

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

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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).

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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).

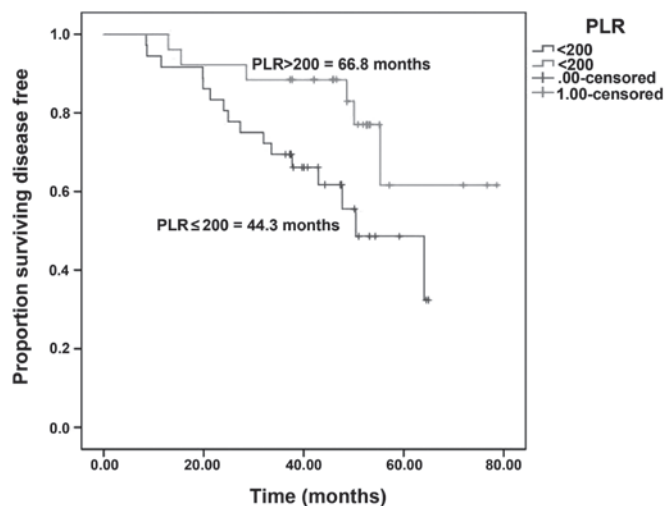


Figure 1. Disease-free survival in patients with platelet-lymphocyte ratio (PLR) ≤ 200 vs. >200 .

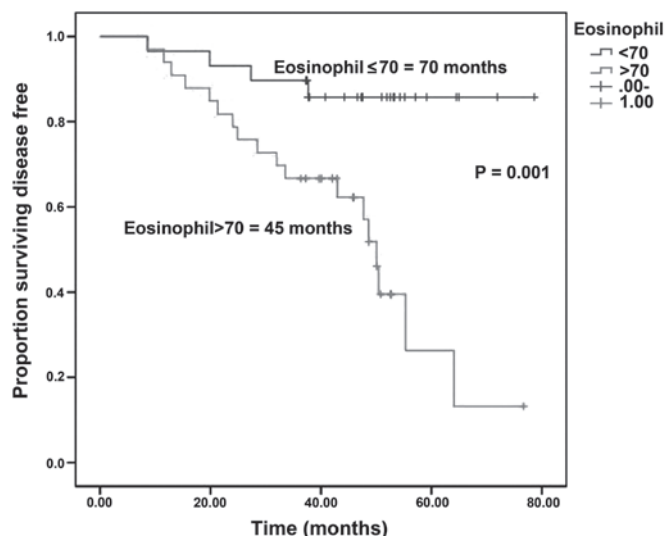


Figure 2. Disease-free survival in patients with an eosinophil count of ≤ 70 vs. $>70 \times 10^3/\text{mm}^3$.

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.

References

1. Jemal A and Bray F: Global Cancer Statistics. *CA Cancer J Clin* 61: 69-90, 2011.
2. Siegel R and DeSantis C: Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 62: 220-241, 2012.
3. Brewster AM, Hortobagyi GN, Broglio KR, *et al*: Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst* 100: 1179-1183, 2008.
4. Vicente Conesa MA, Garcia-Martinez E, Billalabeitia EG, Benito AC, Garcia TG, Garcia VV and Ayala de la Peña F: Predictive value of peripheral blood lymphocyte count in breast cancer patients treated with primary chemotherapy. *The Breast* 21: 468-474, 2012.
5. Mackall CL, Fleisher TA, Brown MR, *et al*: Lymphocyte depletion during treatment with intensive chemotherapy for cancer. *Blood* 84: 2221-2228, 1994.

6. Smith I, Procter M, Gelber RD, *et al*: HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 369: 29-36, 2007.
7. Gennari R, Menard S, Fagnoni F, *et al*: Pilot study of the mechanism of action of preoperativetrastuzumab in patients with primary operable breast tumors overexpressing HER2. *Clin Cancer Res* 10: 5650-5655, 2004.
8. Coussens LM and Werb Z: Inflammation and cancer. *Nature* 420: 860-867, 2002.
9. Nurden AT: Platelets, inflammation and tissue regeneration. *Thromb Haemost* 105 (Suppl 1): 13-33, 2011.
10. Proctor MJ, Morrison DS, Talwar D, *et al*: A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome study. *Eur J Cancer* 47: 2633-2641, 2011.
11. Feng JF, Huang Y and Liu JS: Combination of neutrophil lymphocyte ratio and platelet lymphocyte ratio is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma. *Onco Targets Ther* 6: 1605-1612, 2013.
12. Papatestas AE, Lesnick GJ, Genkins G and Aufses AH Jr: The prognostic significance of peripheral lymphocyte counts in patients with breast carcinoma. *Cancer* 37: 164-168, 1976.
13. Pattison CW, Woods KL and Morrison JM: Lymphocytopenia as an independent predictor of early recurrence in breast cancer. *Br J Cancer* 55: 75-76, 1987.
14. Ray-Coquard I, Cropet C, Van GM, *et al*: Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas and lymphomas. *Cancer Res* 69: 5383-5391, 2009.
15. Le Scodan R, Massard C, Mouret-Fourme E, *et al*: Brain metastases from breast carcinoma: validation of the Radiation Therapy Oncology Group recursive partitioning analysis classification and proposition of a new prognostic score. *Int J Radiat Oncol Biol Phys* 69: 839-845, 2007.
16. Le Scodan R, Massard C, Jouanneau L, Coussy F, Gutierrez M, Kirova Y, Lerebours F, Labib A and Mouret-Fourme E: Brain metastases from breast cancer: proposition of new prognostic score including molecular subtypes and treatment. *J Neurooncol* 106: 169-176, 2012.
17. Delyon J, Mateus C, Lefeuvre D, *et al*: Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. *Ann Oncol* 24: 1697-1703, 2013.
18. Moja L, Tagliabue L, Balduzzi S, *et al*: Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 4: CD006243, 2012.
19. Slamon D, Eiermann W, Robert N, *et al*: Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 365: 1273-1283, 2011.
20. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365: 1687-1717, 2005.
21. Olson EM, Abdel Rausoul M, Maly J, Wu CS, Lin NU and Shapiro CL: Incidence and risk of central nervous system metastases as site of first recurrence in patients in with HER2-positive breast cancer treated with adjuvant trastuzumab. *Ann Oncol* 24: 1526-1533, 2013.
22. Tsuji W, Teramukai S, Ueno M, Toi M and Inamoto T: Prognostic factors for survival after first recurrence in breast cancer: a retrospective analysis of 252 recurrent cases at a single institution. *Breast Cancer* 21: 86-95, 2014.
23. Clark GM, Sledge GW Jr, Osborne CK and McGuire WL: Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 5: 55-61, 1987.
24. Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A and Garcia-Conde J: Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 56: 67-78, 1999.
25. Koenders PG, Beex LV, Kloppenborg PW, Smals AG and Benraad TJ: Human breast cancer: survival from first metastasis. Breast Cancer Study Group. *Breast Cancer Res Treat* 21: 173-180, 1992.