Original Study

Significant Association Between Low Baseline Neutrophil-to-Lymphocyte Ratio and Improved Progression-free Survival of Patients With Locally Advanced or Metastatic Breast Cancer Treated With Eribulin But Not With Nab-Paclitaxel

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Abstract

Both eribulin and nab-paclitaxel are widely used and effective chemotherapy agents for metastatic breast cancer; however, their predictive factors remain unknown. The usefulness of the neutrophil-to-lymphocyte ratio (NLR) in terms of treatment efficacy was investigated. We observed that a low NLR at baseline might be a significant indicator of improved outcomes for patients treated with eribulin but not with nab-paclitaxel.

Introduction: Although eribulin and nab-paclitaxel are chemotherapy agents widely used for locally advanced or metastatic breast cancer (MBC), their predictive factors remain unknown. Because the absolute neutrophil-to-lymphocyte ratio (NLR) is a significant prognostic factor for early-stage breast cancer, we investigated its usefulness in terms of the eribulin or nab-paclitaxel treatment efficacy for MBC. **Patients and Methods:** A total of 85 patients with MBC treated with eribulin (n = 59) or nab-paclitaxel (n = 26) were recruited. NLR values were collected at baseline, after 1 cycle, after 2 cycles, and at the end of treatment. The NLR cutoff value was set at 3. **Results:** The progression-free survival (PFS) of patients with an NLR < 3 at baseline (median, 242 days; n = 24) was significantly better than that of patients with an NLR of ≥ 3 (median, 98 days; n = 35; hazard ratio, 0.37, 95% confidence interval, 0.18-0.71; $P = .0032$). Similarly, the overall survival was marginally significantly better in patients with an NLR < 3 who were treated with eribulin ($P = .058$). However, the NLR was not significantly associated with PFS or overall survival for patients treated with nab-paclitaxel. No significant association was found between the NLR during treatment and PFS in the eribulin group. The significance of the NLR for the efficacy of eribulin was consistent, irrespective of estrogen receptor status, previous anthracycline or endocrine use, and the number of previous chemotherapy regimens. **Conclusion:** A low NLR at baseline was significantly associated with improved PFS in patients treated with eribulin but not in those treated with nab-paclitaxel. Therefore, the baseline NLR might be clinically useful for selecting patients who would benefit from eribulin.

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Introduction

Although both eribulin and nab-paclitaxel are widely used effective chemotherapy agents for locally advanced or metastatic breast cancers (MBC), their predictive factors remain unknown. Eribulin is a synthetic macrocyclic ketone analog of halichondrin B that inhibits the synthesis of microtubule polymerization.[1,2] In the

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EMBRACE (eribulin monotherapy vs. treatment of physician's choice in patients with metastatic breast cancer) trial, the treatment efficacy of eribulin monotherapy was compared with that of the treatment of the physicians' choice in 762 patients with heavily pretreated MBC.[3] Although no statistically significant difference was found in progression-free survival (PFS), the overall survival (OS) of patients assigned to receive eribulin (median, 13.1 months) was significantly better than that for those assigned to receive treatment of the physicians' choice (10.6 months; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.66-0.99; $P = .041$). Similarly, no statistically significant difference was seen in PFS between MBC patients treated with eribulin and those treated with capecitabine (HR, 1.08; 95% CI, 0.93-1.25; $P = .30$). However, the OS for the eribulin group was marginally improved compared with that of the capecitabine group (HR, 0.88; 95% CI, 0.77-1.00; $P = .056$).[4]

The effect on OS induced by eribulin has been further demonstrated in real-world data. In estrogen receptor-positive (ER^+)/human epidermal growth factor receptor 2-negative ($HER2^-$) MBC, the OS of patients who received eribulin (n = 66) was significantly better than that of patients treated with conventional chemotherapy regimens (n = 227; HR, 0.67; 95% CI, 0.47-0.96; $P = .025$).[5] In addition, in a pooled analysis of data from 1644 patients, a significantly superior OS was consistently observed in the eribulin group (n = 946) compared with that of the comparators (n = 698; HR, 0.85; 95% CI, 0.76-0.94; $P = .002$).[6] The improved eribulin treatment efficacy was also observed in the subset of patients with triple-negative (TN) breast cancer (ER^-, progesterone receptor negative [PR^-], $HER2^-$), those with nonvisceral metastasis, and those with > 2 organs involved.[6,7] Thus, eribulin is thought to be superior in these types of MBC subgroups; however, the biomarkers of treatment efficacy for eribulin have not yet been determined.

The results from in vitro and in vivo studies have shown that eribulin suppresses the epithelial–mesenchymal transition (EMT) and induces the mesenchymal–epithelial transition (MET), resulting in a lower potential for metastasis.[8] In addition, eribulin enhances reoxygenation by increasing blood perfusion in the tumor through vasculature remodeling and reduces plasma concentrations of transforming growth factor-β, an EMT inducer.[9,10] Because reoxygenation downregulates hypoxia-inducible factor-1α,[11,12] the MET seems to be generated directly, as well as indirectly mediated, through vascular remodeling by eribulin. The weakened malignant potential through MET with eribulin treatment might be in line with the prolonged survival benefit. Recently, Kashiwagi et al[13] reported that among the TN subset of MBC patients treated with eribulin, the PFS of patients with high frequencies of tumor-infiltrating lymphocytes (TILs) was significantly better than that of patients with low frequencies ($P = .033$). These data might indicate that the prolonged treatment efficacy induced by eribulin stems, at least in part, from an immune reaction.

In addition to TILs, the neutrophil-to-lymphocyte ratio (NLR), a marker of systemic immunity, has been demonstrated to be a significant prognostic factor for early-stage breast cancer.[14,15] However, to the best of our knowledge, the usefulness of the NLR in terms of the efficacy of MBC treatment has yet to be reported. To identify an immune-related biomarker for the treatment efficacy of eribulin, we investigated the usefulness of the NLR in patients with MBC treated with eribulin or nab-paclitaxel.

Materials and Methods

Patient Eligibility

A total of 85 patients with MBC treated with eribulin (n = 59) or nab-paclitaxel (n = 26) at Hyogo College of Medicine from November 2010 to September 2017 were recruited for the present retrospective study. All participants were confirmed to have primary breast cancer through histologic examination, and locally advanced stage or metastasis was confirmed through diagnostic radiography using computed tomography, whole-body bone scintigraphy, or 2-[(18)F]-fluoro-2-deoxy-D-glucose positron emission tomography. Of the 85 patients, the HER2 status was positive in 4, unknown in 1, and negative in the remaining 80 patients (Table 1). One male breast cancer patient was included. All patients were treated with either eribulin or nab-paclitaxel monotherapy. Those patients who received combination therapy with other chemotherapy agents, anti-HER2 therapy, or endocrine therapy were excluded except, for those treated with concurrent use of zoledronic acid (n = 31) or denosumab (n = 16). Zoledronic acid, followed by denosumab, was administered to 3 patients. The patients were eligible if they had received > 1 cycle of chemotherapy.

Eribulin and Nab-Paclitaxel Chemotherapy Schedules

Eribulin was administered intravenously at 1.4 mg/m^2 over 5 minutes on days 1 and 8 of each 21-day cycle. If adverse events occurred, the dose was reduced to 1.1 or 0.7 mg/m^2. For patients with a decreased neutrophil count, the administration was delayed. For nab-paclitaxel, 260 mg/m^2 was administered intravenously over 30 minutes every 3 weeks and was reduced to 220 or 180 mg/m^2 for patients who required a dose reduction or delayed administration. The chemotherapy regimens were continued until disease progression (n = 61) or the appearance of intolerable adverse events (n = 14), with treatment ongoing for 10 patients at the last follow-up visit. The median duration of eribulin and nab-paclitaxel treatment was 106 and 111.5 days, respectively. The median number of previous chemotherapy regimens was 2 (range, 0-7) for the eribulin group and 1 (range, 0-5) for the nab-paclitaxel group. Previous anthracycline and taxane exposure was reported for 52.5% and 83.1% of patients in the eribulin group and 38.5% and 46.2% of patients in the nab-paclitaxel group, respectively (Table 1).

Measurements of NLR and Patient Outcomes

The neutrophil and lymphocyte counts were measured automatically using Sysmex XN-9000 or XN-1000 hematology analyzers (Sysmex Corp, Kobe, Japan). The absolute numbers of neutrophils were calculated using stab plus segment fractions. The NLR for each patient was calculated by dividing the number of neutrophils by the number of lymphocytes. The NLR was determined at baseline, after 1 cycle, after 2 cycles, and at the end of treatment (after the last cycle). The NLR cutoff value was set at 3 in accordance with previous studies.[15,16]

We evaluated PFS, defined as the duration from the start to the end of each treatment because of disease progression or death from any cause. OS was calculated from the start of each treatment to