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TheRelationshipbetweenHighAbsoluteLymphocyteCountsandFavorable Prognosis in Eribulin Therapy is seen in First-Line Chemotherapy for Metastatic Breast Cancer: CombinedAnalysis of Two Phase 2 Studies

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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:Two phase 2 studies (BIRICHEN and OMC-BC 03) were retrospectively assessed to determine the efficacy of first-line eribulin chemotherapy in patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). 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.

Keywords: Metastaticbreastcancer,Overallsurvival,Eribulin,Treatment of 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-lutelymphocytecount(ALC), an immune response measure, was shown to be a predictive predictor of overall survival (OS) following treatment with eribulin[2] in a recent ad hoc analysis of the study.Interestingly,ALCwasnot a diagnostic indicator for the TPC group (physician's choice treatment)[2].In early-stage breast cancer, the neutrophil-to-lymphocyte ratio (NLR) is an important prognostic predictor [2, 3]. In both the eribulin and TPC groups, NLR was associated with improved progression-free survival (PFS) and overall survival (OS) in an ad hoc analysis of the EMBRACE trial[2].However, past chemotherapy must have affected the blood cell count, since that is the treatment that the experiment focused on.Patients undergoing first-line chemotherapy should have their ALC and NLR assessed at the outset to account for the potential impact of prior treatment on blood cell counts.

In two phase 2 studies, we calculated the effectiveness of eribulin as first-line chemotherapy for HER2-negative metastatic breast cancer in Japan, and the results were impressive [4, 5]. To test the hypothesis that ALC is a prognostic marker for first-line eribulin treatment but not for TPC, we compared baseline ALC and NLR in patients who participated in these studies with patients with first-line TPC who were treated at the same time.

PatientsandMethods

Patients

In this analysis, we compared two groups (eribulin and TPC groups). Fifty-nine patients with HER2-negative MBC were enrolled in the eribulin group; 35 were treated with first-line chemotherapy with eribulin in the BIRICHEN trial (UMIN000006086) [4] and 24 were treated with first- and second-line chemotherapy in the OMC-BC 03 trial (UMIN000009568) [5]. At the same time as the OMC-BC 03 trial (1 March 2013–1 March 2017), we recruited 48 patients with HER2-negative MBC who had previously undergone first-line chemotherapy with drugs other than eribulin at Osaka Medical and Pharmaceutical University Hospital for the TPC group. Patients who had prior endocrine treatment were considered, but those who had molecularly targeted therapy (such as CDK4/6 inhibitors or mTOR inhibitors) were not.

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Treatment

Our prior research [4, 5] outlines the dose plan for eribulin in detail. In the TPC group, patients received either FEC (epirubicin 100 mg/m2, 5-fluorouracil [5-FU]500 mg/m2,andcyclophosphamide500 mg/m2every 3 weeks), bevacizumab(Bmab)pluspaclitaxel(PTX)(Bmab 10 mg/kg on days 1 and 8 and PTX 80 mg/m2 on days 1, 8, and 15 every 4 weeks), weeklyPTX

Assessment

Data on blood cell counts were taken on or before the first day of chemotherapy treatment and compared to outcomes. The median value of each parameter and an earlier study[6] were used to determine the cutoff values of ALC (set at 1500/mm3) and NLR (set at 2.5).

Mathematical dissection

For continuous variables, we computed means, medians, and IQRs. For both dichotomous and polychotomous variables, counts and percentages were presented. The Kaplan-Meier technique was used to estimate the PFS and OS curves for ALC and NLR, and the log-rank test was used to compare the two groups. Cox proportional hazards models were used to assess the hazards ratios (HRs) for transitioning from high to low ALC or low to high NLR.Median follow-up time was calculated by averaging the follow-up times of all instances that were censored.

Propensity-score matching (PSM) and unadjusted analyses were used to draw comparisons. To reduce potential baseline confounders, we used nearest-neighbor matching to create a one-to-one (1:1)PSM between the high (H-) and low (L-)ALCor H-NLR and L-NLR groups in both the eribulin and TPC groups [7-9].Disease-free interval (DFI) (2 years, 2 years, or de novo), subtype (estrogen receptor-positive or triple-negative breast cancer), and age (65 or 65 years) were the matching factors. Standardized differences (SDs) were determined after matching, and values below 0.1 were used to indicate satisfactory variable balance following PSM [10]. We used JMP 13 (SAS Institute Inc., Cary, NC, USA) to conduct all of our statistical tests.

EthicsCommittees

Osaka Medical and Pharmaceutical University and Osaka Metropolitan University's respective ethical committees gave their stamp of approval to this research. All participating universities or their own websites implemented an opt-out system to ensure that all participants provided informed permission. Nonconsenting patients were not included in the study.

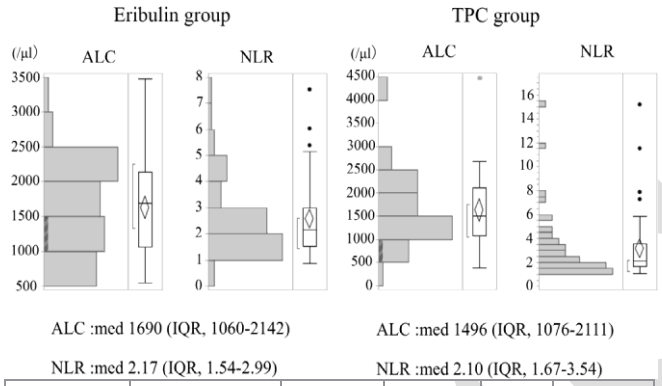
Results

Patients

Table 1 displays the baseline characteristics of the eribulin and TPC patient groups. There were 16 (33.3%) patients given anthracycline (FEC), 12 (25.0%) patients given Bmab + PTX, 3 (6.3%) patients given weekly PTX, 11 (22.9%) patients given S-1, 5 (10.4%) patients given capecitabine, and only 1 (2.1%) patient given vinorelbine in the TPC group. Sixty percent of those with a failed TPC were given eribulin in either course of therapy. Median (Interquartile Range) eribulin and TPC group baseline ALCs were 1690 and 1496 pg/mL, respectively.

Table1: Demographicsandbaselinecharacteristicsofthepatients

		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	Denovo	14	24%	27	56%
	<2y	21	36%	2	4%
	≥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%
Eribulinon eithertreat-ment line	No	59	100%	29	60%
	Yes	0	0%	19	40%



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

InboththeeribulinandTPCgroups,PS0andDFIover2 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.

Propensity-scorematching

H-ALC and L-ALC were subjected to PSM in the eribulin group.Age, subtype, and disease-free interval were significantly different between the H-ALC (n=19) and L-ALC (n=19) groups after matching (Table3).The statistically significant difference in OS between the H-ALC and L-ALC groups was mOS, which was 32.0 months in the H-ALC group and 19.6 months in the L-ALC group (HR,0.43;95%CI:0.18-0.99).There was no statistically significant difference in PFS between the H-ALC and L-ALC groups (HR, 1.05; 95% CI, 0.51-2.15 months): median progression-free survival (mPFS) was 7.2 months in the H-ALC group and 6.2 months in the L-ALC group (Figure 4a, b). Similarly, when NLR was controlled for, Table 3 only revealed statistically significant differences between the L-NLR (n=17) and H-NLR (n=17) groups in terms of subtype and DFI. There was no statistically significant difference between the L-NLR and H-NLR groups in terms of OS (HR, 0.65; 95% CI, 0.27-1.58), with the median OS being 32.0 months in the L-NLR group and 16.1 months in the H-NLR group, respectively. The median progression-free survival (mPFS) between the L-NLR and H-NLR groups was 5.8 months in the former and 5.6 months in the latter (Figure 4c, d), although there was no statistically significant difference between the two groups (HR, 0.76; 95% CI: 0.35- 1.62).

After controlling for ALC, the only significant differences between the H-ALC(n = 15) and L-ALC(n = 15) groups in the TPC group were in age and PS (Table 3).The median overall survival (OS) between the H-ALC and L-ALC groups was 24.7 months (HR,0.69;95%CI,0.28-1.70).

Figure 1: Distribution of ALC and NLR in the eribulin and TPC groupsALCabsolutelymphocytecount;IQRinterquartilerange;med,median; NLR neutrophil-to-lymphocyte ratio; TPC treatment of physician's choice.

Table2: DemographicsandbaselinecharacteristicsofpatientscategorizedbyALCorNLR

		Eribulingroup										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
	<65yr	14	54	15	46	0.16	13	57	16	44	0.26	14	56	10	43	0.25	11	52	13	48	0.08
	≥65yr	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
	<2yr	12	46	9	27	0.40	13	57	8	22	0.77	0	0	2	9	0.44	0	0	2	7	2.16
	≥2yr	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,treatmentofphysician'schoice;ALC,absolutelymphocytecount;NLR,neutrophil-to-lymphocyteratio;SD,standardizeddifference, PS,performancestatus;DFI,disease-freeinterval;IQR,interquartilerange;ER,estorogenreceptor;TN,triple-negative

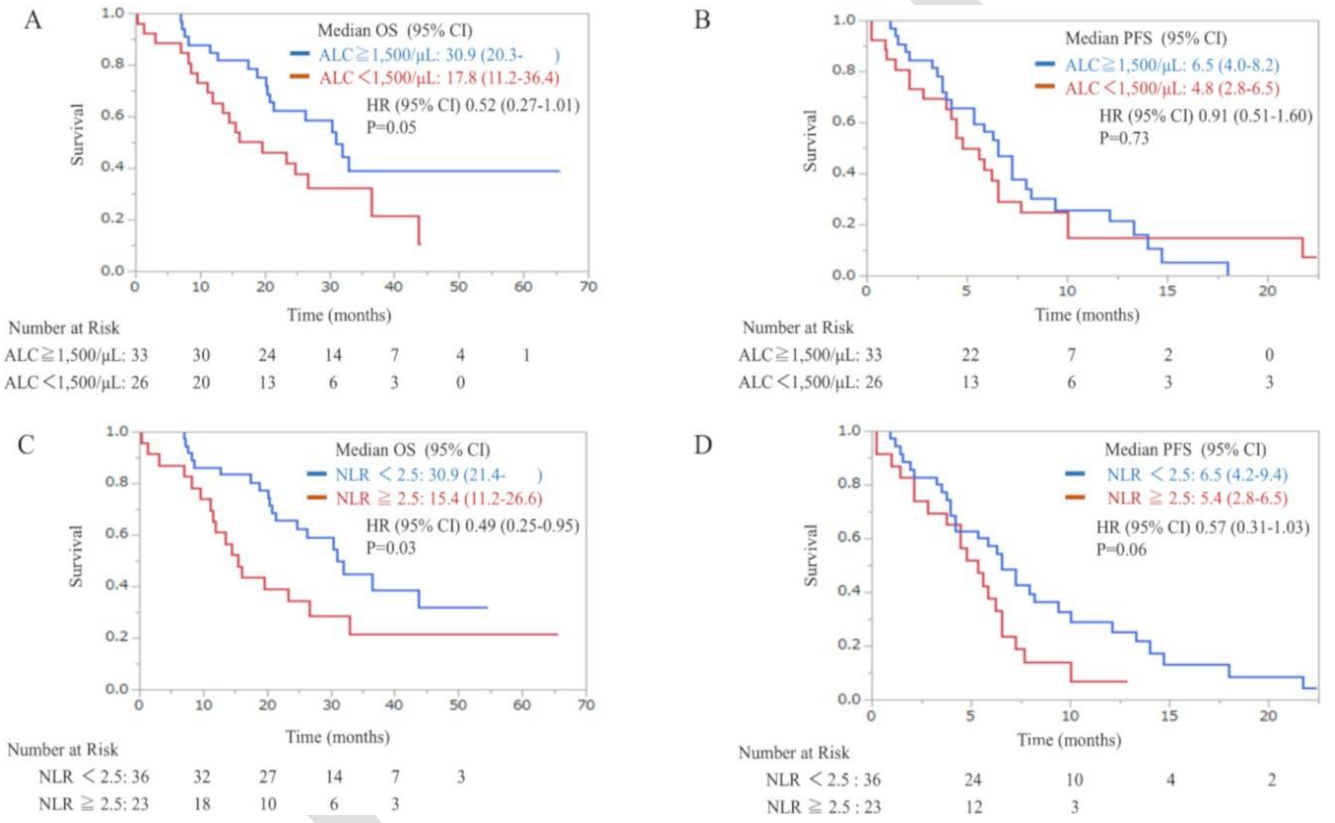


Figure2: Kaplan–MeierplotsofOSinrelationtoALC(a),PFSinrelationtoALC(b),OSinrelationtoNLR(c),andPFSinrelationtoNLR(d)intheeribulingroup.ALC,absolutelymphocytecount;CI,confidenceinterval;HR,hazardratio;NLR,neutrophil-to-lymphocyteratio;OS,overallsurvival;PFS,progression-freesurvival

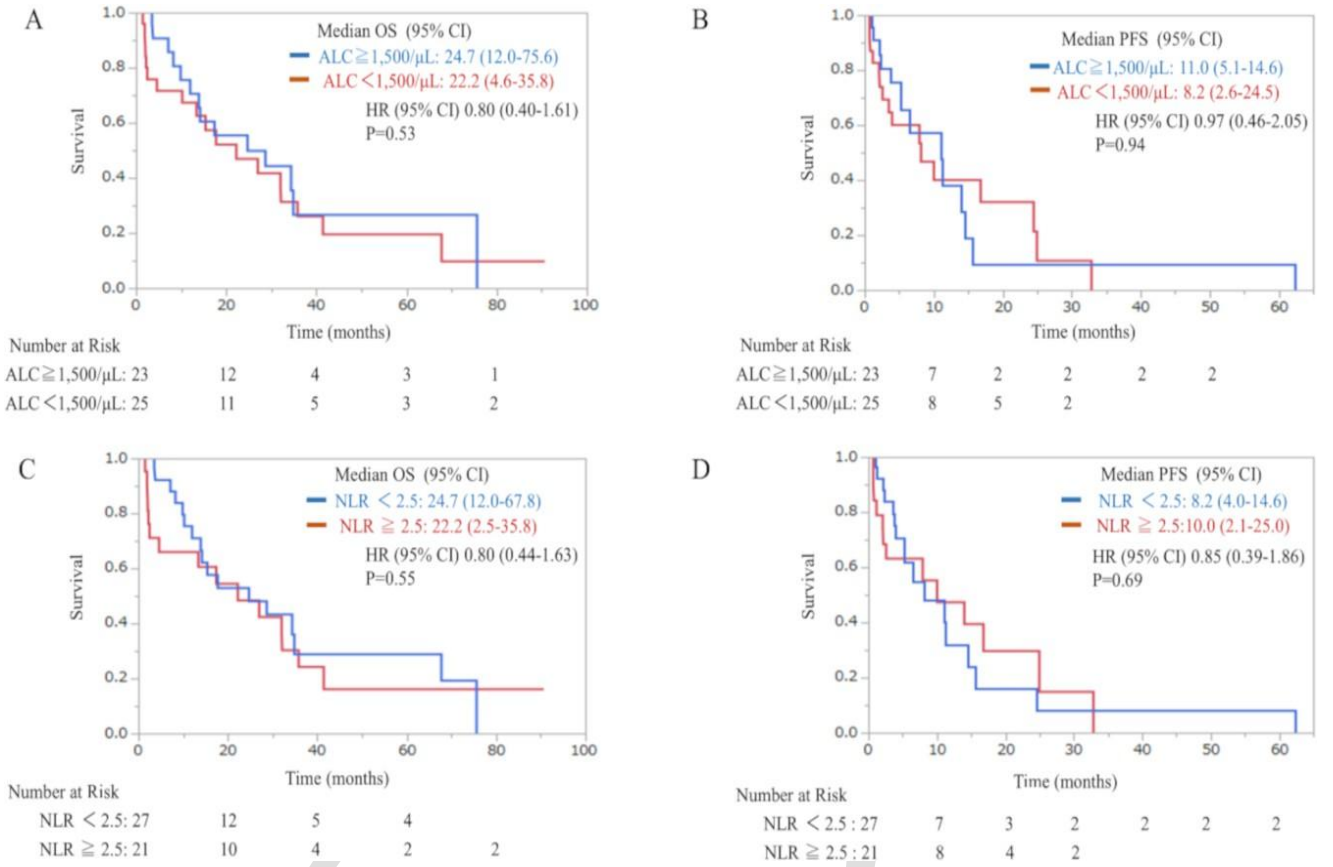


Figure 3: Kaplan–Meier plots of OS in relation to ALC (a), PFS in relation to ALC (b), OS in relation to NLR (c), and PFS in relation to NLR (d) in the TPCgroup.ALC,absolutelymphocytecount;CI:confidenceinterval;HR,hazardratio;NLR,neutrophil-to-lymphocyteratio;OS,overallsurvival;PFS,progression-free survival; TPC, treatment of physician's choice

Table3: DemographicsandbaselinecharacteristicsofpatientscategorizedbyALCorNLRafterPSM

		Eribulingroup										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
	<65yr	10	53	11	58	0.11	8	47	8	47	0.00	7	47	9	60	0.26	5	38	6	46	0.14
	≥65yr	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	Denovo	3	16	4	21	0.14	4	24	3	18	0.15	9	60	9	60	0.00	8	62	7	54	0.16
	<2yr	9	47	8	42	0.11	7	41	7	41	0.00	0	0	0	0	0.00	0	0	0	0	0.00
	≥2yr	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,treatmentofphysician'schoice;ALC,absolute lymphocytecount;NLR,neutrophil-to-lymphocyte ratio;PSM,propensity-score matching; SD,standardizeddifference;PS,performancestatus;DFI,disease-free interval;IQR,interquartilerange;ER,estorogenreceptor; TN,triple-negative

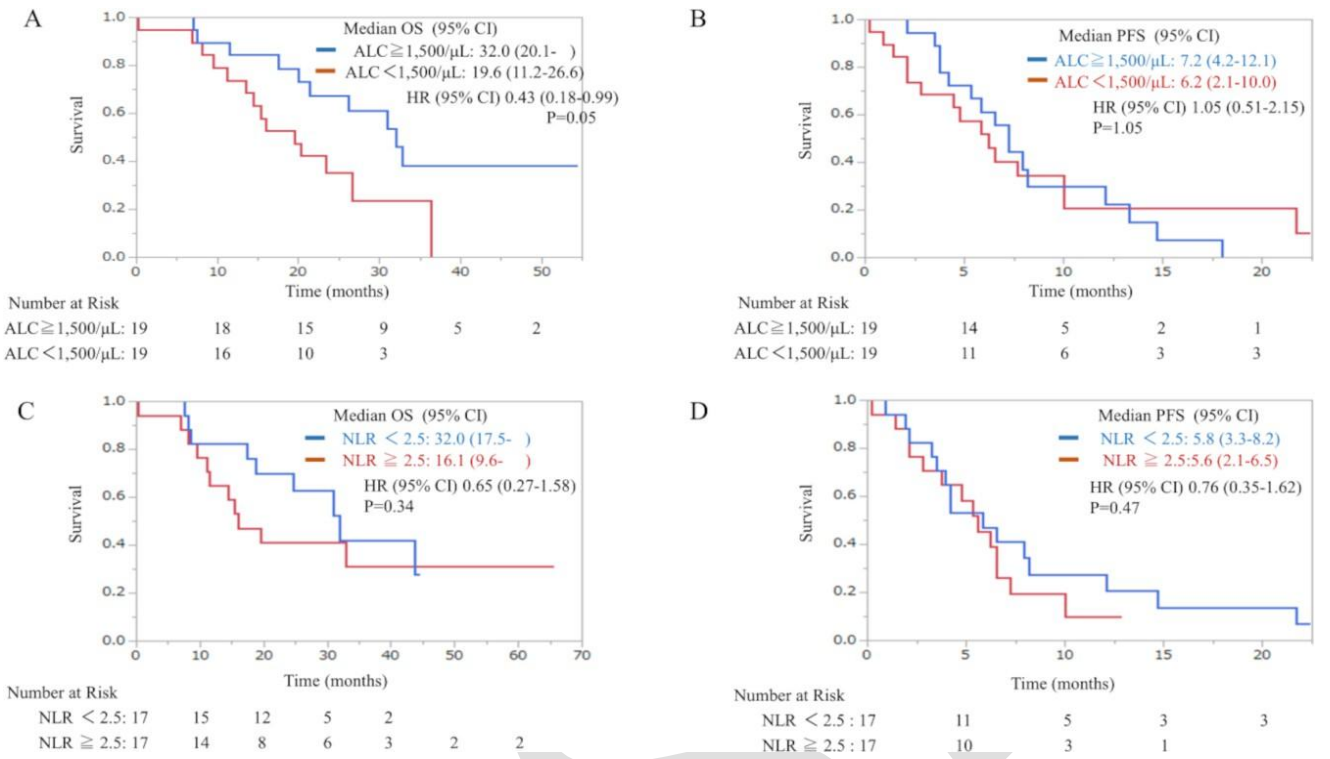


Figure4: Kaplan–MeierplotsofOSinrelationtoALC(a),PFSinrelationtoALC(b),OSinrelationtoNLR(c),andPFSinrelationtoNLR(d)intheeribulingroup after propensity-score matching. ALC, absolute lymphocyte count; CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS,overallsurvival;

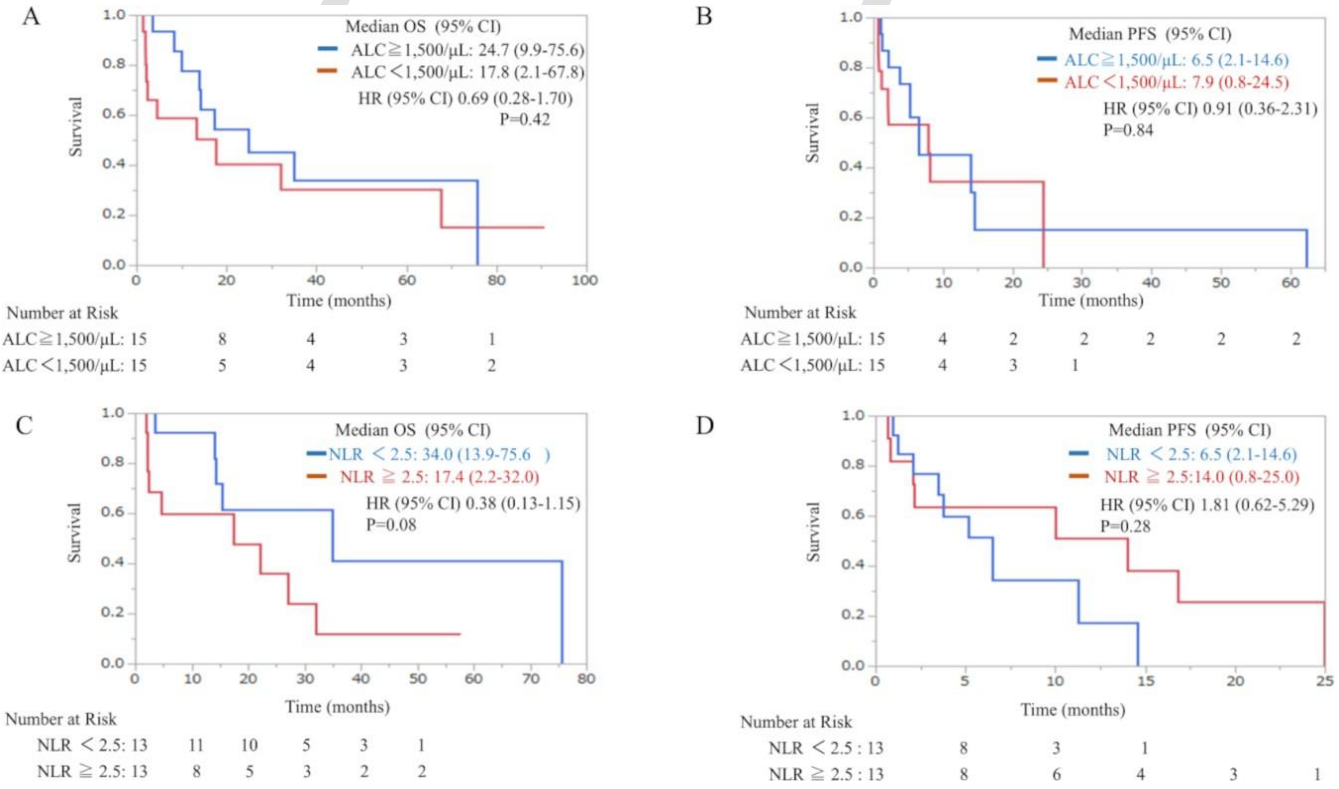


Figure5: Kaplan–MeierplotofOSinrelationtoALC(a),PFSinrelationtoALC(b),OSinrelationtoNLR(c),PFSinrelationtoNLR(d)intheTPCgroupafterpropensity-scorematching.ALC,absolutelymphocytecount;CI:confidenceinterval;HR,hazardratio;NLR,neutrophil-to-lymphocyteratio;TPC,treatment of physician's choice.

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 monthsintheH-ALCgroupversus7.9monthsintheL-ALC group(Figure5a,b).Similarly,aftermatchingforNLR, 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):mPFSwas6.5monthsintheL-NLRgroupversus14.0 months in the H-NLR group (Figure 5c, d).

Discussion

In first-line eribulin treatment, this research found that patients with high ALC had a better prognosis than those with TPC.Patients randomized to the eribulin group with an ALC 1500/L had higher OS than those with an ALC 1500/L in the post-hoc analysis of the EMBRACE trial[2], but no difference was seen in PFS. In addition, this association was not seen in the TPC sample [2]. It is possible that a pretreatment myelosuppressiveeffect affected the results, since the EMBRACEstudyevaluatedalate-linesetting.According to the findings of Miyoshietal., "baseline ALC and NLR should be further evaluated in patientsreceivingfirst-lineeribulintreatment[2]."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). Baseline normalized ratios (NLRs) for both ferritin and TPC were 3.1 (2.1-4.2) [2]. In contrast, the median(IQR) baseline ALCs for eribulin and TPC in this first-line research group were 1690/L (1060-2142/L) and 1496/L (1076-2111/L), respectively. Median (IQR) baseline NLRs for eribulin and TPC were 2.2 (1.5-3.0) and 2.2 (1.5-3)

less reduced bone marrow function, leading to a 2.1 (1.7-3.5) rating. Despite variations in treatment settings and populations, comparable findings were found.

The ALC vs. NLR argument for eribulin biomarkers continues. Based on a retrospective analysis of ALC and NLR in MBC patients receiving eribulin medication, Watanabe et al. [6] concluded that ALC was a more relevant immune-related measure than NLR.However, NLR may be a general prognostic marker, since it was linked to improved PFS and OS in a post-hoc analysis of the EMBRACE trial[2].NLR was linked with better OS in the unadjusted group but not in the PSM cohort receiving first-line eribulin treatment. Therefore, we consider ALC to be a more helpful measure than NLR in eribulin-treated individuals.

Reversal of epithelial-mesenchymal transition [11, 12], reoxygenation via vascular remodeling [13], and enhanced tumor immunity [14] are only a few of the unique modes of action attributed to the tubulin inhibitor eribulin. Patients who responded well to eribulin therapy had higher ALC at baseline, and TGF- levels were significantly decreased before and after treatment [15]. These results corroborate our previous work examining the clinical significance of transforming growth factor- (TGF-), a local marker of host immunity, and ALC, a systemic marker. We conclude that eribulin, which can be measured by ALC, enhances the tumor immune microenvironment by decreasing TGF- expression. Patients with greater levels of ALC in their peripheral blood were thought to have a more conducive immunological milieu, making them better candidates for 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.

There were a number of caveats to this research. In the first place, it was an observational study that wasn't a randomized controlled trial and had certain inherent flaws.Second, we applied PSM to compensate for these biases, however because of the limited sample size of the unadjusted cohort, PSM further decreased the sample size. 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.

In conclusion, ALC is an excellent prognostic marker of eribulin in both the late-line and first-line settings, with high ALC perhaps being a predictive component of overall survival (OS) in the first-line context. This correlation was not seen with other treatments, suggesting that eribulin's special effects, such enhancing the tumor immune microenvironment, are responsible.

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