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ORIGINAL ARTICLE

Retrospective analysis of the efficacy and safety of eribulin therapy for metastatic breast cancer in daily practice

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Chemotherapy; clinical practice; eribulin; metastatic breast cancer; post-treatment therapy.

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Abstract

Background: Evidence of eribulin therapy for metastatic breast cancer (MBC) in clinical practice is not well documented.

Methods: We retrospectively analyzed the safety and efficacy of eribulin in 29 MBC patients from 2011 to 2016 at Fukuoka University Hospital.

Results: The median patient age, number of courses, total dose, and relative dose intensity were as follows: 65 years, five courses, 8.6 mg/m^2, and 75%, respectively. One patient achieved a complete response, (CR) six a partial response (PR), eight stable disease (SD) and 14 patients exhibited progressive disease. The objective response rate (ORR: CR + PR) was 24.1%, and the clinical benefit rate (CBR: CR + PR + SD) was 51.7%. The median progression-free survival was 90 days (95% confidence interval [CI] 67–126) and median overall survival was 264 days (95% CI 198–357). In patients who previously received 2–4 regimens, the ORR was 28.5% and the CBR was 57.1%. In patients who received 5–12 regimens, the ORR was 20% and the CBR was 45%. Chemotherapy was administered to 20 patients (69%) after eribulin administration, and the median overall survival rate of cases that achieved greater than a PR was 1088 days. The most frequent treatment-related grade 3/4 adverse events were neutropenia (55.2%), and febrile neutropenia (20.1%). Grade 3 peripheral neuropathy occurred in 13.8% of patients, but was not exacerbated even if present before treatment.

Conclusion: Eribulin is effective for MBC patients who have received multiple chemotherapies. Neutropenia and febrile neutropenia may develop after heavy prior therapy.

Introduction

Since 1981, cancer has been the leading cause of death in Japan. The number of newly diagnosed cancer cases was approximately 852 000 in 2011, with breast cancer being the leading cancer site for women (20.4%).[1] Metastatic breast cancer (MBC) remains an incurable disease with a median overall survival (OS) of two to three years and a five-year survival rate of 25%.[2] Current therapeutic goals for MBC are to control symptoms with an improved quality of life, and to prolong survival.

Anthracycline or taxane is considered first-line chemotherapy for MBC in patients who have not been exposed to these agents as adjuvants.[3] However, the disease progression ultimately encountered is often attributed to primary or acquired resistance to these regimens.[4] Consequently, few therapeutic options are available for patients with anthracycline-resistant and taxane-resistant or refractory MBC. Despite limited evidence, active chemotherapies are administrated in late-line treatment.

Eribulin is a novel synthetic chemotherapeutic agent that inhibits microtubule movement at a site of action that differs from that of taxanes. Eribulin therapy is one of the few chemotherapy regimens shown to prolong OS in women with heavily pretreated MBC. The EMBRACE phase III study demonstrated a significant and clinically meaningful improvement in survival using eribulin compared to the physician's choice of treatment in women who were

heavily pretreated; median PFS and OS were 3.7 and 13.2 months, respectively.[5] A randomized phase III trial with capecitabine (301 study) showed a tendency for better OS in patients treated with eribulin.[6] Based on these findings, eribulin obtained marketing approval in Japan for the treatment of inoperable and recurrent breast cancer in April 2011.

However, evidence of eribulin in a real-world setting is not well documented. We report here on the safety and efficacy of eribulin in women with MBC in a daily clinical practice setting.

Methods

Patients

This retrospective observational analysis included Japanese women with MBC who were treated between August 2011 and July 2016. Study patients were diagnosed with breast cancer after histological analysis. Eribulin was administered, based on practice guidelines in Japan, via intravenous infusion at a dose of 1.4 mg/m^2 on days 1 and 8, every three weeks.

Evaluation of efficacy and safety

Progression-free survival (PFS) refers to the period from the start of eribulin administration to disease progression or death by any cause. OS is defined as the period from the start of eribulin administration to death, or the last follow-up. An objective response rate (ORR) is the sum of patients with a complete response (CR) + partial response (PR). The clinical benefit rate (CBR) is the sum of CR + PR + stable disease (SD). National Cancer Institute Common Terminology Criteria for Adverse Events (NCI–CTCAE version 4) were used to evaluate toxicity. Tumor responses were assessed by computed tomography, with periods for responses dependent on each patient's condition. Data was collected based on the retrospective evaluation of electronic medical records for descriptive analyses.

Statistical analysis

The final data cut-off date was 31 December 2016. Survival curves for patients were estimated using a Kaplan–Meier test and subgroups were compared using a log-rank test. Ninety-five percent confidence intervals (CIs) were estimated using a Cox proportional hazards model. P values <0.05 were considered statistically significant.

Table 1 Patient characteristics (n = 29)

Characteristic	No. of patients (%)
Age (years)	
Median (range)	65 (36–77)
Menopause	26 (89.7)
Hormone receptor status	
Positive	20 (69.0)
Negative	9 (31.0)
HER2 status (IHC)	
Positive (IHC3+ or 2+ and FISH+)	9 (31.0)
Negative	20 (69.0)
Metastatic site	
Lung	16 (55.1)
Liver	13 (45.0)
Bone	12 (41.3)
Lymph node	13 (45.0)
Previous anticancer therapy (including adjuvant and endocrine therapy)	
2–4	14 (48.3)
5–12	15 (51.7)
Prior chemotherapy regimens	
Anthracyclines	22 (75.9)
Taxanes	27 (93.1)
Fluoropyrimidine	17 (58.6)
Anti-HER2 therapy	8 (27.6)
Others	5 (17.2)
Endocrine therapy	21 (72.4)

FISH, fluorescence in-situ hybridization; IHC, immunohistochemistry.

Results

Patients

A total of 29 patients with MBC underwent eribulin therapy in our department between August 2011 and December 2016. The demographic and baseline characteristics of patients are summarized in Table 1. The median age was 65 years (range 36–77) and the median number of prior treatment regimens was five (range 2–12); 22 (75.9%) and 27 (93.1%) patients had been previously treated with anthracycline-based and taxane-based anti-cancer agents, respectively. Pretreatment regimens in this study included adjuvant and endocrine therapies. For patients with HER2-positive breast cancer, combination therapy of trastuzumab and an anticancer drug was administered; however, patients did not receive combination therapy with eribulin and trastuzumab in this study. Overall, 20 (69%) had hormone receptor (HR)–positive disease. Pathology-based subtype distributions were as follows: 17 (58.6%) HR+/HER2–, three (10.3%) HR+/HER2+, six (20.7%) HER2 type, and three (10.3%) triple negative (TN). The most common metastatic sites were the lungs (16, 55.1%), liver (13, 45%), lymph nodes (13, 45%), and bone (12, 41.3%).

Eribulin therapy

Eribulin was administered for a median of five cycles (range 1–29), at median dose intensity (DI) and relative

Table 2 Eribulin therapy

Eribulin therapy	Median (range)
Cycles	5.0 (1–29)
Total amount (mg)	12.4 (3.8–108)
Total amount (mg/m^2)	8.6 (2.8–75.6)
DI (mg/m^2/weeks)	0.70 (0.37–0.93)
Relative DI (%)	75.4 (41–100)

DI, dose intensity.

dose intensity (RDI) of 0.70 mg/m^2/week (range 0.37–0.93) and 75.4% (range 41–100), respectively. The median total dose was 8.6 mg/m^2 (Table 2). Reasons for the discontinuation of eribulin therapy were as follows: increase in current tumor lesions in 27 (93.1%) patients, the appearance of a new metastatic lesion in one (3.4%) patient, and an adverse event in one (3.4%) patient.

Efficacy

The median observation period was 258 days (range 156–1215). At the time of final observation, six (20.7%) patients were alive. One (3.4%) patient achieved a CR and six (20.7%) patients achieved a PR. Kaplan–Meier survival curves for median OS and PFS are shown in Figure 1a,b. The median OS and PFS rates from the initiation of eribulin therapy were 264 (95% CI 198–357) and 90 days (95% CI 67–126), respectively. We evaluated the efficacy of eribulin therapy for a number of prior treatment regimens. The ORR and CBR for patients who underwent 2–4 regimens were 28.5% and 57.1%, and for those who underwent 5–12 regimens, these were 20% and 45%, respectively (Fig 1c). Significant differences were not noted in the response rate when eribulin was used as a third to fifth or sixth to 13th-line treatment. The best clinical responses to eribulin therapy are summarized in Table 3. Overall, an ORR was recorded in 24.1% (7 patients) and a CBR was recorded in 51.7% (15 patients). The ORR and CBR for each breast cancer subtype were as follows: 29.4% and 52.9% for HR+/HER2−; 16.7% and 50% for HER2 type; 0% and 66.7% for HR+/HER2+; and 0% and 33.3% for triple negative (TN), respectively. Survival times in response to eribulin therapy were examined. The median OS was 740 days (n = 7, 95% CI 171–1063) in the patient group that attained a response greater than a PR, compared to 447 days (n = 14, 95% CI 171–1063) in the group exhibiting a greater response than SD, and 255 days (n = 15, 95% CI 161–329) in the group that showed progressive disease (PD). Thus, the median OS tended to be prolonged in the group that achieved greater than PR, but was not significant (log-rank test; P = 0.2674; data not shown).

Chemotherapy after eribulin (post-treatment) was administered to 20 patients (69%). Survival curves for post-treatment effectiveness are shown in Figure 2a. The median OS of patients who attained a PR in post-treatment therapy (green line) was 1088 days (95% CI 740–). In comparison, the OS rates of the no PR (red line) or no post-treatment groups (blue line) were 258 (95% CI 161–337) and 232 days (95% CI 123–284), respectively. The median OS of the PR group after post-treatment therapy was significantly longer than that of the no PR or no post-treatment groups (log-rank test: P = 0.0004). The influence of the number of chemotherapy regimens used before eribulin administration on PR in post-treatment therapy was analyzed (Fig 2b). In the patients who received 2–4 or 5–12 regimens as prior eribulin therapy, 78.6% and 60.0% received post-treatment therapy, respectively. The ORRs in post-treatment therapy for patients in either the 2–4 or 5–12 regimens of prior eribulin therapy were 45.5% for both, and the CBRs were 45.5% and 55.5%, respectively. The relationship between the effects of post-treatment and eribulin therapies are shown in Figure 2c. In patients who attained greater than a PR, or who showed greater than SD or PD in eribulin therapy, 85.7%, 73.3%, and 71.4% received post-treatment therapy, respectively. In patients who attained greater than a PR or greater than SD in eribulin therapy, 50.0% and 54.5% showed a PR and greater than SD in post-treatment therapy, respectively. In patients who showed only PD in eribulin therapy, 20.0% showed a PR or an effect greater than SD in post-treatment therapy. Moreover, univariate analysis for a PR in post-treatment therapy was conducted for age, the number of prior eribulin therapies, achieving greater than SD in eribulin therapy, and the total dose of eribulin (mg/m^2) (Table 4). The following factors tended to influence the outcomes of post-treatment therapy but were not significant: age, total dose of eribulin, and achieving greater than SD in eribulin therapy (P = 0.079, 0.130, and 0.135, respectively).

Safety

Table 5 lists the adverse events (AEs) and the proportion of patients experiencing AEs during treatment with eribulin. One patient discontinued eribulin therapy because of fatigue. Grade 1 neutropenia was noted in three (10.3%), grade 3 in five (17.2%) and grade 4 in 11 (37.9%) patients, respectively. Grade 4 febrile neutropenia (FN) was observed in six (20.7%) patients. Peripheral neuropathy (PN) of any grade was observed in 21 (72.4%) patients: mild to moderate (grade 1/2) in 9/8 (58.6%) patients. Grade 3 PN was observed in four (13.8%) patients; however, this symptom was caused by a previous treatment and was not exacerbated by eribulin therapy. Other grade 3 and 4 non-hematological toxicities were not documented.

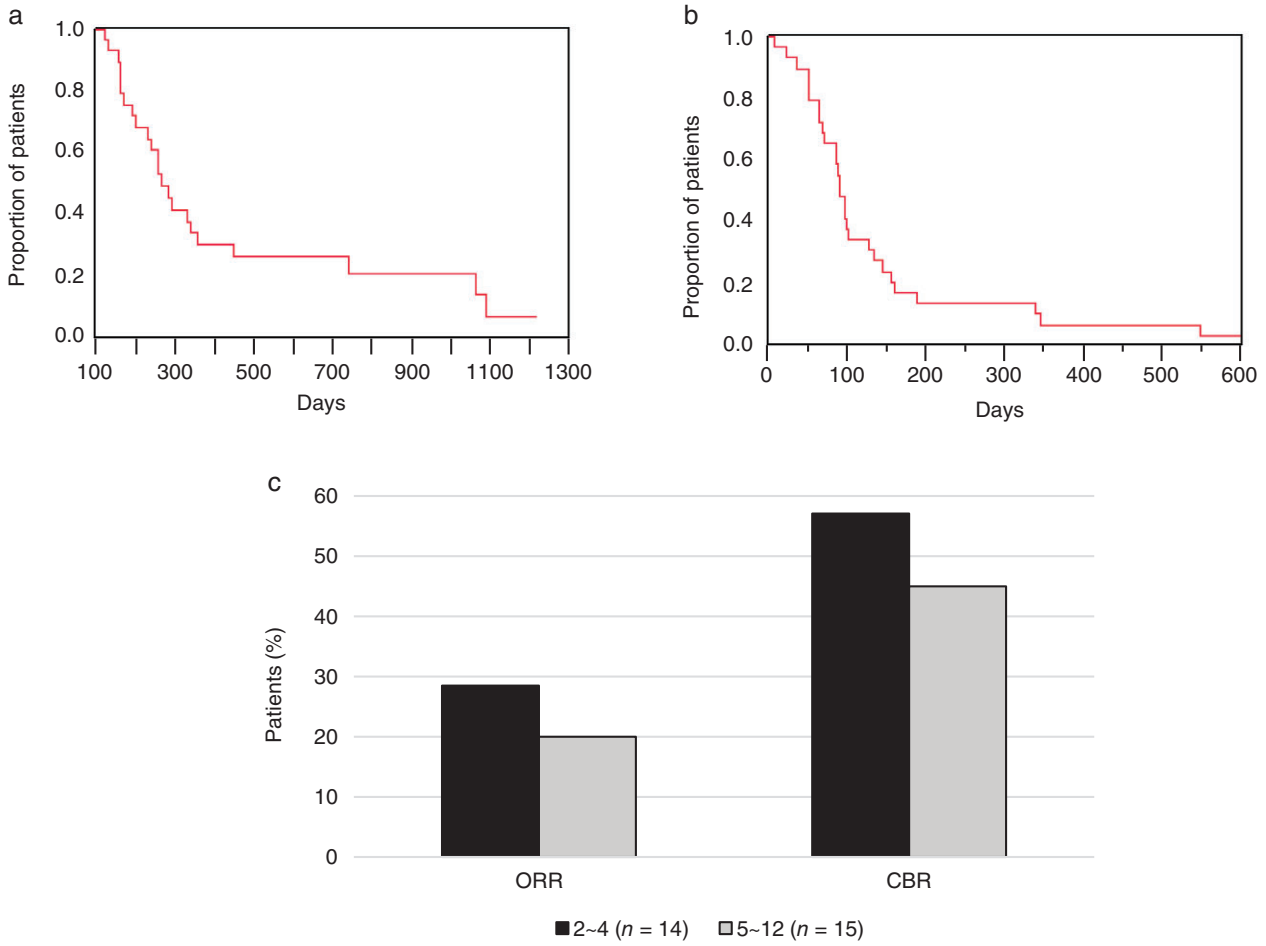

Figure 1 Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) progression-free survival (PFS) in the overall patient population. (**c**) The percentage of patients who responded to eribulin therapy after a number of prior treatment regimens. CBR, clinical benefit rate; ORR, objective response rate.

Table 3 Best clinical response to eribulin therapy in each breast cancer subtype

Best response	Total N = 29 (%)	HR(+)/HER2(–) N = 17 (%)	HR(+)/HER2(+) N = 3 (%)	HER2 type N = 6 (%)	Triple negative N = 3 (%)
CR	1 (3.4)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
PR	6 (20.7)	5 (29.4)	0 (0.0)	0 (0.0)	0 (0.0)
SD	8 (27.6)	4 (23.5)	2 (66.7)	2 (33.3)	1 (33.3)
PD	14 (48.3)	8 (47.1)	1 (33.3)	3 (50.0)	2 (66.7)
ORR	7 (24.1)	5 (29.4)	0 (0.0)	1 (16.7)	0 (0.0)
CBR	15 (51.7)	9 (52.9)	2 (66.7)	3 (50.0)	1 (33.3)

CBR, clinical benefit rate; CR, complete response; HR, hormone receptor; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Discussion

We retrospectively investigated the efficacy and safety of eribulin therapy for MBC patients in daily clinical practice. We found an ORR and CBR of 24.1% and 51.7%, respectively; the median PFS was 90 days and the OS was 264 days. Comparing the therapeutic effects found with previous phase III studies, the ORR and CBR were high, although PFS and OS were shorter than that of the EMBRACE study or Study 301. The reason why the survival time was short may have been because the median age of patients in this analysis was 10 years older than patients in the aforementioned phase III studies. A pooled analysis of data from two phase III studies of eribulin by

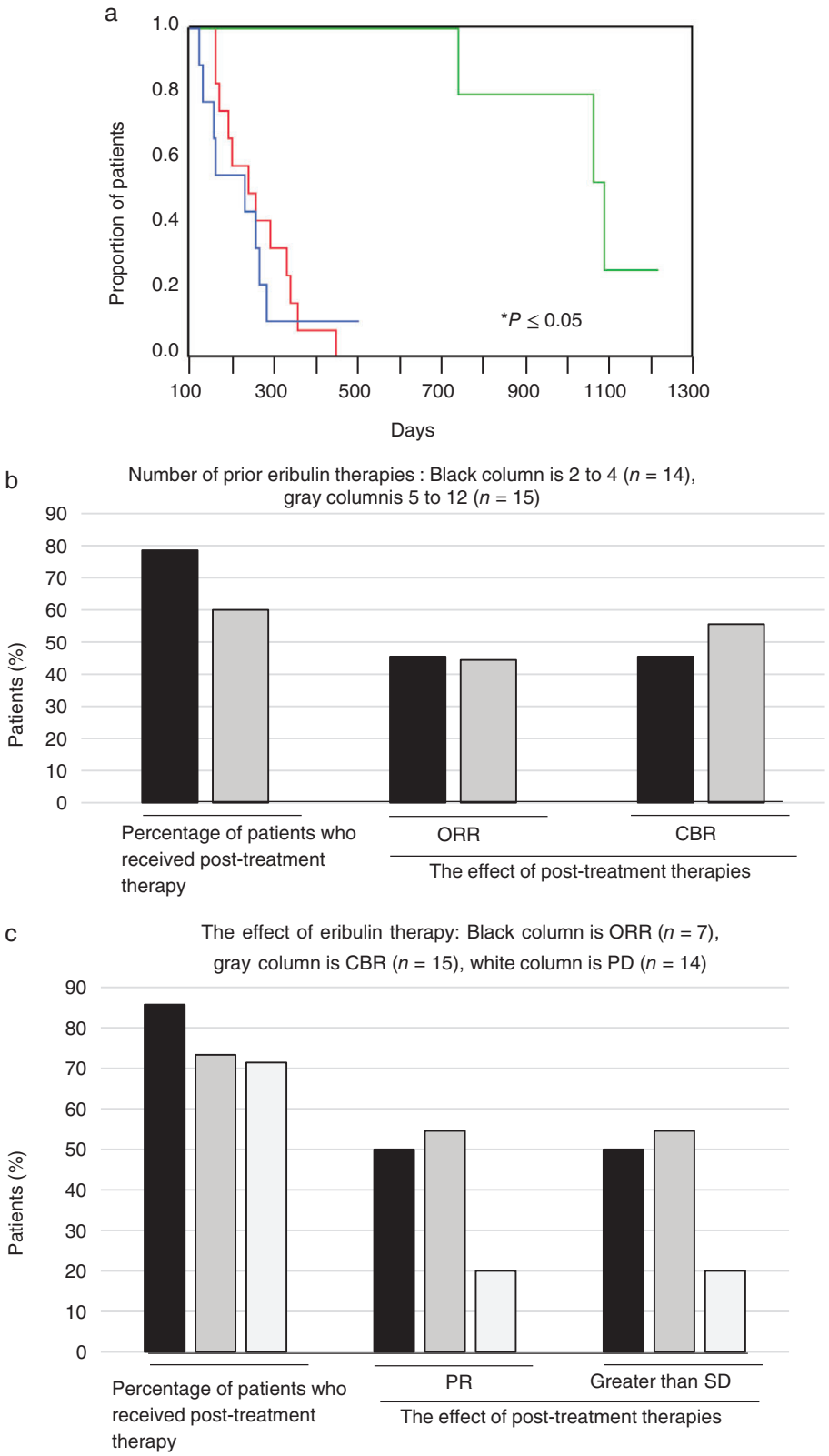

Figure 2 (**a**) Kaplan–Meier curves of overall survival of chemotherapy after eribulin therapy in the post-treatment group. Green line: patients who showed a partial response (PR, *n* = 8); red line: patients who did not show a PR (*n* = 12); blue line: patients who did not receive post-treatment therapy (*n* = 9). The *P* value was determined by a log-rank test. **P* ≤ 0.05. (**b**) The relationship between the number of prior eribulin therapies administered to patients and the effect of post-treatment therapy. The number of prior eribulin therapies: black columns signify 2–4 therapies (*n* = 14), gray columns refer to 5–12 therapies (*n* = 15). (**c**) The relationship between the effects of post-treatment and eribulin therapies. The effect of eribulin therapy: black columns represent the objective response rate (ORR, *n* = 7), gray columns represent the clinical benefit rate (CBR, *n* = 15), and white columns represent progressive disease (PD, *n* = 14). SD, stable disease.

Table 4 Univariate analysis for a PR in post-treatment therapy

	PR (n = 8)	No PR (n = 12)	No post-treatment (n = 9)	P
Number of prior chemotherapies	4 (3–7)	4.5 (2–9)	6 (3–12)	0.264
Age median (years)	57 (36–77)	64.5 (44–76)	66 (61–77)	0.079
Greater than SD in eribulin therapy (%)	75%	41.7%	44.4%	0.135
Total dose of eribulin (mg/m^2)	14.7 (6.9–75.6)	9.07 (5.4–18.2)	6.9 (2.8–20)	0.130

PR, partial response; SD, stable disease.

Table 5 Incidences of adverse events

Adverse event	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	19 (65.5)	3 (10.3)	0	5 (17.2)	11 (37.9)
Febrile neutropenia	6 (20.7)	0	0	0	6 (20.7)
Peripheral neuropathy	21 (72.4)	9 (31.0)	8 (27.6)	4 (13.8)	0 (0.0)
Fatigue	12 (41.4)	7 (24.1)	5 (17.2)	0 (0.0)	0 (0.0)
Anorexia	8 (27.6)	5 (17.2)	3 (10.3)	0 (0.0)	0 (0.0)
Dysgeusia	8 (27.6)	5 (17.2)	3 (10.3)	0 (0.0)	0 (0.0)
Stomatitis	9 (31.0)	8 (27.6)	1 (3.4)	0 (0.0)	0 (0.0)
Constipation	10 (34.5)	4 (13.8)	6 (20.7)	0 (0.0)	0 (0.0)
Nausea	6 (20.7)	5 (17.2)	1 (3.4)	0 (0.0)	0 (0.0)
Arthralgia (joint pain)	3 (10.3)	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (3.4)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Eruption	1 (3.4)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	2 (6.9)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)

the European Medicines Agency assessed whether specific patient subgroups benefited from eribulin.[7] It was found that women with HER2-negative disease gained a significant survival benefit from eribulin (HR 0.82; P = 0.002). In addition, benefits were also seen in those with ER-negative and triple-negative disease. Thus, eribulin improves OS in various patient subgroups, and those with HER2-negative disease are among those who may benefit greatly from eribulin. Our analysis also revealed that, although the number of patients in our sample was small, the response rate of eribulin tended to be high in HER2-negative patients.

The present analysis revealed that the median OS in patients who responded to eribulin therapy tended to be longer than that of patients for whom eribulin therapy had no effect. This suggests that tumor response was not the only contributing factor to affect survival. Half of the eribulin-treated patients had received the drug as a fifth-line or beyond 12-line treatment, and the response of these patients to eribulin was comparable to that observed in those who received eribulin as second-line or fourth-line treatments. The results of EMBRACE and Study 301 suggested that eribulin could prolong survival in MBC patients with late-line therapy, particularly in those who had been heavily pretreated. In other words, eribulin may be beneficial as a treatment for MBC, regardless of the number of prior treatments. The results of the present study support the indication of eribulin use for heavily pretreated patients in clinical practice.

In clinical studies evaluating therapies for metastatic disease, OS may be strongly influenced by subsequent lines of therapy.[8,9] Therefore, we evaluated the efficacy of chemotherapy after eribulin treatment. Post-treatment therapy was administered to 20 patients (69%). Unexpectedly, the frequency of patients receiving further treatment was uniformly higher, irrespective of the effect of eribulin therapy and the number of prior eribulin therapies (Fig 2c). More interestingly, the survival time of patients who displayed a PR with post-treatment therapy was found to be much longer than those of patients with SD and PD. In addition, long-term survival factors tended to include showing greater than SD and the total dose in eribulin therapy. These results suggest that the therapeutic effect of eribulin influences the effects of post-treatment therapies. Recently, epithelial-mesenchymal transition (EMT) has been shown to be a key step for the promotion of metastasis in many cancers.[10] EMT progression is characterized by a transition from an epithelial to mesenchymal phenotype, the loss of proteins involved in cell junctions such as E-cadherin, and the increased expression of mesenchymal markers such as N-cadherin and vimentin. Yoshida *et al.* showed that eribulin suppresses metastasis of breast cancer cells by inducing the conversion of EMT to a mesenchymal–epithelial transition in a preclinical setting.[11] Thus, eribulin has the ability to prolong OS in breast cancer patients without corresponding increases in PFS. This mechanism may explain why eribulin affects post-treatment therapy. Moreover, Kotake *et al.* conducted a multicenter observational

retrospective study aimed at assessing the efficacy of eribulin on post-treatment therapy.[12] In that report, a total dose of eribulin ≥ 10 mg/m^2 and the appearance of a new lesion or metastasis were factors that showed statistically significant correlations with post-progression survival in multivariate analysis. Also, in our analysis, the total eribulin dose in patients who obtained a PR with post-treatment therapy was 14.7 mg/m^2, which was higher than the 9.07 mg/m^2 and 6.9 mg/m^2 of the no PR and no post-treatment groups.

Neutropenia was the most common clinical grade 3 or 4 AE (55.1%) observed with eribulin therapy. The incidences of grade 3 or 4 hematological AEs were similar to those in the EMBRACE and Study 301 trials, except for FN. The incidence of FN with eribulin was higher in our analysis (20.7%) than in the EMBRACE (5%) or Study 301 (2%) trials. Similar to our data, the incidence of FN was higher in a phase II study for Japanese patients who had received a median of three prior chemotherapy regimens, occurring in 13.6% of patients.[13] We postulate that the risk of FN in Japanese patients may tend to be higher. However, the incidence of FN was 8.5% in a phase II study in Japanese patients who had received from one to three lines of eribulin therapy.[14] With regard to non-hematological AEs, PN occurred in 21 (72.4%) patients, at grade 3 in only four (13.8%); however, all AEs occurred during pretreatment, not during eribulin therapy. Notably, PN, the most common AE leading to the discontinuation of eribulin therapy in EMBRACE, was not observed in the present study.

Unlike randomized clinical trials, retrospective studies always have limitations, such as overestimating the effectiveness of the study, a potential bias in the assessment of outcomes, a patient selection bias, and a lack of external validation. However, such studies yield an accurate picture of a drug's activity in a "real world" scenario.

In conclusion, in this analysis, eribulin exhibited efficacy and manageable tolerability in pretreated Japanese MBC patients. The number of pretreatments administered to patients did not influence the survival benefit of eribulin. We conclude that post-treatment therapy for patients who obtained therapeutic effects with eribulin therapy may result in their long-term survival. Our results thus support the indication of eribulin in clinical practice.

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Disclosure

No authors report any conflict of interest.

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