Research Article

Prognostic Role of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Patients with HER-2 Positive Brain Metastatic Breast Cancer

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Abstract

Objectives: Studies have been performed on the parameters that could predict the overall survival (OS) in patients with HER-2 positive breast cancer and have a potential prognostic significance in patients with a high risk of developing brain metastasis. This study was designed to assess the prognostic effect of blood inflammation-based markers, which were previously investigated in various cancers, on OS in brain metastatic HER-2 positive breast cancer.

Methods: 105 patients aged over 18 years with positive HER-2 status and brain metastases and no secondary malignancies were included in the study. Inflammation parameters at the time of brain metastasis development and before steroid initiation were taken into consideration.

Results: Median OS of the population was determined to be 48 months (40.7-55.30, CI 95%). The median OS after brain metastasis (BM) was 14 months (11.76-16.23, CI 95%) in the whole group, following the development of brain metastasis. A significant negative correlation was found between neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) and OS after BM (r=-0.413 p<0.001 for NLR, r=-0.243 p=0.014 for PLR). It was determined that OS after BM had a negative correlation with neutrophil level and positive correlation with lymphocyte level (r=-0.249 p=0.011 for neutrophils, r=0.268 p=0.006 for lymphocytes).

Conclusion: In HER-2 positive brain metastatic breast cancer, increased NLR and PLR levels show a negative prognostic effect on OS after BM, whereas increased lymphocyte count shows a positive prognostic effect.

Keywords: Brain Metastasis, Her-2 positive Breast Cancer, NLR, PLR

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Breast cancer, which is a heterogeneous disease, can metastasize to various organs, particularly bone, lung, liver, and brain. Brain metastases, which are associated with a lower overall survival and quality of life, occur more commonly among triple-negative (25-27%) and HER-2 positive subgroups (11-20%).[1,2] With the use of many new Anti-HER-2 based agents, specifically trastuzumab, better OS and progression-free survival (PFS) values have begun to be achieved in these patients.[3] Albeit previous studies have been performed to find out clinical, pathological, or laboratory markers that predict OS and have prognostic significance in breast cancers, which have metastasized to the central nervous system, yet there is no consensus on it due to conflicting results and the relevant data is still limited.

In recent years, numerous studies performed with inflammation-based markers have obtained useful results in demonstrating the prognosis in various cancers.[4,5] NLR and PLR were the two most common parameters investigated for this purpose. In many studies, higher NLR and PLR values have been found to be associated with poor prognosis.[6] The prognostic value of these inflammation-based markers in brain metastatic breast cancer has not been clearly determined. Hence, this study was designed to assess the prognostic values of inflammation-based markers on OS in central nervous system metastatic breast cancer.

Methods

The data of nearly 3000 patients were reviewed retrospectively and 105 patients who met the inclusion criteria were included in the study. Patients aged over 18 years with positive HER-2 status and brain metastases and no secondary malignancies were included in the study. Inflammation parameters at the time of brain metastasis development and before steroid initiation were taken into consideration. Those with active infections that may affect these parameters were excluded from the study. The demographic data of the patients were recorded from the clinical characteristics files of the disease. The study was approved by the local ethics committee (August 04th, 2020, meeting number: 99).

Statistical Analysis

Statistical analyzes were performed via the software of SPSS 25.0 (SPSS, Chicago, IL, USA). Mann-Whitney U test was used for comparison of nonparametric data while Student T-test was used for comparison of parametric data. Chi-Square or Fisher's Exact test was used for comparison of categorical data. Kaplan – Meier method was used for survival analysis and Log-Rank test was performed for intergroup comparisons. Prognostic factors impacting overall survival were determined by performing multivariate analysis with the Cox proportional hazards model. The results were considered statistically significant at $p < 0.05$.

Results

The median age of the patients at the time of diagnosis of brain metastasis was 49 (27-75 years). 41 (39%) of the patients were negative for hormone receptor (HR), whereas 61 (58.1%) of them were HR-positive. The hormone status of 3 patients could not be obtained from their files. Nine (8.6%) of the patients who were included in the study had brain metastases at the time of diagnosis (Table 1). The median OS of the population was found to be 48 months (40.7-55.30, CI 95%). The median OS was determined to be 14 months (11.76-16.23, CI 95%) in the whole group, following the development of brain metastasis.

Table 1. Patients characteristics

Median age	48 (27-75) years
Hormon receptor status	
Positive	41 (39%)
Negative	61 (58.1%)
Unknown	3 (2.9%)
Metastasis site at the time of the diagnosis	
Brain	9 (8.6%)
Other site	26 (24.8%)
Non metastasis	70 (66.6%)
Median anti HER 2 treatment line	2 (1-5)
Median Overall Survive	48 months

When the correlation between inflammatory parameters measured at the time of brain metastasis and OS after BM was examined, a significant negative correlation was determined between NLR and PLR and OS after BM (r=-0.413 p<0.001 for NLR, r=-0.243 p=0.014 for PLR). It was found that OS after BM had a negative correlation with neutrophil level and positive correlation with lymphocyte level; (r=-0.249, p=0.011 for neutrophils; r=0.268, p=0.006 for lymphocytes).

Discussion

In this study, in which 105 HER-2 positive patients with brain metastasis were analyzed retrospectively, it was determined that NLR, PLR, neutrophil, and lymphocyte parameters, which were measured before brain metastasis, predicted overall survival after brain metastasis. It has been demonstrated that NLR, PLR, and neutrophil count are negative prognostic factors and lymphocyte count is positive prognostic factors in terms of OS after BM. Albeit various studies have previously been performed with inflammation parameters, particularly in early-stage breast cancer, data on survival and inflammation parameters after metastasis in HER-2 positive brain metastatic disease are limited in the literature.

The median OS in the study was 48 months, and albeit there are varying results in the literature, in general terms a better result was obtained compared to previous studies.[7] This difference can be explained by the fact that the rate of non-metastatic disease was 66.6% at the time of diagnosis in the presented study and 8.6% of the general group had brain metastases at the time of diagnosis. Moreover, multiple variables such as HR-positive disease incidence, number of brain metastases, whether surgery was performed for metastasis are other reasons that cause the differences in the literature.

In the study, the median OS after BM was 14 months. It is well-known that the development of brain metastasis is

one of the primary reasons impacting the disease prognosis and survival.[8,9] Thus, parameters predicting survival at the time of brain metastasis gain importance. Inflammatory blood parameters, which have been studied previously in various cancers, providing a simple and rapid assessment, were also assessed in the presented study for this purpose.

The correlation between inflammation and tumor has been well-documented for a long time.[10] The more severe the inflammation in the micro-periphery of the tumor, the easier it is for tumor development, invasion, angiogenesis, and metastasis.[11,12] Neutrophils and platelets in the peripheral or tumor microenvironment play an active role in neoplasia steps by releasing various cytokines, notably Vascular endothelial growth factor (VEGF) and Transforming growth factor beta TGF-β.[12,13] Hence, it has been revealed in studies that high neutrophil, thrombocyte, NLR, and PLR parameters generally show negative prognostic features in different states and stages in various cancers.[14-15] Lymphocytes also play an active role in the neoplasia process. Previous studies have demonstrated that tumor-infiltrating lymphocytes reduce tumor growth in various many cancers and have a favorable prognostic effect.[16]

In the present study, as the blood NLR and PLR levels of the patients increased, OS after BM was worse. In a meta-analysis of 17079 breast cancer patients and 39 studies, it was determined that higher NLR and PLR levels are associated with poorer survival and higher risk of recurrence. In the subgroup analyzes of the study, it was verified that NLR and PLR had a prognostic effect in HER-2 positive patients.[17] In another study, which investigated the prognostic factors in 154 metastatic HER-2 positive breast cancer patients, advanced age, increased PLR and alkaline phosphatase level, and brain metastasis were found to be poor prognostic factors.[18] In another meta-analysis, which was performed on patients with stage II-IV breast cancer, high PLR levels were determined to be associated with poor prognosis and this impact was significant in the HR-positive group, while in the study of Ulas et al., which was performed on patients who received adjuvant trastuzumab in early-stage breast cancer, it was found that the NLR has impact on OS and the effect of PLR on OS and DFS could not be demonstrated.[12,15] These differences in the literature can be explained by the difference in demographic data, stages, and HR status of the patients in the studies. In the presented study, nearly 58% of patients were HR-positive whereas 39% of them were HR negative.

Moreover, in another meta-analysis, in which 8563 breast cancer patients were included and 15 studies were examined, it was suggested that high NLR, regardless of HR, HER-2 status, and disease stage, had a prognostic effect on DFS and OS; however, this effect was more significant in triple-negative disease. It has been revealed that this can be explained by the occurrence of relapse later in HR-positive patients and the relatively shorter median follow-up period in studies.[19]

In the presented study, there was a positive correlation between increased lymphocyte level and BM after OS. It is well-known that lymphocytes play a crucial role in cell-mediated anti-tumor immune responses and tumor immunological surveillance, and suppress tumor progression and metastasis.[20] It was shown in a study, which was in line with the presented study, that the increase in tumor-infiltrating lymphocytes in patients with node-positive breast cancer was associated with a better prognosis.[21] Furthermore, lymphopenia could indicate the immune deficiency state caused by the tumor cells. Hence, higher platelet count and/or lower lymphocyte count and higher PLR are associated with a lower antitumor activity and poor prognosis.[15]

This study has some limitations. It was a retrospective study, so a prospective multicenter study would be much better in terms of evaluating inflammatory parameters in HER-2 positive breast cancer with brain metastasis. In this study, there is a risk of bias in some results due to the low number of patients and missing data.

Conclusion

In HER-2 positive brain metastatic breast cancer, increased NLR and PLR levels indicate a negative prognostic effect on OS after BM, whereas increased lymphocyte count shows a positive prognostic effect. Based on these data, blood inflammatory parameters at the time of brain metastasis in breast cancer may be useful in predicting survival and prognosis. Large prospective studies on this subject would provide better information and could reduce the possibility of bias.

References

1. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes.

J Clin Oncol 2010;28:3271–7. [CrossRef]

2. Leone JP, Leone BA. Breast cancer brain metastases: the last frontier. Exp Hematol Oncol 2015;4:33. [CrossRef]

3. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPA-TRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:519–30. [CrossRef]

4. Fu H, Zheng J, Cai J, Zeng K, Yao J, Chen L, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients after liver transplantation for hepatocellular carcinoma within hangzhou criteria. Cell Physiol Biochem 2018;47:293-301. [CrossRef]

5. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju124. [CrossRef]

6. Cho U, Park HS, Im SY, Yoo CY, Jung JH, Suh YJ, et al. Prognostic value of systemic inflammatory markers and development of a nomogram in breast cancer. PLoS One 2018;13:e0200936

7. Andersson M, Lidbrink E, Bjerre K, Wist E, Enevoldsen K, Jensen AB, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2–positive breast cancer: The HERNATA Study. J Clin Oncol 2011;29:264–71. [CrossRef]

8. Pestalozzi BC, Zahrieh D, Price KN, Holmberg SB, Lindtner J, Collins J, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol 2006;17:935.

9. Park YH, Park MJ, Ji SH, Yi SY, Lim DH, Nam DH, et al. Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. Br J Cancer 2009;100:894. [CrossRef]

10. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7. [CrossRef]

11. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44. [CrossRef]

12. Ulas A, Avci N, Kos T, Cubukcu E, Olmez OF, Nilufer Bulut N, et al. Are neutrophil / lymphocyte ratio and platelet / lymphocyte ratio associated with prognosis in patients with HER2-positive early breast cancer receiving adjuvant trastuzumab? JBUON 2015;20:714–22. [CrossRef]

13. Kuang DM, Zhao Q, Wu Y, Peng C, Wang J, Xu Z, et al. Peritumoral neutrophils link inflammatory response to disease progression by fostering angiogenesis in hepatocellular carcinoma. J Hepatol 2011;54:948–55. [CrossRef]

14. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, Mc-Millan C, Clarke SJ. The systemic inflammation-based neutrophil lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol 2013;88:218–30. [CrossRef]

15. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with breast cancer: a meta-analysis. Biomed Res Int 2017;2017:9503025. [CrossRef]

16. Diederichsen AC, Hjelmborg JB, Christensen PB, Zeuthen J, Fenger C. Prognostic value of the CD4+/ CD8+ ratio of tumour infiltrating lymphocytes in colorectal cancer and HLA-DR expression on tumour cells. Cancer Immunol Immunother 2003;52:423–8. [CrossRef]

17. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W, et al. Prognostic value of neutrophil-to-lymphocyte ratio and plateletto- lymphocyte ratio for breast cancer patients: An updated metaanalysis of 17079 individuals. Cancer Medicine 2019;8:4135–48. [CrossRef]

18. Blanchette PS, Desautels DN, Pond GR, Bartlett JMS, Nofech-Mozes S, Yaffe MJ, et al. Factors influencing survival among patients with HER2-positive metastatic breast cancer treated with trastuzumab. Breast Cancer Res Treat 2018;170:169–77. [CrossRef]

19. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res 2017;19:2.

20. Hopewell EL, Zhao W, Fulp WJ, Bronk CC, Lopez AS, Massengill M, et al. Lung tumor NF-κB signaling promotes T cell-mediated immune surveillance. J Clin Invest 2013;123:2509–22. [CrossRef]

21. Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 2013;31:860–7. [CrossRef]