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High Absolute Lymphocyte Counts Correlate with a Better Outcome After Eribulin Therapy for Metastatic Breast Cancer in First-Line Chemotherapy Studies

P. Satish, K. Madhavi , K. Vineetha , B. Jyothsna

Abstract

Background: The impact of prior chemotherapy on blood cell counts may necessitate an evaluation of baseline absolute lymphocyte count (ALC) and neutrophil- to-lymphocyte ratio (NLR) in first-line chemotherapy patients, despite their association with improved PFS and OS.
Methods: This retrospective study assessed the outcomes of patients with HER2-negative MBC who participated in two phase 2 studies (BIRICHEN and OMC-BC 03) and underwent first-line eribulin chemotherapy. For the sake of comparison, data from HER2-negative MBC patients treated at Osaka Medical and Pharmaceutical University Hospital between March 2013 and March 2017 who underwent first-line chemotherapy other than eribulin (treatment of physician's choice; TPC) were also studied. The results showed that in the eribulin group, the median overall survival (mOS) was 30.9 months for those with low neutrophil-to-lymphocyte ratios (L-NLR; n = 23) and 15.4 months for those with high NLRs (H-NLR; n = 36) (hazard ratio [HR], 0.52; 95% confidence interval [CI]: 0.27-1.01). Neither ALC nor NLR were linked to longer OS or PFS among TPC patients. The median overall survival (mOS) in the eribulin group was 32.0 months in the H-ALC group and 19.6 months in the L-ALC group after propensity score matching (HR, 0.43; 95% CI: 0.18-0.99), but there were no significant differences between the mOS in the L-NLR and H-NLR groups. As a result, we conclude that ALC is a prognostic predictor for first-line eribulin chemotherapy but not for other drugs.

Keywords: Metastatic breast cancer, Overall survival, Eribulin, Treatmentof physician's choice, Absolute lymphocyte count

Introduction

The EM- BRACE study [1] showed that eribulin improved OS in patients with HER2-negative metastatic breast cancer (MBC) without causing serious non-hematologic side effects. Abso- lute lymphocyte count (ALC), a measure of the immunological response, was shown to be a predictive predictor of OS following eribulin therapy, according to a recent ad hoc analysis of the study [2]. Curiously, in the TPC group, ALC did not serve as a predictive marker [2]. In early-stage breast cancer, the neutrophil-to-lymphocyte ratio (NLR) is an important predictive factor [2, 3]. The NLR is a measure of systemic immunity. Ad hoc analysis of the EMBRACE study demonstrated a correlation between NLR and improved PFS and OS in the eribulin and TPC groups [2]. However, given the experiment aimed at a late-line treatment, the blood cell count must have been affected by prior chemotherapy. Patients undergoing first-line chemotherapy may benefit from a review of their ALC and NLR at baseline due to the potential impact of prior chemotherapy on blood cell counts.

Two phase 2 studies estimating the effectiveness of eribulin as first-line chemotherapy for HER2-negative MBC were done earlier by us in Japan, and the results were remarkable [4, 5]. This study aimed to test the hypothesis that ALC is a prognostic factor for first-line eribulin treatment but not for TPC by comparing the baseline ALC and NLR of patients treated with eribulin in these trials with those of patients treated for TPC in the same cohort.

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History of Medicine Studies
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Patients and Methods

Patients

We evaluated two groups (eribulin and TPC groups) in this study. The eribulin group included 59 patients with HER2- negative MBC, including 35 patients in the BIRICHEN trial (UMIN000006086) who received first-line chemotherapy with eribulin [4] and 24 patients who received first-line che- motherapy in the OMC-BC 03 trial targeting first- and sec- ond-line chemotherapy (UMIN000009568) [5]. For the TPC group, we retrospectively and constitutively recruited 48 pa- tients with HER2-negative MBC who received first-line che- motherapy with agents other than eribulin at Osaka Medical and Pharmaceutical University Hospital at the same time as the OMC-BC 03 study (March 1, 2013, to March 1, 2017). Patients who received endocrine therapies before first-line chemotherapy were included, but those who received mo- lecular-targeted therapy (e.g., CDK4/6 inhibitors or mTOR inhibitors) were excluded.

Treatment

Details of the dosing schedule of eribulin have been pub-lished in our previous study [4, 5]. In the TPC group, treat- ments included FEC (epirubicin 100 mg/m^2, 5-fluorouracil [5-FU] 500 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks), bevacizumab (Bmab) plus paclitaxel (PTX) (Bmab 10 mg/kg on days 1 and 8 and PTX 80 mg/m^2 on days 1, 8, and 15 every 4 weeks), weekly PTX (75 mg/m^2 every week), oral 5-FU (capecitabine 900–1,200 mg orally twice daily on days 1–21 every 4 weeks or S-1 40–60 mg orally twice daily on days 1–14 every 3 weeks), and vinorelbine (25 mg/m^2 on days 1 and 8 every 3 weeks).

Assessment

Pretreatment blood cell count data were collected on or just before the first day of chemotherapy administration and compared with survival data. The cutoff value for ALC was set at 1500/mm^3 and that for NLR was set at 2.5, based on the median value of each parameter and a previous study [6].

Statistical analysis

Means, medians, and interquartile ranges (IQRs) were calculated for continuous variables. Counts and percentages were reported for dichotomous and polychotomous variables. In both eribulin and TPC groups, the median values with 95% confidence intervals (CIs) for PFS and OS curves for ALC and NLR were estimated using the Kaplan–Meier method and analyzed using the log-rank test. Hazard ratios (HRs) for high to low ALC or low to high NLR were estimated us- ing Cox proportional hazards models. The median follow-up duration was defined as the median follow-up duration for censored cases.

Comparative analyses were conducted using unadjusted and propensity-score matching (PSM) methods. One-to-one (1:1) PSM between the high- (H-) and low- (L-) ALC or H-NLR and L-NLR groups in each of the eribulin and TPC groups was conducted using the nearest-neighbor matching method to minimize baseline confounders [7-9]. The matched variables were age (≥65 or <65 years), performance status (PS) (0 or ≥1), subtype (estrogen receptor-positive or triple- negative breast cancer), and disease-free interval (DFI) (<2 years, ≥2 years, or de novo). After matching, standardized differences (SDs) were calculated, and values less than 0.1 were considered to indicate adequate variable balance after PSM [10]. All statistical analyses were performed using the JMP version 13 (SAS Institute Inc., Cary, NC, USA).

Ethics Committees

The ethics committees of Osaka Medical and Pharmaceu- tical University and Osaka Metropolitan University approved this study. Informed consent was obtained in the form of an opt-out at all institutions or the websites of each institution. Patients who did not provide consent were excluded.

Results

Patients

Baseline characteristics of patients in the eribulin and TPC groups are shown in Table 1. In the TPC group, 16 patients (33.3%) received anthracycline (FEC), 12 (25.0%) received Bmab + PTX, three (6.3%) received weekly PTX (6.3%),11 (22.9%) received S-1, 5 (10.4%) received capecitabine, and only 1 patient (2.1%) received vinorelbine. After TPC failure, 60% of the patients received eribulin in either treat- ment line. The median (IQR) baseline ALCs in the eribulin and TPC groups were 1690/μL (1060–2142/μL) and 1496/μL

Table 1: Demographics and baseline characteristics of the patients

		Eribulin	(n = 59)	TPC	(n = 48)
Age (years)	Median (IQR)	65 (38-75)		64 (38-82)	
Sex	Female	59	100%	48	100%
PS	0	44	75%	27	56%
	≥1	15	25%	21	44%
Subtype	ER-positive	44	75%	38	79%
	TN	15	25%	10	21%
DFI	De novo	14	24%	27	56%
	<2 y	21	36%	2	4%

History of Medicine Studies
ISSN:1300-669
Volume 18 Issue 2 Oct 2022

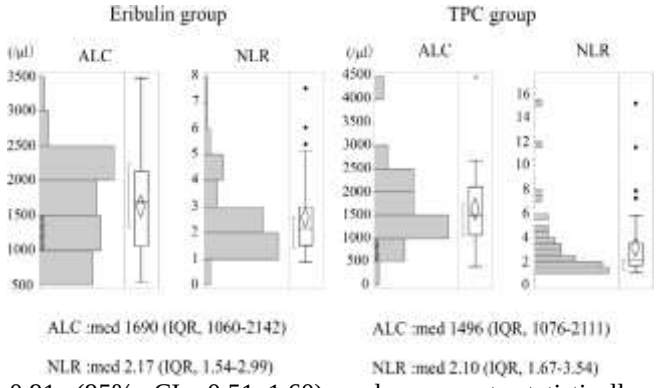
	≥2y	24	41%	19	40%
Regimen	Eribulin	59	100%	0	0%
	Anthracycline	0	0%	16	33%
	Bmab + PTX	0	0%	12	25%
	PTX	0	0%	3	6%
	S-1	0	0%	11	23%
	Capecitabine	0	0%	5	10%
	Vinorelbine	0	0%	1	2%
Eribulin on either treatment line	No	59	100%	29	60%
	Yes	0	0%	19	40%

(1076–2111/μL), respectively. The median (IQR) baseline NLRs in the eribulin and TPC groups were 2.2 (1.5–3.0) and 2.1 (1.7–3.5), respectively (Figure 1).

In both the eribulin and TPC groups, PS0 and DFI over 2 years were higher in H-ALC or L-NLR cases (Table 2). The median follow-up duration was 31.7 months (range, 17.0–65.6 months) in the eribulin group and 23.6 months (range, 2.3–90.7 months) in the TPC group.

Eribulin group

In comparisons based on the ALC, median OS (mOS) was 30.9 months in the H-ALC group (≥1500/μL; n = 33) and 17.8 months in the L-ALC group (<1500/μL; n = 26); the HR was 0.52 (95% CI: 0.27–1.01) but was not statistically significant. Median PFS (mPFS) was 6.5 months in the H-ALC group and 4.8 months in the L-ALC group; HR was



0.91 (95% CI: 0.51–1.60) and was not statistically significant (Figure 2a, b). In comparisons based on NLR, mOS was 30.9 months in the L-NLR group (<2.5; n = 36) and 15.4 months in the H-NLR group (≥2.5; n = 23); HR was 0.49 (95% CI: 0.25–0.95) and was statistically significant. In contrast, there was no statistical significance for PFS (mPFS was 6.5 months in the L-NLR group and 5.4 months in the H-NLR group, HR 0.57 [95% CI: 0.31–1.03]) (Figure 2c, d).

TPC group

ALC-based comparisons showed no statistically significant differences in OS and PFS (mOS was 24.7 months in the H-ALC group [n = 23] and 22.2 months in the L-ALCgroup [n = 25], HR 0.80 [95% CI: 0.40–1.61], and mPFS was 11.0 months in the H-ALC group and 11.0 months in the L-ALC group, HR 0.97 [95% CI: 0.46–2.05]). (Figure 3a, b). Similarly, in comparisons based on NLR, mOS was 24.7 months in the L-NLR group (n = 27) versus 22.2 months in the H-NLR group (n = 21); HR was 0.80 (95% CI: 0.44– 1.63), and mPFS was 8.2 months in the L-NLR group versus 10.0 months in the H-NLR group; HR was 0.85 (95% CI: 0.39–1.86) and was not statistically significant (Figure 3c, d).

Propensity-score matching

In the eribulin group, PSM was performed between the H-ALC and L-ALC groups. After matching, the H-ALC (n = 19) and L-ALC (n = 19) groups showed statistically significant differences in age, subtype, and DFI (Table 3). OS in the H-ALC and L-ALC groups showed statistical significance (HR, 0.43; 95% CI: 0.18–0.99): mOS was 32.0 months in the H-ALC group and 19.6 months in the L-ALC group. PFS in the H-ALC and L-ALC groups showed no statistical significance (HR, 1.05; 95% CI: 0.51–2.15 months): mPFS was 7.2 months in the H-ALC group and 6.2 months in the L-ALC group (Figure 4a, b). Similarly, after matching for NLR, the L-NLR (n = 17) and H-NLR (n = 17) groups showedstatistically significant differences only for subtype and DFI (Table 3). OS in the L-NLR and H-NLR groups showed no statistical significance (HR, 0.65; 95% CI: 0.27–1.58): mOS was 32.0 months in the L-NLR group versus 16.1 months in the H-NLR group. PFS in the L-NLR and H-NLR groups showed no statistical significance (HR, 0.76; 95% CI: 0.35– 1.62): mPFS was 5.8 months in the L-NLR group versus 5.6 months in the H-NLR group (Figure 4c, d).

In the TPC group, after matching for ALC, the H-ALC (n = 15) and L-ALC (n = 15) groups showed statistically significant differences only for age and PS (Table 3). OS in the H-ALC and L-ALC groups showed no statistical significance (HR, 0.69; 95% CI: 0.28–1.70): mOS was 24.7 months in the H-ALC group versus 17.8 months in the L-ALC group.

History of Medicine Studies
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Figure 1: Distribution of ALC and NLR in the eribulin and TPC groups ALC absolute lymphocyte count; IQR interquartile range; med, median;NLR neutrophil-to-lymphocyte ratio; TPC treatment of physician's choice.

Table 2: Demographics and baseline characteristics of patients categorized by ALC or NLR

		Eribulin group										TPC group									
		ALC					NLR					ALC					NLR				
		<1500	%	≥1500	%	SD	≥2.5	%	<2.5	%	SD	<1500	%	≥1500	%	SD	≥2.5	%	<2.5	%	SD
		n = 26	44	n = 33	56		n = 23	39	n = 36	61		n = 25	44	n = 23	56		n = 21	44	n = 27	56	
Age	Median (IQR)	64 (38-75)		67 (40-75)		0.16	64 (38-75)		66 (42-75)		0.27	64 (40-82)		66 (38-82)		0.07	64 (39-79)		64(38-82)		0.18
	<65 yr	14	54	15	46	0.16	13	57	16	44	0.26	14	56	10	43	0.25	11	52	13	48	0.08
	≥65 yr	12	46	18	55	0.18	10	43	10	28	0.34	11	44	13	57	0.25	10	48	14	52	0.08
PS	0	16	62	28	85	0.54	15	65	29	81	0.37	11	44	16	70	0.53	8	38	19	70	0.68
	≥1	10	39	5	15	0.56	8	35	7	19	0.37	14	56	7	30	0.53	13	62	8	30	0.68
Subtype	ER-positive	19	73	25	76	0.07	18	78	26	72	0.14	20	80	18	78	0.04	16	76	22	81	0.05
	TN	7	27	8	24	0.07	5	22	10	28	0.14	5	20	5	22	0.04	5	24	5	19	0.06
DFI	De novo	6	23	8	24	0.02	4	17	10	28	0.27	13	52	14	61	0.18	14	67	13	48	0.39
	<2 yr	12	46	9	27	0.40	13	57	8	22	0.77	0	0	2	9	0.44	0	0	2	7	2.16
	≥2 yr	8	31	16	49	0.37	6	26	18	50	0.51	12	48	7	30	0.37	7	33	12	44	0.23

TPC, treatment of physician's choice; ALC, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; SD, standardized difference, PS, performance status; DFI, disease-free interval; IQR, interquartile range; ER, estorogen receptor; TN, triple-negative

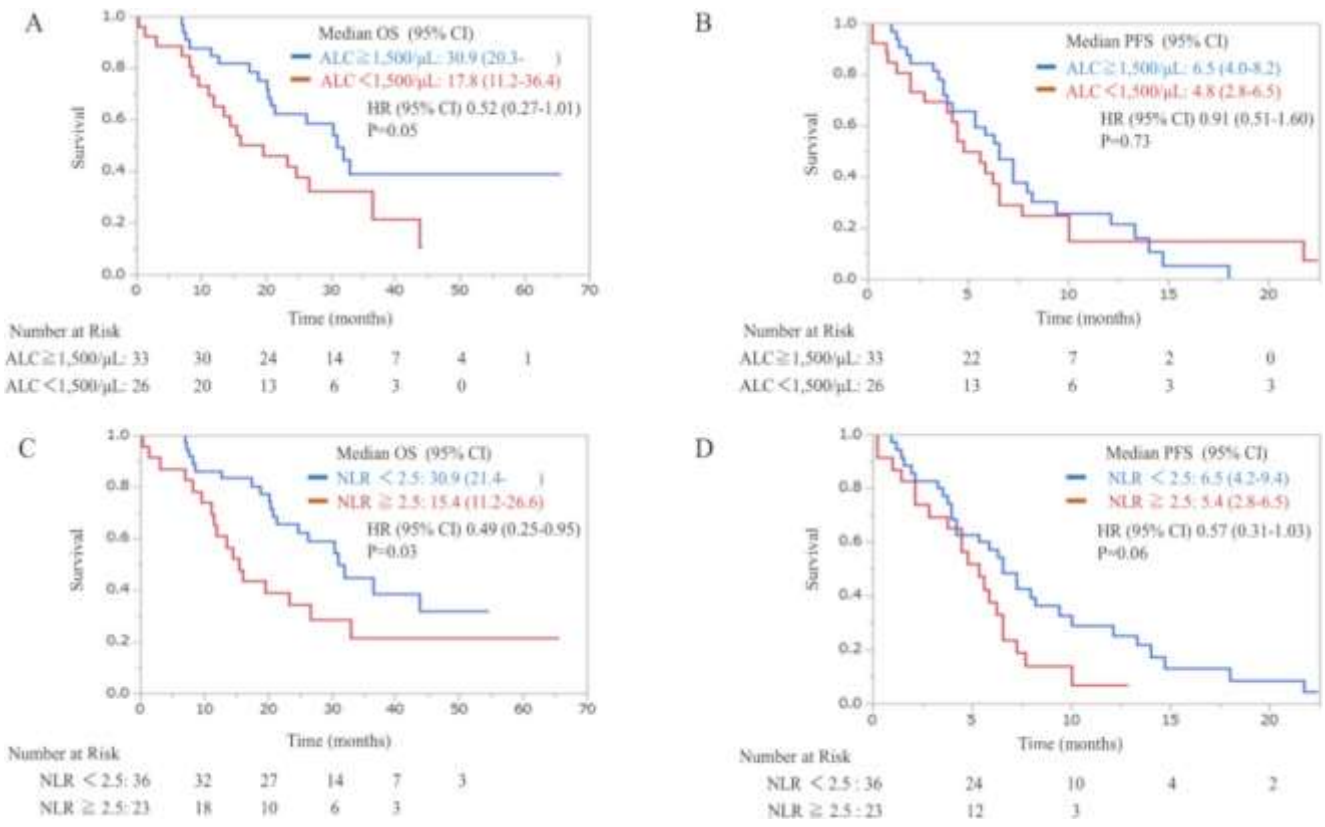

Figure 2: Kaplan–Meier plots of OS in relation to ALC (a), PFS in relation to ALC (b), OS in relation to NLR (c), and PFS in relation to NLR (d) in the eribulin group. ALC, absolute lymphocyte count; CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival

History of Medicine Studies
ISSN:1300-669
Volume 18 Issue 2 Oct 2022

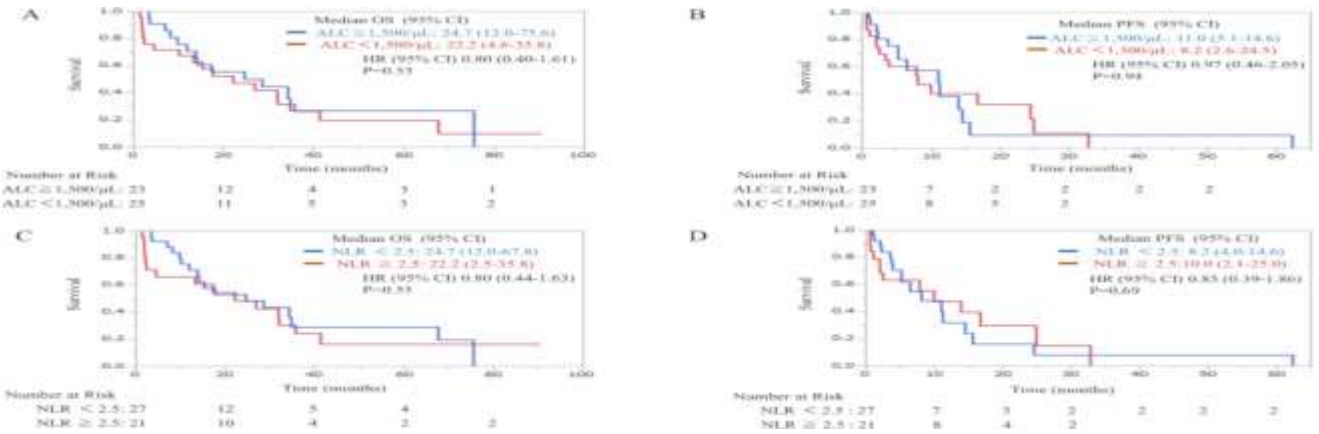

Figure 3: Kaplan–Meier plots of OS in relation to ALC (a), PFS in relation to ALC (b), OS in relation to NLR (c), and PFS in relation to NLR (d) in the TPC group. ALC, absolute lymphocyte count; CI: confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice

Table 3: Demographics and baseline characteristics of patients categorized by ALC or NLR after PSM

		Eribulin group										TPC group									
		ALC					NLR					ALC					NLR				
		<1500	%	≥1500	%	SD	≥2.5	%	<2.5	%	SD	<1500	%	≥1500	%	SD	≥2.5	%	<2.5	%	SD
		n = 19	50	n = 19	50		n = 17	50	n = 17	50		n = 15	50	n = 15	50		n = 13	50	n = 13	50	
Age	Median (IQR)	64 (42-75)		63 (40-75)		0.07	67 (40-72)		65 (47-73)		0.09	69 (39-75)		63 (38-81)		0.02	69 (39-75)		64 (43-82)		0.18
	<65 yr	10	53	11	58	0.11	8	47	8	47	0.00	7	47	9	60	0.26	5	38	6	46	0.14
	≥65 yr	9	47	8	42	0.11	9	53	9	53	0.00	8	53	6	40	0.26	8	62	7	54	0.16
PS	0	15	79	15	79	0.00	12	71	12	71	0.00	8	53	10	67	0.29	7	54	7	54	0.00
	≥1	4	21	4	21	0.00	5	29	5	29	0.00	7	47	5	33	0.29	6	46	6	46	0.00
Subtype	ER-positive	14	74	15	70	0.12	13	76	14	82	0.12	12	80	12	80	0.00	11	85	11	85	0.00
	TN	5	26	4	21	0.12	4	24	3	18	0.15	3	20	3	20	0.00	2	15	2	15	0.00
DFI	De novo	3	16	4	21	0.14	4	24	3	18	0.15	9	60	9	60	0.00	8	62	7	54	0.16
	<2 yr	9	47	8	42	0.11	7	41	7	41	0.00	0	0	0	0	0.00	0	0	0	0	0.00
	≥2 yr	7	37	7	37	0.00	6	35	7	41	0.12	6	40	6	40	0.00	5	38	6	46	0.14

TPC, treatment of physician's choice; ALC, absolute lymphocyte count; NLR, neutrophil-to-lymphocyte ratio; PSM, propensity-score matching; SD, standardized difference; PS, performance status; DFI, disease-free interval; IQR, interquartile range; ER, estorogen receptor; TN, triple-negative

History of Medicine Studies
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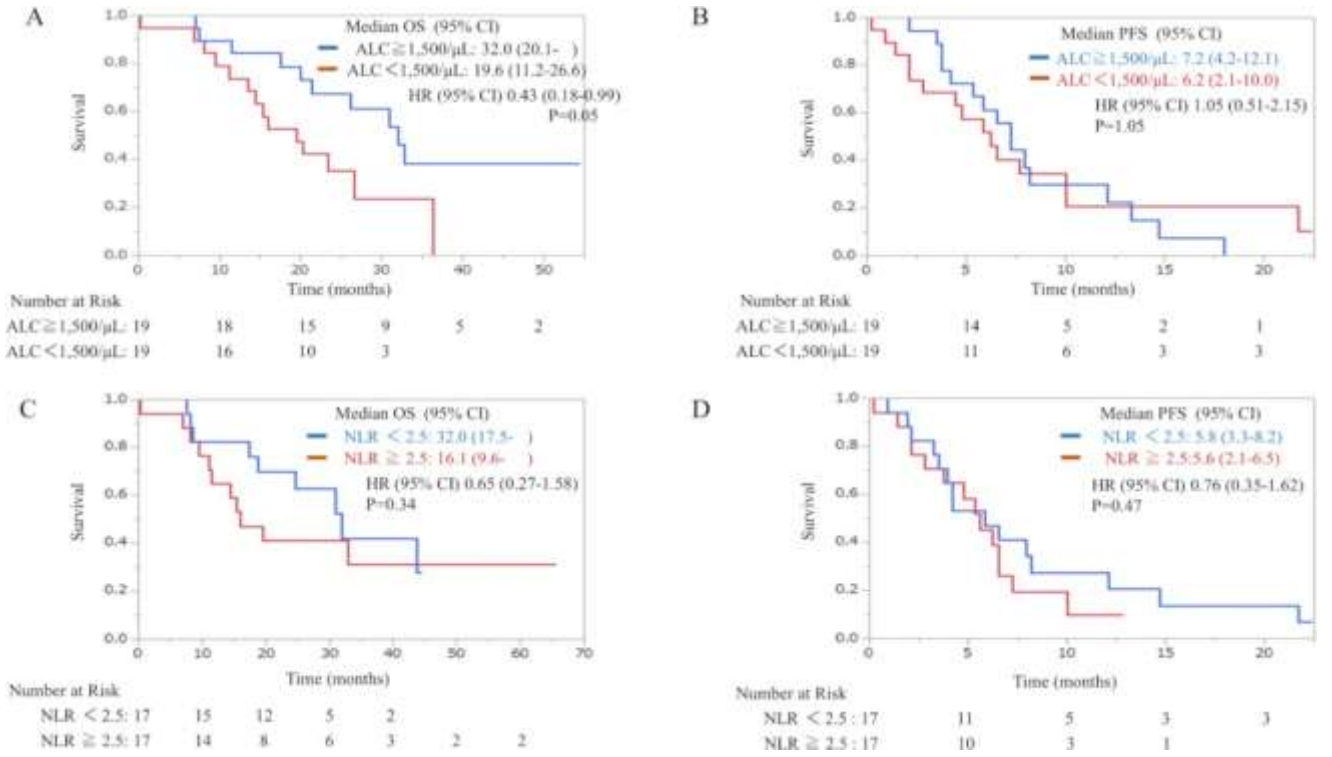

Figure 4: Kaplan–Meier plots of OS in relation to ALC (a), PFS in relation to ALC (b), OS in relation to NLR (c), and PFS in relation to NLR (d) in the eribulin group after propensity-score matching. ALC, absolute lymphocyte count; CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival;

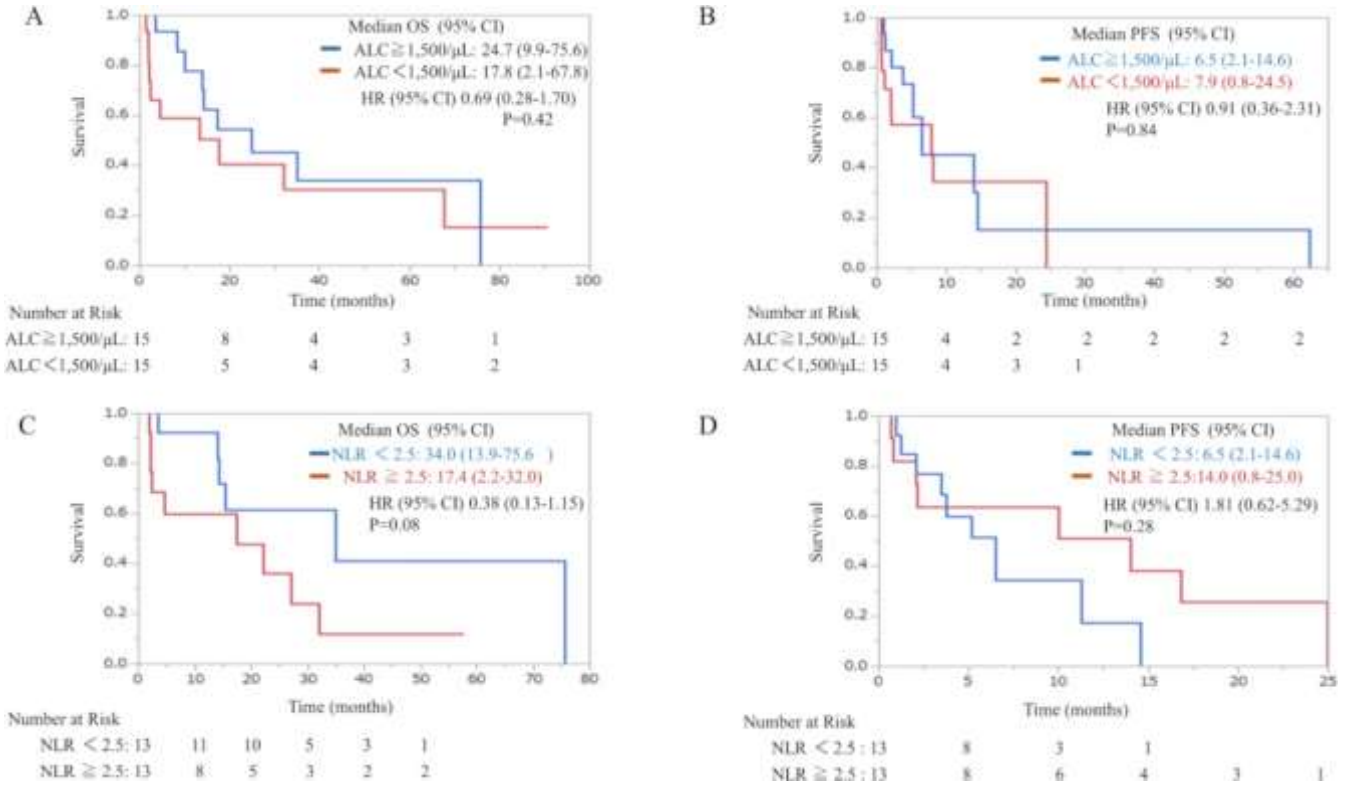

Figure 5: Kaplan–Meier plot of OS in relation to ALC (a), PFS in relation to ALC (b), OS in relation to NLR (c), PFS in relation to NLR (d) in the TPC group after propensity-score matching. ALC, absolute lymphocyte count; CI: confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; TPC, treatment of physician's choice.

PFS in the H-ALC and L-ALC groups showed no statistical significance (HR, 0.91; 95% CI: 0.36–

2.31): mPFS was 6.5 months in the H-ALC group versus 7.9 months in the L-ALC group (Figure 5a, b). Similarly, after matching for NLR,the L-NLR (n = 13) and H-NLR (n = 13) groups showed statistically significant differences only for age and DFI (Table 3). OS in the L-NLR and H-NLR groups showed no statistical significance (HR, 0.38; 95% CI: 0.13–1.15): mOS was 34.0 months in the L-NLR group versus 17.4 months in the H-NLR group. PFS in the L-NLR and H-NLR groups showed no statistical significance (HR, 1.81; 95% CI: 0.62– 5.29): mPFS was 6.5 months in the L-NLR group versus 14.0 months in the H-NLR group (Figure 5c, d).

Discussion

Results showed that high ALC was associated with a better prognosis in patients treated with first-line eribulin chemotherapy, but not with TPC. Patients in the eribulin group who had an ALC 1500/L had higher OS than those in the eribulin group who had an ALC 1500/L, but there was no difference in PFS in the post-hoc analysis of the EMBRACE study [2]. Moreover, the TPC group failed to demonstrate this correlation [2]. However, a pretreatment myelosuppressive impact may have affected the results of the EMBRACE research as it was conducted in a late-line context. Therefore, "baseline ALC and NLR should be further evaluated in patients receiving first-line eribulin treatment [2]," as stated by Miyoshi et al. Our research is the first to evaluate the prognostic significance of baseline ALC and NLR in individuals with MBC who were first given eribulin or TPC. Baseline ALCs for eribulin and TPC in the EMBRACE study were, respectively, 1308/L (1000-1814/L) and 1307/L (991-1697/L). Both eribulin and TPC had median (IQR) baseline NLRs of 3.1 (2.1-4.4) and 3.1 (2.1-4.2), respectively [2]. Baseline ALCs for eribulin and TPC in this first-line research group, in comparison, were 1690 (range, 1060-2142) and 1496 (range, 1076-2111) ng/mL, respectively. Due to less compromised bone marrow function, eribulin and TPC baseline NLRs were 2.2 (1.5-3.0) and 2.1 (1.7-3.5), respectively. It's intriguing that consistent outcomes were seen across treatment groups and line configurations.

There is ongoing discussion on whether biomarker, ALC or NLR, is the better fit for eribulin. In a retrospective study of ALC and NLR in MBC patients treated with eribulin, Watanabe et al. [6] found that ALC was a more relevant immune-related measure than NLR. NLR may be a universal prognostic factor, according to a post hoc analysis of the EMBRACE trial [2], which found that it was related with good PFS and OS in both the eribulin and TPC groups. NLR in this research was related with better OS in the unadjusted group, but it was not associated with better OS in the PSM cohort receiving first-line eribulin treatment. Therefore, we consider ALC to be a more informative measure than NLR in eribulin-treated individuals.

Reversal of epithelial-mesenchymal transition [11, 12], reoxygenation through vascular remodeling [13], and enhanced tumor immunity [14] are only a few of the unique modes of action attributed to the tubulin inhibitor eribulin. Our previous research [15] into the clinical significance of transforming growth factor- (TGF-), a local marker of host immunity, and alpha-lactamase activity (ALC), a systemic marker, revealed that patients who benefited from eribulin therapy had higher baseline ALC and TGF- levels were significantly decreased before and after treatment. We conclude that eribulin, which can be measured by ALC, enhances the tumor immune microenvironment by decreasing TGF- expression. Thus, it was hypothesized that individuals with more ALC in the peripheral blood sustain a more conducive immunological milieu, increasing the likelihood that they would respond favorably to eribulin treatment. The findings do not suggest that eribulin is preferable to other medicines for patients with high ALC, although it should be emphasized that this trial did not compare the effectiveness of eribulin to that of other drugs.

Several problems plagued this research. To begin with, it was not a randomized trial but rather a retrospective observational study with several inherent flaws. Second, we used PSM to account for these biases, however the already small size of the unadjusted cohort meant that the sample size was further decreased by PSM. Third, following PSM, there were still differences between the eribulin and TPC groups on several characteristics. Therefore, it is important to assess the results of our research carefully and draw only limited conclusions from them.

Therefore, high ALC may be a predictive factor of OS even in first-line treatment with eribulin, and ALC is an effective prognostic marker of eribulin in both the late-line and first-line settings. This correlation was not seen with other treatments, suggesting that eribulin's novel effects, such enhancing the tumor immune microenvironment, are responsible.

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Conflicts of interests

Author Tsutomu Takashima received honoraria from Eisai Co., Ltd., Chugai Pharmaceutical Co. Ltd, Pfizer Japan Inc., Daiichi-Sankyo Co., Ltd., and Kyowa Kirin Co., Ltd.

The remaining authors have no relevant financial or non-financial conflicts of interests.

Author contributions

All authors contributed to the conception and design of this study. Material preparation, data collection, and analysis were performed by Kosei Kimura and Tsutomu Takashima. The first draft of the manuscript was edited by Kosei Kimura, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to Ethical Guidelines for Medical and Health Research Involving Human Subjects but are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Osaka Medical and Pharmaceutical University (2020-188, March 24, 2021) and
Osaka Metropolitan University (April 06, 2021).

Consent to participate

Informed consent was obtained from all institutions or websites of each institution in the form of an opt-out. Patientswho did not provide consent were excluded.

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