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Pre-treatment Neutrophil-to-Lymphocyte Ratio Predicts Efficacy of Eribulin for Soft-tissue Sarcoma

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Abstract. *Background: Eribulin is widely used for the treatment of breast cancer and soft-tissue sarcoma (STS). Previous studies identified the pre-treatment absolute lymphocyte count, baseline neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein concentration as potential prognostic markers in patients with breast cancer treated with eribulin. However, prognostic factors for eribulin treatment in patients with STS have not been identified. Patients and Methods: This was a retrospective analysis of data collected prospectively from 53 patients who were treated with eribulin for recurrent or metastatic STS between March 2016 and August 2019. Univariate and multivariate analyses were performed to determine the predictive factors of durable clinical benefit, progression-free survival, and overall survival. Results: L-Sarcoma histology [hazard ratio (HR)=28.20, 95% confidence intervaI (CI)=1.67-476.00; p=0.021] and pre-treatment NLR <3.0 (HR=9.96, 95% CI=1.28-77.7; p=0.028) were independent factors predictive of durable clinical benefit. In addition, pre-treatment NLR <3.0 (HR=0.34, 95% CI=0.16-0.74; p=0.0059) and male sex (HR=0.23, 95% CI=0.10-0.52; p<0.001) were independent factors predictive of better progression-free survival. Conclusion: This retrospective study found that baseline NLR predicts the efficacy of eribulin for STS.*

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Eribulin mesylate (eribulin), a synthetic analog of halichondrin B that was originally isolated from the marine sponge *Halichondria okadai*, targets microtubules by suppressing dynamic instability at their positive ends through the inhibition of microtubule growth, with minimal effect on shortening (1, 2).

Eribulin was demonstrated to significantly improve overall survival (OS) in patients with locally advanced and metastatic breast cancer in a randomized phase III trial (EMBRACE) comparing eribulin with the physician's choice of treatment (3). In another phase III trial, eribulin also provided OS benefits in patients with advanced liposarcoma or leiomyosarcoma (hereafter referred to as L-sarcoma) who had received previous systemic chemotherapy with anthracycline compared with patients who were administered dacarbazine (4). Moreover, the findings of a Japanese phase II study of patients with soft-tissue sarcoma (STS) other than L-sarcoma supported the approval of eribulin for all histological subtypes of STS in Japan (5). Based on these results, eribulin was approved as a monotherapy for the treatment of inoperable and recurrent breast cancer and for recurrent or metastatic STS in Japan.

A *post hoc* analysis of the EMBRACE study identified the baseline absolute lymphocyte count (ALC) at a cut-off value of 1,500/μl as a potential predictor of OS in patients with breast cancer treated with eribulin. It also established the baseline neutrophil-to-lymphocyte ratio (NLR) at a cut-off value of 3.0 as a general prognostic marker of OS in patients with breast cancer but not a specific predictor of OS in eribulin-treated patients (6). Furthermore, a retrospective study of 74 patients with breast cancer treated with eribulin showed that baseline C-reactive protein (CRP) along with baseline ALC and NLR were associated with OS (7). However, prognostic predictors of eribulin for patients with STS have not been identified. The present study aimed to assess factors

predictive of the efficacy of eribulin monotherapy, including ALC, NLR and CRP, for patients with STS.

Patients and Methods

Patients. We retrospectively analyzed prospectively collected data from 53 consecutive patients with recurrent or metastatic STS who began treatment with eribulin at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR) between March 2016 and August 2019. The database comprised the following patient characteristics: Age, sex, histological diagnosis, location of the primary tumor, Eastern Cooperative Oncology Group performance status (ECOG PS), number of previous systemic chemotherapies, and the absolute neutrophil count (ANC), ALC, and CRP of blood samples collected within a week before the first infusion. These factors were categorized as follows: Age: <65 years and ≥65 years; histology: L-sarcoma (leiomyosarcoma and liposarcoma) and non-L-sarcoma; location of the primary tumor: extremities and non-extremities; ECOG PS: 0 and ≥1; number of previous systemic chemotherapies: 0-1 and ≥2; ALC: <1,500/μl and ≥1,500/μl; NLR (calculated as the ANC divided by the ALC): <3.0 and ≥3.0; and CRP:<0.3 mg/dl and ≥0.3 mg/dl.

Eribulin was administered at a dose of 1.4 mg/m^2 on days 1 and 8 every 3 weeks. Dose reductions to 1.1 and 0.7 mg/m^2 were permitted at the physician's discretion. Dosing was adjusted or discontinued depending on the condition of each individual patient. All treatment was continued until the occurrence of unacceptable adverse effects or disease progression.

The requirement for informed consent was waived because the data were reported anonymously. This study was approved by the Institutional Review Board of the Cancer Institute Hospital of the JFCR.

Statistical analysis. PFS and OS were estimated using the Kaplan–Meier method and the log-rank test. Data were censored on October 31, 2020. Patients who were lost to follow-up were censored at the date of last contact or follow-up. PFS was calculated from the date of eribulin initiation to the date of disease progression or death from any cause. OS was calculated from the date of eribulin initiation to the date of death from any cause. Patients who were alive on October 31, 2020 were censored for OS analysis. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (8), based on computed tomographic findings. The best overall response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The overall response corresponded to the sum of the CR and PR, and disease control to the sum of the CR, PR, and SD rates. Durable clinical benefit (DCB) was defined as CR, PR, or SD that lasted more than 6 months. We performed univariate and multivariate analyses estimating factors potentially prognostic of PFS, OS, and DCB; we calculated hazard ratios (HRs) using a Cox proportional hazards model for PFS and OS, and logistic regression analysis for DCB. The level of significance was set to $p<0.1$ for the univariate analysis and $p<0.05$ for the multivariate analysis, and was two-sided. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (www.r-project.org). More precisely, it is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics (9).

Table I. *Baseline characteristics of the study patients (n=53).*

Characteristic		n (%)
Age	≥65 Years	23 (43)
Gender	Male	21 (40)
Histology	L-Sarcoma	34 (64)
Location of primary lesion	Extremity	13 (25)
ECOG PS	0	32 (60)
	1	20 (38)
	2	1 (2)
No. of previous chemotherapies	1	22 (42)
	≥2	31 (58)
ALC	≥1,500/μl	13 (25)
	<1,500/μl	39 (74)
	Not evaluated	1 (2)
NLR	≥3.0	26 (48)
	<3.0	26 (48)
	Not evaluated	1 (2)
CRP	≥0.3 mg/dl	21 (60)
	<0.3 mg/dl	32 (40)

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein.

Table II. *Efficacy of eribulin monotherapy in the study patients (n=53).*

		n (%)
Best overall response	CR	0 (0)
	PR	3 (6)
	SD	19 (36)
	PD	30 (57)
	Not evaluable	1 (2)
Objective response		3 (6)
Disease control		22 (42)
Durable clinical benefit		15 (28)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Results

Patient characteristics. A total of 53 patients with STS were treated with eribulin between March 2016 and August 2019. The 53-patient cohort included 21 men and the median age was 61 years (range=23-76). The median duration of observation was 12.8 months (range=1.2-54.7 months). All patients had received doxorubicin as a perioperative or an earlier-line chemotherapy, regardless of histological subtype. The patient characteristics are shown in Table I. Of the 53 patients, one (2%) had no available baseline blood cell count data. The median pretreatment ANC was 3,210/μl (range=1370-24,950/μl), while the ALC was 1,135/μl (range=100-3,420/μl) and the median NLR was 2.99/μl (range=0.89-91.20/μl).

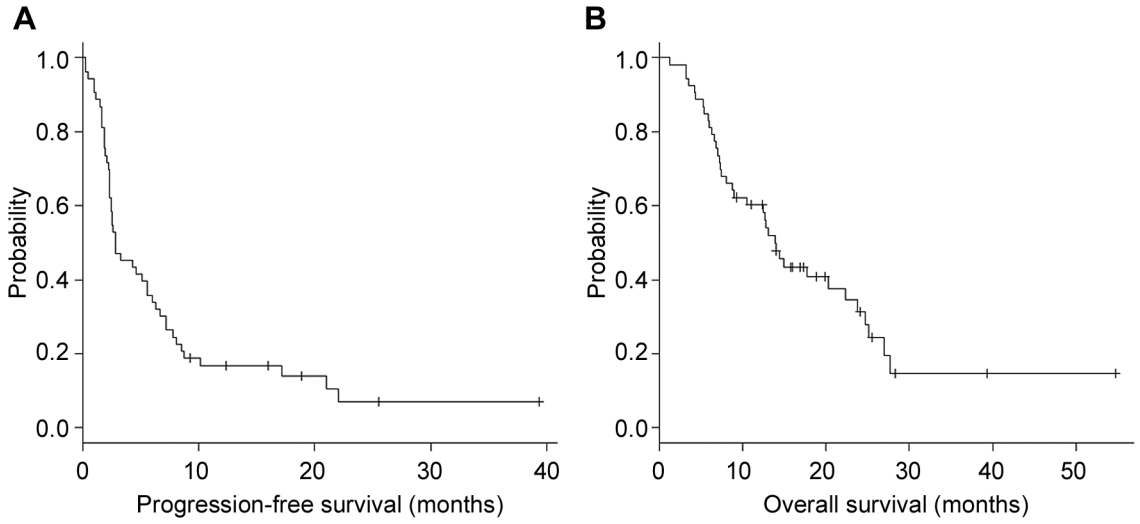

Figure 1. *Kaplan–Meier curves for progression-free (A) and overall (B) survival of patients treated with eribulin for soft-tissue sarcoma (n=53).*

Clinical efficacy of eribulin. The overall response rate was 6% (n=3) and the DCR rate was 42% (n=15) (Table II). Eribulin was withdrawn in one patient without evaluation of best overall response because of a deterioration in their general condition. The median PFS and OS were 2.8 [95% confidence interval (CI)=2.3-5.5] and 13.9 (95% CI=8.8-22.3) months, respectively (Figure 1).

Predictive factors for DCB, PFS, and OS. As shown in Table III, multivariate analysis indicated that L-sarcoma histology (HR=28.20, 95% CI=1.67-476.00; p=0.021) and pre-treatment NLR <3.0 (HR-9.96, 95% CI-1.28-77.7; p=0.028) were independent predictors of DCB. Age, ECOG PS, primary lesion, ECOG PS, ALC, and CRP were not associated with DCB.

Moreover, as shown in Table IV, multivariate analysis indicated that pre-treatment NLR <3.0 (HR=0.34, 95% CI=0.16-0.74; p=0.0059) and male sex (HR=0.23, 95% CI=0.10-0.52; p<0.001) were independent predictors of better PFS. However, only the number of previous chemotherapies ≥2 (HR=2.65, 95% CI=1.17-6.01; p=0.020) was associated with worse OS (Table V).

Discussion

In this study, we investigated predictive factors of eribulin monotherapy for patients with STS, including ALC and NLR. Notably, we identified low pre-treatment NLR (<3.0) and L-sarcoma histology as independent predictors of DCB. Low pre-treatment NLR (<3.0) and male sex were also established as independent predictors of prolonged PFS. Unlike breast cancer, ALC was not a predictive factor of eribulin for patients with STS.

To the best of our knowledge, no other study has evaluated NLR in eribulin-treated patients with STS. In the present study, low baseline NLR (<3.0) was identified as an independent predictive marker of DCB and better PFS for patients with STS treated with eribulin. A previous study of 85 patients with breast cancer treated with eribulin reported that the PFS of patients with a low baseline NLR (<3.0) was better than that of patients with a high NLR (≥3.0) (10). These data suggested that the NLR may be a potential predictive marker of eribulin monotherapy in multiple cancer types.

Some previous reports suggested that the NLR may reflect the antitumor immunity status and associated prognosis of cancer patients. Rosenberg *et al*. reported that neutrophils promote tumor progression, while lymphocytes are associated with the elimination of cancer cells (11). A systematic review and meta-analysis showed that the NLR reveals the balance of the immune system, while being associated with survival in patients with solid tumors (12). Moreover, Chen *et al*. reported that the NLR reflects the profile of the cytokines and chemokines activating $CD4^+$ and $CD8^+$ T-lymphocytes, which regulate antitumor immunity (13).

Unlike breast cancer, the baseline NLR was not correlated with the OS of patients with eribulin-treated STS, and only the number of previous chemotherapies was an independent predictor of OS. It is reasonable that OS was shorter in later-line chemotherapy, and our results suggested that the therapeutic impact of eribulin for STS was not sufficient to extend OS in these cases.

In the present study, L-sarcoma histology was also an independent predictor of DCB. Previous studies evaluated the differences in the efficacy of eribulin between the histological subtypes of STS. A phase II trial of patients with

Table III. *Univariate and multivariate analyses of factors associated with durable clinical benefit.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥65 *vs.* <65 years	0.56 (0.16-1.94)	0.36	0.25 (0.040-1.58)	0.14
Gender	Male *vs.* female	3.25 (0.94-11.2)	**0.062**	4.45 (0.65-30.70)	0.13
Histology	L-Sarcoma *vs.* other	12.60 (1.50-106.0)	**0.020**	28.20 (1.67-476.0)	**0.021**
Primary lesion	Extremity *vs.* other	1.87 (0.50-7.07)	0.35		
ECOG PS	≥1 *vs.* 0	0.15 (0.031-0.78)	**0.023**	0.49 (0.062-3.81)	0.49
No. of previous chemotherapies	≥2 *vs.* 0-1	0.35 (0.10-1.19)	**0.092**	1.03 (0.17-6.15)	0.97
ALC	<1,500 *vs.* ≥1,500/μl	1.31 (0.30-5.68)	0.71		
NLR	<3.0 *vs.* ≥3.0	3.44 (0.91-13.00)	**0.068**	9.96 (1.28-77.7)	**0.028**
CRP	<0.3 *vs.* ≥0.3 mg/dl	3.25 (0.94-11.20)	**0.062**	2.15 (0.31-15.00)	0.44

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein. Statistically significant *p*-values are shown in bold.

Table IV. *Univariate and multivariate analyses of factors associated with progression-free survival.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥65 *vs.* <65 Years	1.48 (0.81-2.68)	0.20	1.34 (0.69-2.62)	0.38
Gender	Male *vs.* female	0.36 (0.19-0.70)	**0.0023**	0.23 (0.10-0.52)	**<0.001**
Histology	L-Sarcoma *vs.* other	0.51 (0.27-0.94)	**0.032**	0.55 (0.27-1.12)	0.098
Primary lesion	Extremity *vs.* other	0.96 (0.50-1.85)	0.90		
ECOG PS	≥1 *vs.* 0	2.48 (1.34-4.58)	**0.0039**	0.90 (0.40-1.99)	0.79
No. of previous chemotherapies	≥2 *vs.* 0-1	2.38 (1.27-4.48)	**0.0071**	1.65 (0.84-3.26)	0.15
ALC	<1,500 *vs.* ≥1,500/μl	0.85 (0.44-1.66)	0.64		
NLR	<3.0 *vs.* ≥3.0	0.59 (0.33-1.06)	**0.076**	0.34 (0.16-0.74)	**0.0059**
CRP	<0.3 *vs.* ≥0.3 mg/dl	0.43 (0.23-0.78)	**0.0061**	0.63 (0.30-1.29)	0.21

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein. Statistically significant *p*-values are shown in bold.

Table V. *Univariate and multivariate analyses of factors associated with overall survival.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥65 *vs.* <65 Years	1.19 (0.62-2.27)	0.60	1.26 (0.61-2.58)	0.52
Gender	Male *vs.* female	0.65 (0.32-1.31)	0.23	0.56 (0.25-1.27)	0.16
Histology	L-Sarcoma *vs.* other	0.40 (0.20-0.80)	**0.0090**	0.55 (0.26-1.15)	0.11
Primary lesion	Extremity *vs.* other	1.22 (0.58-2.56)	0.59		
ECOG PS	≥1 *vs.* 0	4.44 (2.15-9.16)	**<0.001**	2.11 (0.88-5.08)	0.096
No. of previous chemotherapies	≥2 *vs.* 0-1	3.51 (1.63-7.54)	**0.0013**	2.65 (1.17-6.01)	**0.020**
ALC	<1,500 *vs.* ≥1,500/μl	1.27 (0.59-2.71)	0.54		
NLR	<3.0 *vs.* ≥3.0	0.48 (0.24-0.95)	**0.036**	0.53 (0.23-1.23)	0.14
CRP	<0.3 *vs.* ≥0.3 mg/dl	0.29 (0.14-0.62)	**0.0013**	0.48 (0.18-1.27)	0.14

ECOG PS: Eastern Cooperative Oncology Group performance status; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein. Statistically significant p-values are shown in bold.

different STS histological subtypes suggested that the survival benefit associated with eribulin for STS was greater in patients with L-sarcoma (14), which was the basis of the inclusion criteria for the subsequent phase III trial (4). Several prospective (5) and retrospective (15, 16) studies of Japanese patients with STS, including our recent retrospective report that evaluated differences in the efficacy and safety of eribulin for patients with STS by histological subtype or number of previous systemic treatments (17), also showed a similar tendency. Our data were consistent with these previous results.

Several limitations of this study should be acknowledged. Firstly, this was a retrospective study with a small number of patients, and a selection bias may have resulted from physician subjectivity when determining which patients should receive eribulin at which line. Secondly, the observation period was short, mainly because eribulin was only approved for recurrent or metastatic STS in Japan less than 5 years ago. Thirdly, the NLR value is easily changed, not only by tumor factors, but also by infection, corticosteroids, radiotherapy, or other physiological stresses. Although we used a cut-off value of 3.0 for the NLR according to the findings of previous breast cancer studies, the appropriate cut-off value is still under debate. We plan to continue accumulating data from a larger number of patients in future studies.

This retrospective study evaluated the predictive factors of eribulin monotherapy for STS patients. Notably, we found that low baseline NLR (<3.0) and L-sarcoma histology were independent predictors of DCB, and low baseline NLR (<3.0) and male sex were independent predictors of prolonged PFS.

Conflicts of Interest

YS reports personal fees from ONO Pharmaceutical Co., Ltd, Bristol-Myers Squibb Company, MSD KK and TAIHO Pharmaceutical Co., Ltd, outside the submitted work. NF and JT report personal fees from Eisai. ST reports grants and personal fees from Bristol- Myers Squibb KK, grants and personal fees from ONO Pharmaceutical Co., Ltd, grants and personal fees from MSD, grants and personal fees from AstraZeneca, grants and personal fees from Chugai, and grants and personal fees from BAYER, outside the submitted work. The other Authors report no competing interests to disclose.

Authors' Contributions

YS designed the study and wrote the article. KN designed the study and revised the article. NF, XW, TU, AO, MY, MO, TJ, KH, YF, TT, KA, SM and TT contributed critical revisions of the article. All Authors read and approved the final version of the article.

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