteristics | Patient no. (%) (n=62) |
|--|---------------------------|
| Age, years | |
| Median | 52 |
| Range | 24-73 |
| Stage | |
| I | 7 (11.3) |
| II | 33 (53.2) |
| III | 21 (33.9) |
| Missing | 1 (1.6) |
| Menopausal status | |
| Premenopausal | 26 (41.9) |
| Postmenopausal | 36 (58.1) |
| Tumor type | |
| Ductal invasive | 48 (77.4) |
| Lobular invasive | 14 (22.6) |
| Tumor grade | |
| I | 6 (9.7) |
| II | 25 (40.3) |
| III | 30 (48.4) |
| Missing | 1 (1.6) |
| Hormone receptor status | |
| Positive | 35 (56.5) |
| Negative | 27 (43.5) |
| Chemotherapy regimens | |
| FAC ^a -docetaxel | 46 (74.2) |
| FEC ^b -docetaxel | 9 (14.5) |
| TAC ^c | 6 (9.7) |
| CMF ^d | 1 (1.6) |
| Operation | |
| Breast conserving surgery | 15 (24.2) |
| Modified radical mastectomy | 47 (75.8) |
| Baseline eosinophil count, x10 ³ /mm ³ | |
| Median | 70 |
| Range | 10-680 |
| Baseline PLR | |
| 200≥ | 36 (58.1) |
| 200< | 26 (41.9) |

^aFluorouracil, doxorubicin, cyclophosphamide. ^bFluorouracil, epirubicin, cyclophosphamide. ^cDocetaxel, doxorubicin, cyclophosphamide. ^dFluorouracil, methotrexate, cyclophosphamide. PLR, platelet-lymphocyte ratio.

count [P= 0.017 (95% CI for HR: 1.23-8.69)] retained significance with multivariate analysis.

The median DFS was 44.3 vs. 66.8 months in patients with PLR ≤200 vs. >200 (log-rank test; P=0.001) (Fig. 1) and 70 vs. 45 months in patients with eosinophil count ≤70 vs. >70x10³/mm³ (log-rank test; P=0.001) (Fig. 2).

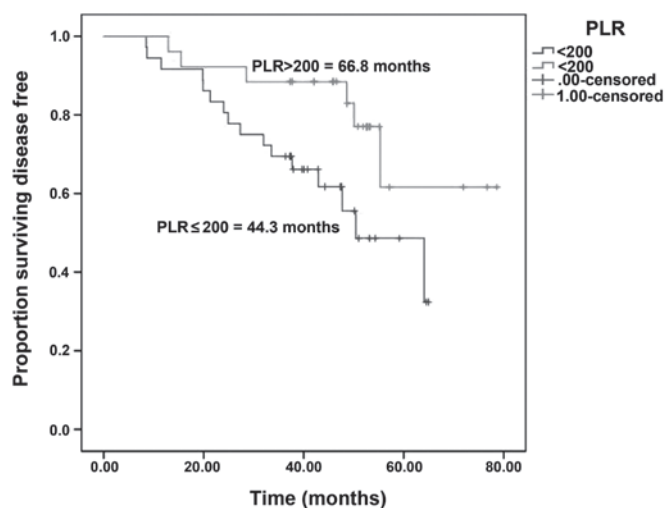


Figure 1. Disease-free survival in patients with platelet-lymphocyte ratio (PLR) ≤ 200 vs. >200 .

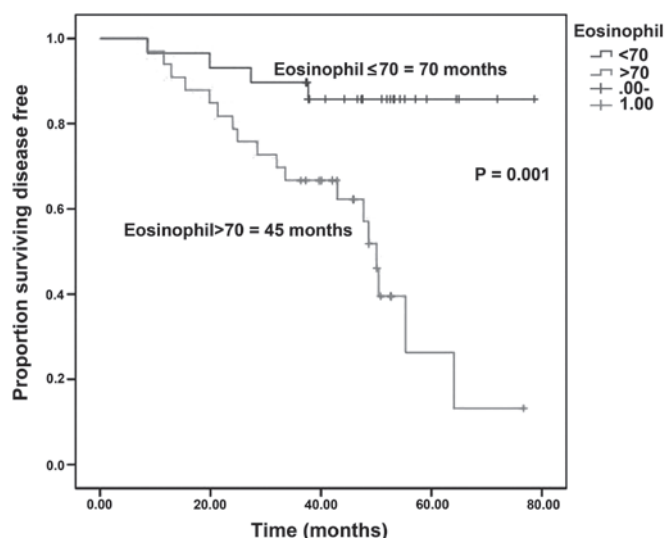


Figure 2. Disease-free survival in patients with an eosinophil count of ≤ 70 vs. $>70 \times 10^3/\text{mm}^3$.

Discussion

To the best of our knowledge, this study is the first to demonstrate the significance of PLR and eosinophil count in breast cancer patients receiving adjuvant trastuzumab therapy.

Blood markers such as PLR and eosinophil count are simple, rapidly available laboratory markers. A previous study, including $>25,000$ patients, demonstrated the significance of inflammatory markers in the prediction of the outcome of various types of cancer (10). Feng *et al* found that PLR is associated with tumor progression and may be considered as an independent marker of poor prognosis in patients who undergo esophagectomy for esophageal squamous cell carcinoma without neoadjuvant or adjuvant treatment (11). Certain studies demonstrated that the presence of pretreatment lymphopenia is associated with poor cancer survival or tumor response and it has not only prognostic, but also predictive potential (12-14). In a study conducted by

the Radiation Therapy Oncology Group, lymphopenia and hormone receptor negativity were found to be independent prognostic factors indicating poor survival in breast cancer patients with brain metastases (15). A more recent study conducted by the same group concluded that lymphocyte count and LDH levels may predict overall survival (16). Peritumoral lymphocyte infiltration in trastuzumab therapy is known to enhance treatment response and survival (7). Combination chemotherapies were shown to reduce peripheral lymphocyte count in cancer patients. These findings suggest that treatment-induced lymphopenia may be associated with an increased tumor response (17). In our study, we demonstrated that patients with PLR >200 and eosinophil count $<70 \times 10^3/\text{mm}^3$ exhibited better DFS rates.

In early-stage breast cancer, the recurrence rate varies between 20 and 30%. Trastuzumab therapy is known to significantly reduce recurrence and mortality, with a 50% reduced risk of breast cancer recurrence and 30% improved survival rate. In patients with HER2-overexpressing early-stage breast cancer treated with trastuzumab-based therapy, the most common location for disease progression is the isolated central nervous system (18-20). This has been associated with the inability of trastuzumab to penetrate the blood-brain barrier or the brain-metastatic breast tumor cells losing the expression of HER2; it may also be explained by the overall effectiveness of trastuzumab in disease control, except in the central nervous system (21). In our study, 35.3% of our patients receiving adjuvant trastuzumab therapy developed recurrence. Of these patients, 3 (6.3%) developed isolated brain metastases. The respective percentage was 2.56% in the study conducted by Olson *et al* (21).

When recurrence of breast cancer is diagnosed, the initial evaluation should include hormone receptor status, DFS, age and menopausal status. Previous research in this field has demonstrated that estrogen and progesterone receptor status are independent predictors of survival after the first recurrence (22). While Clark *et al* (23) and Insa *et al* (24) found that these were independent predictors of patient survival following relapse, Koenders *et al* (25) found no such association. In our study, we observed no correlations between hormone receptor status, menopausal status and disease-free survival.

In conclusion, PLR and eosinophil count are cost-effective, readily available worldwide, non-invasive and safe and, when combined with other markers, such as patient age, tumor stage and tumor histology, may be effectively used for patients with breast cancer.

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