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Prevention of New Metastatic Lesions by Eribulin Monotherapy Is Associated with Better Prognosis in Patients with Metastatic Breast Cancer

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Background: Eribulin therapy has been reported to prolong overall survival (OS) but not progression-free survival, probably because it prevents the development of metastatic lesions; however, this effect has not yet been confirmed.

Methods: We reviewed the medical charts of 50 patients with metastatic breast cancer who underwent eribulin monotherapy at our hospital between 2014 and 2019. Patients were divided into two groups, namely, those who discontinued eribulin because of disease progression due to development of new lesions (NL group) and those who discontinued eribulin for other reasons, such as lesion growth and unacceptable side effects (non-NL group). Survival times were estimated for both groups and we investigated if eribulin-mediated suppression of new metastasis increased OS.

Results: Median OS for all patients, from eribulin initiation, was 14.4 months (range 1.2-60.1), whereas it was 4.6 months (range 1.7-24.7) in the NL group and 16.8 months (range 1.2-60.1) in the non-NL group. OS was significantly poorer in the NL group than in the non-NL group ($p < 0.05$).

Conclusion: Eribulin monotherapy-mediated suppression of new metastatic lesions results in a better prognosis in patients with metastatic breast cancer. (J Nippon Med Sch 2022; 89: 494–499)

Key words: eribulin, overall survival

Introduction

Breast cancer is the most prevalent malignant disease among women in Japan, and most patients with metastatic breast cancer are treated with either hormone therapy or chemotherapy. Eribulin chemotherapy has been approved in Japan for inoperable or recurrent breast cancer after treatment with anthracycline or taxane-based chemotherapy. Even though eribulin was originally developed as a microtubule inhibitor, it has been reported to have additional antitumor effects, most notably reversal of epithelial-mesenchymal transition (EMT)[1–5], which may contribute to the prolongation of overall survival (OS)[1–3]. Notably, results of the EMBRACE trial (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) suggested that eribulin prolongs OS but not progression-free survival (PFS)[6]. Typically, prolonged OS is difficult to prove, and longer OS but not PFS is unique to eribulin therapy.

The development of new metastatic lesions is associated with poor prognosis in patients with metastatic breast cancer[7], and Fujii et al. have reported that the risk of disease progression after the development of new metastases is lower with eribulin treatment than with previous regimens. Thus, the lower risk of new metastatic lesions with eribulin therapy may contribute to longer OS[8], but this effect has not been confirmed. Therefore, we conducted a retrospective study to investigate the frequency of new metastatic lesions during treatment with eribulin or other regimens. Then, we determined whether eribulin-mediated suppression of new metastatic lesions affects survival.

Patients and Methods

Records of patients with metastatic and recurrent breast

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cancer who underwent eribulin monotherapy at the Nihon University Itabashi Hospital between 2014 and 2019 were reviewed. Fifty patients met these criteria.The efficacy of chemotherapy was evaluated using imaging, such as computed tomography and ultrasonography. We evaluated disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

A chemotherapy regimen is typically continued until detection of disease progression or the occurrence of unacceptable side effects; however, recently, mechanisms underlying disease progression due to the development of new metastatic lesions versus due to growth of existing lesions have been recognized as divergent[7]. These 50 patients received eribulin and an average of 2.66 ± 1.42 other chemotherapy regimens. Thus, these patients were administered one eribulin and 133 non-eribulin regimens.

First, as a preliminary study, we examined the reasons for the discontinuation of the eribulin and other 133 non-eribulin regimens that were administered to these patients. The reasons for discontinuation were categorized into disease progression due to new lesion appearance, existing metastases growth, and unacceptable side effects. Next, as the core research, we divided our study patients into two groups wherein one group comprised patients those who discontinued eribulin because of disease progression due to development of new lesions (NL group) while the other group consisted of patients who had discontinued eribulin for reasons other than new lesions, such as lesion growth or unacceptable side effects (non-NL group). OS, measured from the date of eribulin initiation until date of death from any cause, was compared between these two groups, and it was censored on the last date the patient was known to be alive.

The χ^2 test was used to compare the reasons for regimen discontinuation. OS curves were estimated using the Kaplan-Meier method and were compared between the two groups using a two-sided log-rank test. Results were considered significant at a p-value of <0.05. The Student's *t*-test was used to assess between-group differences in mean values if variances were equal (as determined by the F-test), else, the Welch's t-test was employed. For factors that showed differences between NL group and non-NL group backgrounds, we analyzed their impact on overall survival using a Cox proportional hazards model.

This study was approved by the Clinical Research Ethics Review Committee of our hospital (Approval number 2020-256). All procedures in human participants were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Under the regulations of our institutional ethics board, informed consent was obtained in the form of an opt-out system on the website and in posters, and those who declined were excluded.

Table 1 Regimens other than eribulin that patients received after metastases or recurrence

Regimen	
Anthracycline	28
Taxanes	43
Oral 5-FU[a)] derivatives	23
Paclitaxel + Bevacizumab	31
Others	8
Total	133

Abbreviations: [a)] 5-FU, 5-fluorouracil

Results

One hundred and ninety-nine patients underwent chemotherapy for metastatic and recurrent breast cancer at our hospital between 2014 and 2019, and we included 53 cases who had received at least one dose of eribulin. Three patients who did not complete eribulin therapy because of transfer to another hospital (n = 2) or voluntary discontinuation of hospital visits (n = 1) were excluded.

First, we present the results of preliminary studies. All 50 patients in the present study were administered one eribulin monotherapy regimen for recurrent metastatic breast cancer. Moreover, they received 133 other chemotherapy regimens. The regimens used for recurrent metastatic breast cancer, excluding eribulin, are summarized in **Table 1**.

The reasons for the discontinuation of eribulin compared with other regimens are presented in **Figure 1**. When patients were treated with eribulin, 11 (22%) regimens were discontinued because of disease progression due to development of new lesions, 34 (68%) were discontinued because of disease progression due to lesion growth, and 5 (10%) were discontinued because of unacceptable side effects. Of the non-eribulin regimens, 43 (32%) regimens were discontinued because of disease progression due to development of new lesions, 58 (44%) were discontinued because of disease progression due to lesion growth, and 32 (24%) were discontinued because of unacceptable side effects. A significantly lower number of patients discontinued eribulin because of disease progression due to new lesion appearance (p = 0.01).

Next are the results of the core study. In terms of rea-

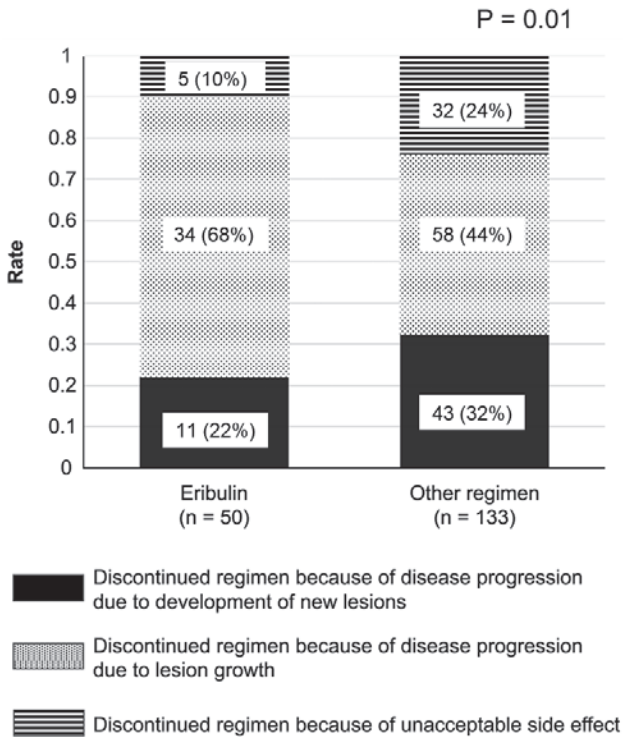


Fig. 1 Difference in reasons for discontinuing chemotherapy regimens
When eribulin was administered, new lesions appeared in 11 regimens, and a decision of diseases progression was made. When regimens other than eribulin were administered, new lesions appeared in 43 regimens, leading to a decision of disease progression. The number of new lesions was significantly lower when eribulin was used ($p<0.05$).

sons for discontinuation when using eribulin, there were 11 cases in the NL group and 39 in the non-NL group. **Table 2** summarizes patient characteristics. Median age of the cohort was 64 years (range, 29-86), but median age was significantly higher in the non-NL group (65 years [range, 33-86]) than in the NL group (54 years [range, 29-70]; $p < 0.05$). Analysis of immunohistological subtypes revealed that there were 36 cases (72%) of the luminal type, two cases (4%) of the HER2-enriched type, and 12 cases (24%) of the triple-negative type in the entire cohort. Metastasis sites were liver (n = 22), lung (n = 30), bone (n = 22), extra-regional lymph nodes (n = 14), brain (n = 4), and others (n = 13). There was no difference in the distribution of subtypes, but there was a difference in the distribution of liver metastases between the two groups. The median treatment line of eribulin was the 3rd (range, 1st-6th) line in the NL group and the 2nd (range, 1st-4th) line in the non-NL group. The median number of regimens after eribulin was 1 (range, 0-3) in the NL group and 1 (range, 0-7) in the non-NL group. The median number of eribulin treatment courses was 5 (range, 3-12) in the NL group and 7 (range, 2-31) in the non-NL group. No significant differences were observed between the two groups ($p = 0.08$) for the treatment line of eribulin, number of regimens after eribulin administration ($p = 0.44$), and number of eribulin treatment courses ($p = 0.06$). Further, disease-free survival (DFS) from surgery to first recurrence was compared between the two groups, except for the 21 patients with de novo stage IV disease. The median DFS was 11.7 (range, 1.9-67.2) months in the NL group and 31.1 (range, 4.2-158.3) months in the non-NL group; however, the differences between the two groups were not significant ($p = 0.12$).

The two patients with the HER2-enriched type received eribulin monotherapy, rather than anti-HER2 therapy, because of cardiac failure.

Because the differences in background between the two groups were age and liver metastasis presence, we discussed the impact on OS whether or not eribulin was discontinued due to new lesions and those two factors. Hazard ratios of disease progression due to new lesions, age, and liver metastasis by the Cox proportional hazards model are shown in **Table 3**. The presence or absence of progression due to new lesions was the most influential factor on OS.

Figure 2 shows the Kaplan-Meier curves for OS. Median OS from the date of eribulin initiation was 14.4 months (range 1.2-60.1) for the entire cohort but 4.6 months (range 1.7-24.7) in the NL group and 16.8 months (range 1.2-60.1) in the non-NL group. Thus, OS was significantly poorer in the NL group than in the non-NL group ($p < 0.05$).

Discussion

In our preliminary study, disease progression due to a new lesion occurred less frequently with eribulin than with other regimens. EMT has been shown to have essential roles in tumor metastasis[1], and eribulin exerts antineoplastic activity in metastatic breast cancer by reversing EMT and inducing vascular remodeling[1]. Thus, these processes may contribute to the suppression of new metastatic lesions[1].

Next, in the core study, we compared OS between patients who discontinued eribulin due to development of new lesions (NL group) with those who did so for other reasons (non-NL group), and our results suggest that suppression of new metastatic lesions by eribulin is associated with longer OS among patients with metastatic and recurrent breast cancer because prognosis was better

Table 2 Characteristics of patients treated with eribulin

	Total (n = 50)	NL[b] group (n = 11)	Non-NL[b] group (n = 39)	p-value (NL group vs. Non-NL group)
Median age (range)	64 (29–86)	54 (29–70)	65 (33–86)	<0.05
Immunohistological subtypes (cases)				
Luminal	36 (72%)	5 (45%)	31 (79%)	
HER-2 enriched	2 (4%)	0 (0%)	2 (5%)	
Triple-negative	12 (24%)	6 (55%)	6 (15%)	0.06
Metastatic site (cases)				
Liver	22 (44%)	3 (27%)	18 (46%)	<0.05
Lung (including pleura)	30 (60%)	9 (81%)	21 (54%)	0.09
Bone	22 (44%)	4 (36%)	18 (46%)	0.82
Lymph nodes	14 (28%)	3 (27%)	11 (28%)	0.75
Brain	4 (8%)	1 (9%)	3 (7%)	0.63
Other	13	4	9	
Treatment line of eribulin	2nd	3rd	2nd	0.08
Median (range)	(1st–6th)	(1st–6th)	(1st–4th)	
Number of regimens after eribulin				
Median (range)	1 (0–7)	1 (0–3)	1 (0–7)	0.44
Number of eribulin treatment courses				
Median (range)	6 (2–31)	5 (3–12)	7 (2–31)	0.06
Cases of recurrence	29	5	24	0.49
DFS[a] of cases of recurrence	28.1	11.7	31.1	0.12
Median months (range)	(1.9–158.3)	(1.9–67.2)	(4.2–158.3)	

Abbreviations: [a] DFS, Disease-free suvival; [b] NL, new leision

Table 3 Cox proportional hazards model of prognostic factors associated with overall survival

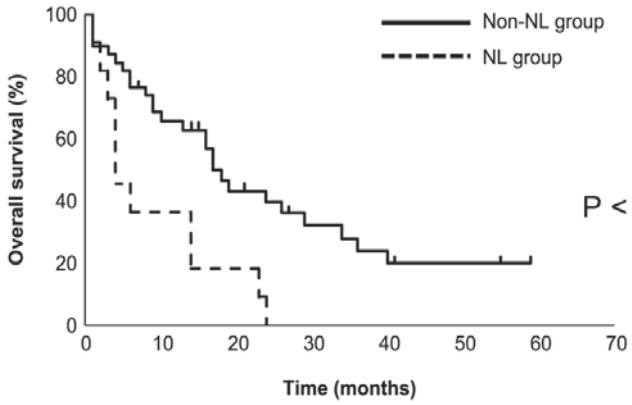
	HR[a] (95% CI[b])	p-value
Age	0.96 (0.23–4.30)	0.95
Liver metastasis		0.02
+	2.35 (1.13–4.90)	
–	0.43 (0.20–0.89)	
Progressive disease due to new lesion		<0.01
+	4.38 (1.85–10.45)	
–	0.23 (0.09–0.55)	

Abbreviations: [a] HR, hazard ratio; [b] CI, confidence interval

in the non-NL group than in the NL group.

We compared our results with those from the EMBRACE trial where patients treated with eribulin achieved an OS of 13.1 months[6]. The overall OS in our cohort was 14.4 months, which was similar or slightly longer than that of the EMBRACE trial. We posit that the slightly longer OS in our cohort may be due to the use of eribulin at an earlier time point in the treatment strategy compared to the EMBRACE trial− specifically, while eribulin was used as the third-to-sixth line of treatment in the EMBRACE trial, it was the second (first-to-sixth) in our study.

Median age was lower in the NL group than in the non-NL group, probably because we included five patients in the non-NL group who had discontinued eribulin treatment due to unacceptable side effects (median age, 72 years [range, 62-85]). Also, there were more patients in the non-NL group with liver metastases, which is thought to adversely affect life expectancy. Despite these differences, the non-NL group had a median life expectancy that was approximately 10 months longer than that of the NL group. It is possible that eribulin, which exerts inhibitory effects on new lesions, has more impact on suvival outcome than liver metastasis. How-



Months	0	10	20	30	40	50
Non-NL group	39	27	16	10	7	2
NL group	11	5	2	0	0	0

Fig. 2 Overall survival curves for the new lesions (NL) and non-NL groups
The median OS was 4.6 months (range, 1.7–24.7) in the NL group and 16.8 months (range, 1.2–60.1) in the non-NL group, and was significantly shorter than in the NL group ($p<0.05$).
Abbreviations: OS, overall survival; NL, new lesions; non-NL, no new lesions

ever, further research is needed to answer this question.

A comparison of the DFS showed no statistical difference between the two groups, although the median DFS was longer in the non-NL group. Six patients in the NL-group and 15 patients in the non-NL group with de novo stage IV disease were excluded from this comparison because DFS was not quantifiable. This may have resulted in a small number of patients in the NL-group with no statistical significance.

Our results show that the prevention of new metastatic lesions by eribulin monotherapy is associated with a better prognosis in patients with metastatic breast cancer. Thus, based on RECIST, progression due to the development of new metastatic lesions or due to the growth of existing lesions is similar and they can both trigger a change in therapy. However, it is possible that progression due to the development of new metastatic lesions may be more predictive of prognosis compared to other types of disease progression. Disease progression without the development of new lesions may indicate the potential for options that do not involve an immediate change in treatment. Further, to make better treatment choices in the long term, we should differentiate between the two types of progression when determining disease stage. Because the effects of hormone therapy and anti-HER2 therapy differ depending on the subtype, we would like to increase the number of cases and conduct subtype-specific analysis.

In summary, we show that the prevention of new metastatic lesions by eribulin monotherapy results in better prognosis in patients with metastatic and recurrent breast cancer. Since all the patients in this study received eribulin, it is unclear whether eribulin is more likely to inhibit the development of new lesions compared with other treatments; thus, further studies are warranted.

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