Real-world effectiveness of eribulin in heavily pretreated patients with metastatic breast cancer in China: a multicenter retrospective study

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Abstract

Background: Eribulin is a nontaxane microtubule inhibitor approved in China for patients with advanced breast cancer who show progression after ⩾2 lines of chemotherapy. The aim of this study was to determine the efficacy and safety profile of eribulin and explore potential predictive factors for the efficacy of eribulin among Chinese women with metastatic breast cancer (MBC) in real-world practice.

Patients and Methods: A total of 272 consecutive MBC patients who were treated with eribulin between November 2019 and October 2020 in 9 institutions nationwide were included in this study. Eribulin was administered intravenously at a dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. Efficacy outcomes included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR). Adverse events (AEs) were graded according to The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.0.

Results: Eribulin showed a median PFS of 4.1 months (95% confidence interval [CI] 3.6–4.6); however, the OS data were immature. The ORR was 17.6% and the CBR was 24.6%. A total of 51.8% of patients received eribulin monotherapy, while 48.2% of patients were treated with eribulin plus targeted therapy or other chemotherapy. The number of metastatic sites, duration of previous taxane treatment for MBC, and combination with bevacizumab were significant in Cox multivariate analysis ($p = 0.023$, $p = 0.048$, and $p = 0.046$, respectively) and were significantly associated with PFS of eribulin. The most common AEs with eribulin treatment were hematological toxicities, including neutropenia, leukopenia, and anemia.

Conclusion: Eribulin was effective with a manageable toxicity profile in clinical practice. Furthermore, when prescribed in combination with other agents, eribulin did not increase the toxic effects of each agent. Eribulin monotherapy or plus other agents is an alternative for the heavily pretreated patients with MBC.

Keywords: Chinese women, eribulin, metastatic breast cancer, predictive factors, real-world effectiveness

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Introduction

Breast cancer is the most common malignancy and the leading cause of the death in women worldwide.[1] Roughly 10% of women are newly diagnosed with *de novo* stage IV breast cancer, and nearly 30% of early breast cancer patients eventually developed recurrence and/or metastasis.[2–3] Metastatic breast cancer (MBC) is an

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incurable disease, and although novel agents have been found to improve the prognosis of these patients, the median overall survival (OS) of MBC patients is only 2–3 years.[4–6] Chemotherapy is the primary treatment for patients with metastatic triple-negative (TN) or human epidermal growth factor receptor 2 (HER2)-positive breast cancer or hormone receptor (HoR)-positive breast cancer resistant to endocrine therapy. [7] Anthracyclines and taxanes, as the backbone of breast cancer treatment, are administered in adjuvant/neoadjuvant settings. [7] Optional chemotherapeutic agents for MBC are limited, especially for those who experienced anthracyclines and taxanes, and there is an urgent need of a novel chemotherapeutic agent for later line treatment of MBC.

Eribulin is a nontaxane microtubule dynamics inhibitor, [8] isolated from the marine sponge *Halichondria okadai*.[9] Eribulin, as a synthetic analogue of halichondrin B, exerts its antitumor activity by binding with high affinity to the growing plus ends of microtubules; this mechanism is distinct from those of taxanes and vinca alkaloids.[9–11] The EMBRACE trial indicated improved survival of eribulin treatment compared to treatment of physician's choice in patients with heavily pretreated MBC; [12] these findings contributed to the approval of eribulin (Halaven®, Eisai Inc., Woodcliff Lake, NJ, USA) in the USA, Europe, and Japan. A series of studies compared the efficacy of eribulin to common chemotherapies in the metastatic setting. In a phase 3 trial (Study 301), eribulin was proven to confer a superior survival benefit compared to capecitabine in MBC patients pretreated with anthracycline and taxane in the TN and HER2-negative subgroups.[13–15] Study 304, conducted in China, found that eribulin significantly prolonged progression-free survival (PFS) compared with vinorelbine.[16]

Based on the results of Study 304, eribulin was approved in China in 2019 for patients with locally recurrent or MBC who progressed after at least two lines of chemotherapy, including anthracycline and taxane. Further research is warranted to study the 'real effectiveness' of eribulin and explore the potential determinants of treatment outcomes. Eribulin and taxanes are both microtubule inhibitors, although they bind to different targets to microtubules. The sensitivity of tumors to previously used taxanes may indicate the sensitivity of eribulin. However, previous studies have only discussed the benefit of eribulin in the subgroup with different non-progression interval of last taxanes.[15] In this study, we investigated the predictive value of the duration of previous taxane treatment for the efficacy of eribulin. Due to the limitation of the data with regard to eribulin in real-world clinical practice in China, we conducted a multicenter, retrospective study to evaluate the effectiveness and safety of eribulin in heavily pretreated patients with MBC in China and to identify predictive factors of the efficacy of eribulin.

Patients and methods

Patients and treatment

The study included MBC patients treated with eribulin between November 2019 and October 2020 across 9 institutions, including Fudan University Shanghai Cancer Center, Hunan Cancer Hospital, Jiangsu Province Hospital, the First Affiliated Hospital of Nanchang University, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University Cancer Center, Cancer Hospital of China Medical University, Zhejiang Cancer Hospital, and The First Affiliated Hospital of Jilin University. All data were retrospectively collected from medical records. MBC was defined as *de novo* stage IV and recurrent breast cancer confirmed by clinical, imaging, histological, or cytological measures. Patients received eribulin intravenously at a dose of 1.4 mg/m^2 over 2–5 minutes on days 1 and 8 of a 21-day cycle. The patients received treatment until disease progression, intolerable toxicity, or voluntary refusal. All patients provided written informed consent, and the study protocol was approved by Shanghai Cancer Center ethics committees and institutional review boards (No. 1812195-6). This study was retrospectively registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT04541420).

Assessment variables included PFS, overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR). PFS was defined as the time from the first eribulin treatment to disease progression or death due to various causes, according to the Response Evaluation Criteria in Solid tumors (RECIST) 1.1. OS was defined as the time from the first eribulin treatment to death from various causes or the last follow-up visit. ORR was defined as the percentage of evaluable patients at baseline who had either complete response (CR) or partial response (PR) as the best objective tumor response. CBR was defined as the percentage of evaluable patients at baseline who had CR, PR, or stable disease (SD) for ⩾24 weeks

as the best objective tumor response. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAEs) version 5.0.

Statistical analysis

Clinicopathologic characteristics were analyzed using descriptive statistics. Kaplan–Meier plots were used to calculate median PFS and OS and the corresponding 95% confidence intervals (CIs). Potential variables for efficacy prediction were tested using a stepwise multivariate Cox proportional hazard model (forward selection). The effects of variables were expressed as hazard ratios (HRs) with corresponding 95% CIs and *p*-values. Variables with *p*-values below 0.1 in the univariate analysis were entered into the multivariate model. Potential variables included Eastern Cooperative Oncology Group (ECOG) performance status (0–1 *versus* 2), disease characteristics (*de novo* stage IV *versus* recurrent disease), previous taxanes in the adjuvant/neoadjuvant setting (yes *versus* no), visceral metastasis (yes *versus* no), liver metastasis (yes *versus* no), number of lines of chemotherapy for MBC (1 *verus* ⩾2), number of prior chemotherapy regimens for MBC (⩽2 *versus* ⩾3 regimens), subtype [hormone receptor (HoR)+/human epidermal growth factor receptor 2 (HER2)−, HER2+ *versus* HoR−/HER2−], use of an agent in combination with eribulin (no *versus* bevacizumab), and the number of metastatic sites (1–2 *versus* ⩾3). For patients who received taxane in metastatic settings, the duration of previous taxane therapy (<6 months *versus* ⩾6 months) was also included as a potential variable. The duration of previous taxane therapy was defined as the time from initial taxane treatment for MBC to disease progression and sub-grouped into <6 months and ⩾6 months. Visceral metastasis was defined as visceral organ involvement, including lung, liver, peritoneal, or pleural and central nervous system (CNS) recurrence. SPSS software (SPSS version 21.0, SPSS Inc., Chicago, IL) was used for statistical evaluations. $p < 0.05$ was considered statistically significant.

Result

Patient characteristics

A total of 272 patients treated with eribulin across 9 institutions between November 2019 and October 2020 were included in this study. Baseline patient characteristics are presented in Table 1. The median number of prior chemotherapy regimens for MBC was 4 (interquartile range 2–5). Almost all patients (258/272, 94.9%) had received taxanes, while the majority (225/272, 82.7%) had received anthracyclines in adjuvant and/or metastatic settings. The majority of MBC patients had HoR-positive and HER2-negative tumors, followed by HoR-negative/HER2-negative and HER2-positive tumors. More than half of the patients (150/272, 55.1%) had ⩾3 metastatic sites; visceral metastasis was the most common. Taxanes were rechallenged in 149 (54.8%) patients in the metastatic setting though they were administered as adjuvant/neoadjuvant chemotherapy.

Most (141/272, 51.8%) patients received eribulin as a single agent, while some received eribulin with targeted agents or other chemotherapy (131/272, 48.2%). Anti-angiogenesis agents were most commonly combined with eribulin (72/272, 26.4%), including bevacizumab (58/272, 21.3%) and vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitors (TKIs) (apatinib or multi-target TKI anlotinib) (14/272, 5.9%). All HER2-positive patients received eribulin plus anti-HER2 agents, 9 (3.3%) of whom received dual anti-HER2 therapy (4 pyrotinib and 5 pertuzumab). Immune checkpoint inhibitors, including programmed cell death protein 1 (PD-1) and PD-1 ligand (PD-L1) inhibitors, were administered to 8 (2.9%) metastatic TN breast cancer patients with eribulin, and 5 (1.8%) of them received eribulin + bevacizumab/apatinib + a PD-1 inhibitor. One patient with a *breast cancer type 1* (*BRCA1*) germline mutation received eribulin + olaparib, while one patient with a phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation received eribulin + alpelisib. A total of 31 (11.4%) patients received combination chemotherapy, and capecitabine, platinum agents, and gemcitabine were administered with eribulin to 12 (4.4%), 8 (2.9%), and 11 (4.0%) patients, respectively.

The mean number of treatment cycles was 4 (range: 1–10), and 31 (11.4%) patients were still receiving eribulin at the cutoff date (22 March 2021). Treatment was discontinued due to disease progression (54.7%), intolerable toxicity (6.2%), unwillingness to follow the treatment plan (11.7%), economic reasons (7.7%), and loss of follow-up (8.1%). Dose reduction occurred in 19 of 272 (7.0%) patients, the most common

Table 1. Patient characteristics.

Characteristics	Patients	%
Age, years		
Median	52	
Range	28–78	
De novo stage IV cancer	28	10.3
Recurrent disease	244	89.7
ECOG		
0	42	15.4
1	199	73.2
2	31	11.4
Subtypes		
HoR+/HER2–	151	55.5
HER2+	31	11.4
HoR–/HER2–	89	32.7
Unknown	1	0.4
Grade		
II	82	30.2
III	132	48.5
Unknown	58	21.3
Ki67		
<14%	27	9.9
15–24%	33	12.1
25–44%	72	26.5
>45%	108	39.7
Unknown	32	11.8
No. of metastatic sites		
1	44	16.2
2	78	28.7
⩾3	150	55.1
Metastatic sites		
Visceral	216	79.4
Liver	141	51.8
Lung	129	47.4
Bone	159	58.5
Lymph nodes	166	61.0
No. of prior chemotherapy regimens for MBC		
0	5	1.8
1	34	12.5
2	41	15.1
3	54	19.9
4	49	18.0
5	36	13.2
⩾6	53	19.5
Previous chemotherapy		
Taxanes	258	94.9
Anthracyclines	225	82.7
Taxanes and anthracyclines	219	80.5
Setting of previous taxanes		
Absent	11	4.0
Adjuvant/neoadjuvant	190	69.8
Metastatic	217	79.8
Both	149	54.8
Unknown	3	1.1
Setting of previous anthracyclines		
Absent	44	16.2
Adjuvant/neoadjuvant	211	77.6
Metastatic	24	8.8
Both	10	3.7
Unknown	3	1.1
Taxanes rechallenge		
Yes	149	54.8
No	120	44.1
Unknown	3	1.1

(continued)

Table 1. (continued)

Characteristics	Patients	%
Duration of previous taxane treatment for MBC		
⩽6 months	167	61.4
>6 months	50	18.4
Combination therapy		
No	141	51.8
Bevacizumab	58	21.3
Anti-HER2 agents	31	11.4
VEGFR-TKIs	14	5.1
ICIs	8	2.9
VEGFR-TKI + ICIs	5	1.8
Platinum	8	2.9
Platinum + bevacizumab	5	1.8
Capecitabine	12	4.4
Gemcitabine	11	4.0
PARP inhibitors	1	0.4
Alpelisib	1	0.4

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; ICIs, immune checkpoint inhibitors; MBC, metastatic breast cancer; PARP, poly ADP-ribose polymerase; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

reasons for which were neutropenia and neuropathy.

Efficacy

At the cutoff date (22 March 2021), 178 (65.4%) patients experienced disease progression and 36 (13.2%) patients had died. After the median follow-up of 7.1 months [interquartile range (IQR) 4.0–9.6 months], the median PFS was 4.1 months (95% CI 3.6–4.6 months), and the median OS were immature (Figure 1). The ORR was 17.6% (48/272) while the CBR was 24.6% (67/272) (Table 2).

Univariate analysis (Table 3) indicated that the ECOG performance status, number of metastatic sites, number of prior chemotherapy regimens for MBC, duration of previous taxane treatment for MBC, and combination with bevacizumab were significantly related to PFS in patients treated with eribulin. Multivariate analysis (Table 3) demonstrated that the number of metastatic sites, duration of previous taxane treatment for MBC, and combination with bevacizumab were independent predictive factors for PFS. Patients with 1–2 metastatic site(s) had significantly longer PFS than those with ⩾3 metastatic sites (median PFS 5.3 *versus* 3.6 months, $p=0.023$) [Figure 2(a)]. Patients who received eribulin plus bevacizumab and eribulin monotherapy for MBC had a median PFS of 5.4 and 3.5 months, respectively ($p=0.046$) [Figure 2(b)]. 217 (79.8%) patients received taxane in metastatic settings. In this subgroup, patients previously treated with taxanes for <6 months in the metastatic setting showed a median PFS of 3.7 months, whereas those previously treated with taxanes for ⩾6 months showed a median PFS of 6.5 months ($p=0.048$) [Figure 2(c)].

A secondary analysis was conducted in combination therapy, eribulin monotherapy, and HER2 positive subgroup. In HER2 positive population, all patients received anti-HER2 therapy (Table S2) and the median PFS was 6.6 months (95% CI 2.3–11.0) (Table S3). For patients treated with combination therapy, characteristics were similar to overall population, while all HER2+ patients received concomitant anti-HER2 treatments (Table S4). The median PFS was 5.1 months (95% CI 4.2–6.0) (Table S5) and the duration of previous taxane treatment for MBC was the only predictive factor in combination therapy subgroup (Table S6). For patients treated with eribulin monotherapy, no HER2+ patients were observed (Table S7) and the median PFS was 3.5 months (95% CI 2.9–4.1) (Table S8). Patients with HoR+/HER2− tumors showed a significantly longer PFS compared with HoR−/HER2− when treated with eribulin monotherapy (Table S9).

Safety

The most common AEs with eribulin treatment were neutropenia, leukopenia, anemia, aspartate aminotransferase elevation, and alanine aminotransferase elevation (Table 4). The most commonly reported grade 3/4 AEs were neutropenia, leukopenia, anemia, and febrile neutropenia. Febrile neutropenia occurred in 8 patients, requiring dose reduction. The frequency of neuropathy was 1.1% (3/272) in this study.

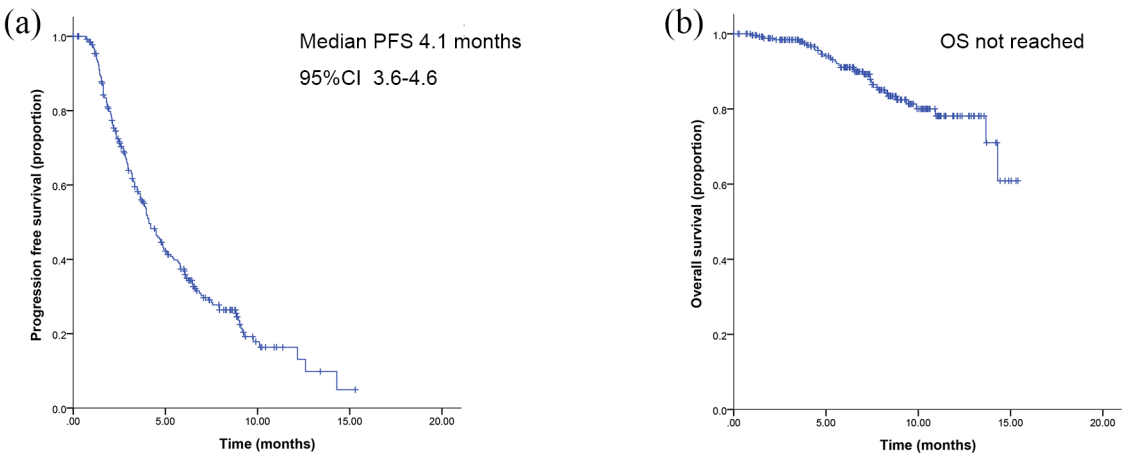

Figure 1. Kaplan–Meier plot for PFS and OS in patients treated with eribulin. (a) Kaplan–Meier plot for PFS; (b) Kaplan–Meier plot for OS.
OS, overall survival; PFS, progression-free survival.

Table 2. Evaluation of efficacy.

Variable	No. (%)
PFS	
Events — No. (%)	178 (65.4)
Duration — months	
Median	4.1
95% CI	3.6–4.6
Overall survival	
Events — No. (%)	36 (13.2)
Duration — months	
Median	Not reached
95% CI	Not reached
Best overall response — No. (%)	
Complete response	1 (0.4)
Partial response	47 (17.3)
Stable disease	120 (44.1)
Duration of SD of ⩾24 weeks	19 (7.0)
Progressive disease	74 (27.2)
NE	30 (11.0)
ORR	48 (17.6)
CBR	67 (24.6)

CBR, clinical benefit rate; CI, confidence interval; NE, inevaluable; ORR objective response rate; PFS, progression-free survival; SD, standard deviation.

Discussion

This multicenter, retrospective study found that 272 heavily pretreated Chinese women with MBC receiving eribulin showed a median PFS of 4.1 months; however, the OS data were immature. Anti-angiogenesis agents, anti-HER2 agents, and capecitabine were the most common co-therapies prescribed with eribulin. The number of metastatic sites, duration of previous taxane treatment for MBC, and combination with bevacizumab were independent predictors of the efficacy of eribulin. The toxicity of eribulin was tolerable, and hematologic toxicities were the most common AEs observed in this study. This study provides first-hand data of the post-marketing efficacy and safety profile of eribulin in China in routine clinical practice.

Eribulin was found to have antitumor activity in Chinese patients with MBC in clinical practice and the median PFS was similar to that reported by other studies for this population (Table S1). The median PFS with eribulin treatment in the EMBRACE study, Study 301, and Study 304 were 3.7, 4.1, and 2.8 months, respectively.[12–13,16] Previous retrospective, multicenter studies concerning eribulin showed that the median PFS ranged from 3.3 to 5.1 months.[17–22] The ORR was also comparable to previous data. It is important to note that the median number of lines of prior chemotherapy administered for MBC was 4 (range: 1–10) in our study; this indicated that a more heavily pretreated population tended to receive eribulin in China, compared with the

Table 3. Univariate and multivariate analyses of factors predicting progression-free survival in patients treated with eribulin.

	N	Event	Univariate			Multivariate		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value
ECOG performance status								
0–1	241	153	1.3	1.0–1.7	0.031*	1.3	0.7–2.6	0.36
2	31	25						
Disease characteristic								
De novo stage IV	28	15	1.2	0.8–2.2	0.37			
Recurrent disease	244	163						
Previous taxanes in the adjuvant/neoadjuvant setting								
No	82	48	1.4	1.0–2.0	0.062	1.2	0.7–1.7	0.16
Yes	190	130						
Subtype								
HoR+/HER2–	151	99	1.1					
HER2+	31	18		0.9–1.3	0.20			
HoR–/HER2–	89	61						
Liver metastasis								
No	131	82	1.1	0.8–1.5	0.47			
Yes	141	96						
Visceral metastasis								
No	56	34	1.3	0.9–2.0	0.10			
Yes	216	144						
No. of metastatic sites								
1–2	122	76	1.4	1.0–1.9	0.024*	1.5	1.0–2.3	0.023*
⩾3	150	102						
No. of prior chemotherapy regimens for MBC								
⩽2 lines	80	43	1.2	1.0–1.4	0.031*	1.1	0.8–1.4	0.58
⩾3 lines	192	135						
Duration of previous taxane treatment for MBC								
⩽6 months	167	115	0.7	0.5–0.9	0.022*	0.6	0.4–1.0	0.048*
>6 months	50	35						
Agents used in combination								
No	141	101	0.5	0.3–0.9	0.024*	0.7	0.4–1.0	0.046*
Bevacizumab	58	32						

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor-2; HoR, hormone receptor; MBC, metastatic breast cancer.
*$p < 0.05$ was considered significant.

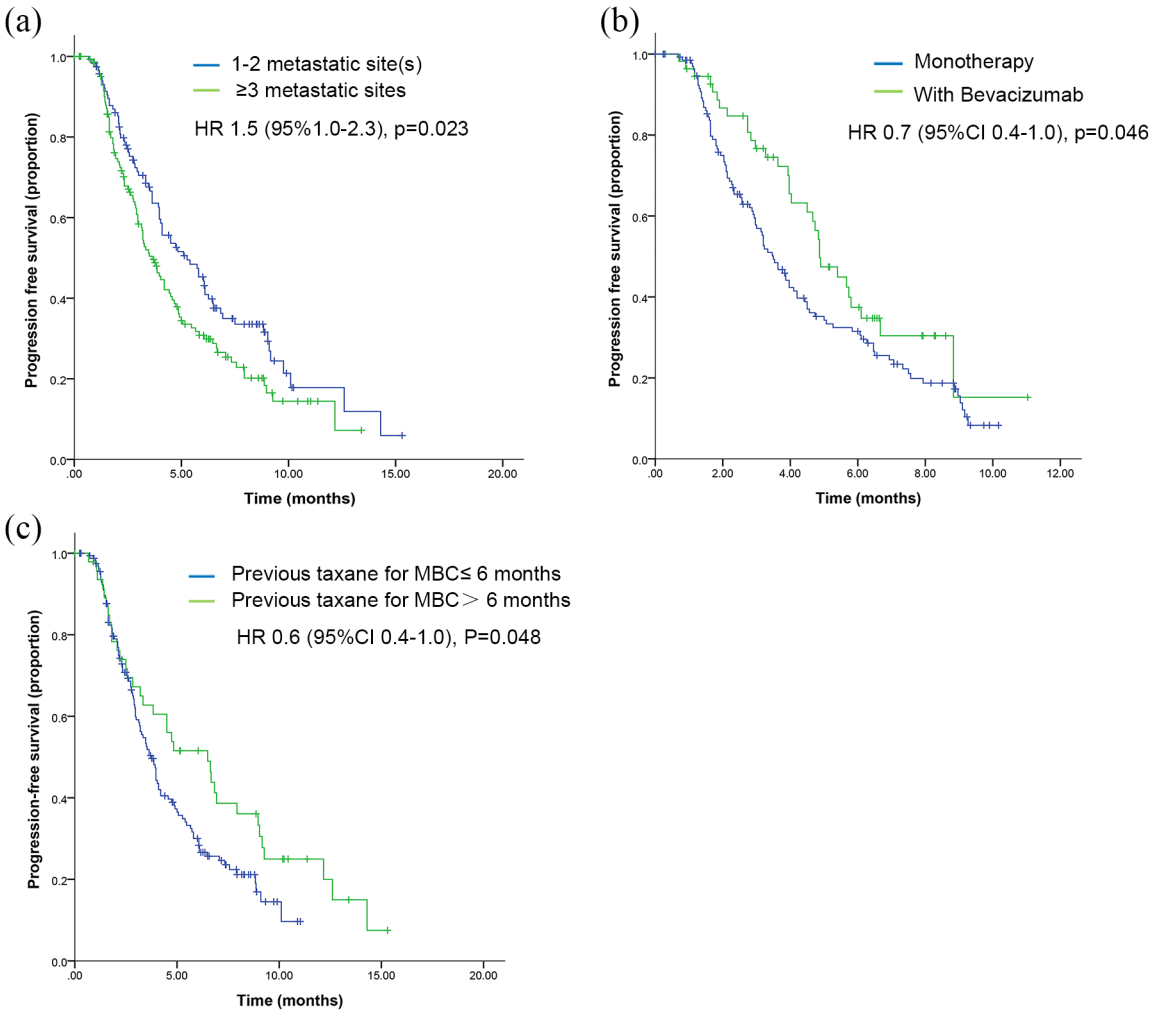

Figure 2. Kaplan–Meier curves for PFS according to potential predictive factors. (a) Number of metastatic sites, (b) Combination with bevacizumab, (c) Duration of previous taxane treatment for MBC.
CI, confidence interval; MBC, metastatic breast cancer; PFS, progression-free survival.

populations in most of the above studies (median number of lines of prior chemotherapy: 2–3). However, the efficacy of eribulin in our study was in the upper range of previous ones. This may be partly explained by nearly half of patients receiving eribulin-based combination treatments; the antitumor activity was improved compared to monotherapy, counteracting the effects caused by a later line of eribulin.

Recent studies have focused on the combination of eribulin and targeted agents, including anti-HER2 agents,[23] poly ADP-ribose polymerase inhibitors,[24] immune checkpoint inhibitors,[25] and anti-angiogenesis agents.[26] Investigators have applied these novel combinations in patients in clinical practice, based on tumor subtypes and gene signatures. More than one-fifth of patients treated with the combination of eribulin and bevacizumab showed prolonged PFS compared to those treated with eribulin monotherapy; a similar conclusion was reached in the E2100 trial of paclitaxel plus bevacizumab.[27] Eight patients received concurrent PD-1/PD-L1 inhibitors, while five patients received VEGFR-TKIs plus PD-1/PD-L1 inhibitors. However, the population was too small to exhibit the effects of the combination of eribulin and immune checkpoint inhibitors in patients with MBC, though recent studies have shown promising results with this combination in various cancers. [28–30] These combinations did not cause additional AEs, and the safety profile was consistent with the known toxic effects of each agent.

Table 4. Adverse events.

AEs	Grade 1	Grade 2	Grade 3	Grade 4	All grade (%)	Grade 3/4 (%)
Leukopenia	24	35	11	4	74 (27.2)	15 (5.5)
Neutropenia	7	30	35	14	86 (31.6)	49 (18.0)
Anemia	16	20	3	0	39 (14.3)	3 (1.1)
Febrile neutropenia	0	0	8	0	8 (2.9)	8 (2.9)
Thrombocytopenia	5	5	1	0	11 (4.0)	1 (0.4)
Neuropathy	1	1	1	0	3 (1.1)	1 (0.4)
Anorexia	4	0	0	0	4 (1.5)	0 (0.0)
Fatigue	10	3	0	0	13 (4.8)	0 (0.0)
ALT increased	11	3	0	0	14 (5.1)	0 (0.0)
AST increased	24	4	1	0	29 (10.7)	1 (0.4)
Nausea	3	1	0	0	4 (1.5)	0 (0.0)
Vomiting	4	1	1	0	6 (2.2)	1 (0.4)
Blood bilirubin increased	4	1	0	0	5 (1.8)	0 (0.0)
Myalgia	1	1	0	0	2 (0.7)	0 (0.0)
Creatinine increased	1	1	0	0	2 (0.7)	0 (0.0)
Cough	2	0	0	0	2 (0.7)	0 (0.0)
Mucositis oral	4	1	2	0	7 (2.6)	2 (0.7)
Fever	0	4	0	0	4 (1.5)	0 (0.0)
Alopecia	1	8	0	0	9 (3.3)	0 (0.0)
Headache	3	1	0	0	4 (1.5)	0 (0.0)
Hypomagnesemia	1	0	0	0	1 (0.4)	0 (0.0)
Hyponatremia	0	1	0	0	1 (0.4)	0 (0.0)
Epistaxis	1	0	0	0	1 (0.4)	0 (0.0)
Urinary tract infection	0	1	0	0	1 (0.4)	0 (0.0)
Hypertriglyceridemia	1	0	0	0	1 (0.4)	0 (0.0)
Cholesterol high	1	0	0	0	1 (0.4)	0 (0.0)
Bronchopulmonary hemorrhage	0	1	0	0	1 (0.4)	0 (0.0)
Lung infection	0	1	0	0	1 (0.4)	0 (0.0)
Constipation	0	1	0	0	1 (0.4)	0 (0.0)
Ileus	0	0	1	0	1 (0.4)	1 (0.4)

(continued)

Table 4. (continued)

AEs	Grade 1	Grade 2	Grade 3	Grade 4	All grade (%)	Grade 3/4 (%)
Ischemia cerebrovascular	0	1	0	0	1 (0.4)	0 (0.0)
Dysgeusia	0	1	0	0	1 (0.4)	0 (0.0)
Hypercalcemia	1	0	0	0	1 (0.4)	0 (0.0)
Abdominal distention	1	0	0	0	1 (0.4)	0 (0.0)
Hyperglycemia	0	0	1	0	1 (0.4)	1 (0.4)
Depressed level of consciousness	1	0	0	0	1 (0.4)	0 (0.0)
GGT elevation	0	0	1	0	1 (0.4)	1 (0.4)
Conjunctivitis infective	0	1	0	0	1 (0.4)	0 (0.0)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase

As survival was different between biological subgroups,[5] previous studies explored the difference of efficacy of eribulin in different molecular subtypes and showed an OS benefit of eribulin in patients with HER2-negative, ER-negative, and TN breast cancer (comparison with capecitabine), but the PFS benefit was similar between different cancer subtypes.[15] In this study, there was no significant difference in PFS between metastatic HoR+, HER2+, and TN breast cancer patients, indicating similar antitumor activity across different subtypes. The metastatic site was also an important factor for determining the benefit of eribulin according to previous study.[17] We found that in our study visceral or liver metastasis did not lead to a difference in PFS, indicating that eribulin is also effective in patients with visceral or liver metastasis. We further found that eribulin showed poor efficacy in patients with extensive metastasis and a heavy tumor burden. Interestingly, patients with the duration of previous taxane treatment >6 months had a longer PFS to those with $\leqslant 6$ months in our study. A prior study reported a trend for improved OS with eribulin treatment to capecitabie in patients with disease progression more than 60 days after the last dose of taxanes, but significance was not reached. The controversy has been caused by the fact that patients with a clinical benefit under a previous taxane therapy also showed a better CBR and PFS when treated with eribulin.[17] Our study indicates that patients showing long-term disease control of microtubule inhibitor taxane tend to be sensitive to eribulin, and a certain degree of cross resistance between microtubule inhibitors may exist, resulting in the need for further studies.

Prospective clinical trials highly selected patients with a better PS, adequate organ functions and younger age. Patients' ineligible to clinical trials were treated with eribulin in daily clinical practice, and the real-world study is an important method to explore the efficacy and toxicity in these patients. Previous studies including the patients with preserved PS, pre-existing dysfunctions, or elder age showed a similar efficacy of eribulin with prospective studies, [17,33–34] indicating eribulin may be a viable option in a broader patient population. In our study, a higher proportion of ECOG = 2, a later line of eribulin administration, and more patients treated with combined agents with eribulin were observed. Multivariate analysis indicated that patients with different ECOG and line of prior chemotherapy regimens reached the similar PFS, but patients receiving the combined bevacizumab showed a longer PFS with no additional toxicity. These results suggested that eribulin was effective in patient's ineligible to clinical trials.

This study is limited by the nature of the retrospective research. Recall bias was inevitable, as the frequency of AEs involving subjective assessment, such as neuropathy, fatigue, and myalgia, was lower than that reported by prospective

studies. As most subjects included in this study were outpatients, some of them might be unable to remember the detailed discomfort during the use of eribulin and reported no neuropathy. It also indicated that the neuropathy was minor and had little influence on activity of daily life. Another reason was the duration of exposure to eribulin. The median cycle of eribulin in our study was less than some prospective studies such as Study 301 and Study 304 (median cycle 4 *versus* 5–6). Long treatment duration (>3 months) was significantly associated with heavier neuropathy induced by eribulin.[35] Secondly, the short follow-up period made it difficult to observe a sufficient number of death events (13.2%) at the cutoff date. As an OS benefit rather than PFS was obtained by eribulin group in prospective studies, immature OS data could not examine the prognostic factors of OS with the current cutoff date. In addition, the exact evaluation of the CBR was also precluded. A long follow-up for this study is warranted to draw a conclusion of OS and CBR with eribulin and determinants for OS in Chinese patients.

Taken together, this study provides new evidence for the use of eribulin in heavily pretreated patients with MBC with different subtypes. The effectiveness and safety profile of eribulin were consistent with those reported by prospective studies. As a result, eribulin may be a new option for patients pretreated with taxanes and anthracyclines in China. The identified predictive factors can help physicians in distinguishing patients who will benefit from eribulin treatment. Our study indicates further prospective assessment of the post-marketing efficacy and safety of eribulin in Chinese women with MBC.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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