Therapeutic Efficacy, Safety and Predictive Indicators of Eribulin Plus Anti-Angiogenic Medicine for Metastatic Breast Cancer

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ABSTRACT

Objective: To evaluate the efficacy and safety of eribulin plus anti-angiogenic medicine in metastatic breast cancer (MBC), and explore the potential biomarkers.

Study Design: Observational study.

Place and Duration of the Study: Department of Medical Oncology, Xi'an International Medical Centre Hospital, Xi'an, China, from May 2022 to 2023.

Methodology: A total of 40 MBC patients treated with eribulin were enrolled. Patients were divided into two groups based on whether they received eribulin monotherapy or combined therapy. Median progression-free survival (mPFS), the time from the start of erbium treatment to the time of disease progression, was calculated using the Kaplan-Meier method.

Results: The eribulin plus anti-angiogenic medicine treatment group had a significantly prolonged mPFS compared to the group without anti-angiogenic medicine treatment (7.0 months *vs*. 2.0 months, p <0.001). The multivariate analysis identified that the combination of anti-angiogenic therapy (HR = 0.043, p = 0.004) and the occurrence of grade 3-4 neutropenia after the treatment were two predictive factors for longer PFS (HR = 0.322, p = 0.009). In contrast, prior resistance to taxane was predictive of shorter PFS (HR = 4.583, p = 0.019). Other clinic-pathological factors were not significantly associated with PFS. Fisher's exact test showed no significant increase in treatment-related adverse events (all grades) after combination with anti-angiogenic medicine.

Conclusion: The eribulin plus anti-angiogenic combination may act as a potential therapy for late-line MBC patients with clinically beneficial therapeutic effects.

Key Words: *Metastatic breast cancer, Eribulin, Anti-angiogenic therapy, Predictive indicators of efficacy.*

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INTRODUCTION

Eribulin can block tumour cell mitosis by inhibiting microtubules.[1,2] In addition, eribulin can also induce tumour angiogenesis.[3] The patients treated with eribulin have smaller adverse reactions and it is an important chemotherapeutic medicine for MBC.

However, the single-agent treatment of eribulin has limited efficacy in MBC. STUDY-301 showed that for MBC patients treated with anthracyclines and taxanes, the overall survival (OS) (15.9 months *vs*. 14.5 months, p = 0.056) and PFS (4.1 months *vs*. 4.2 months, p = 0.30) with eribulin compared to capecitabine have no difference.[4]

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In STUDY-304, the comparison between eribulin and vinorelbine showed no enhancement in terms of OS (13.4 months *vs*. 12.5 months, p = 0.838) or PFS (2.8 months *vs*. 2.8 months, p = 0.36).[5] Therefore, for the treatment of MBC patients, especially those receiving later-line treatment, eribulin needs to be combined with other treatments to further improve its efficacy.

Bevacizumab is a recombinant humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF), which can specifically bind to VEGF and inhibit tumour angiogenesis. Multiple phase III randomised controlled clinical studies, such as ECOG 2100, AVADO, RIBBON-1, and RIBBON-2 have shown that the addition of bevacizumab to chemotherapy can significantly improve PFS in MBC patients.[6-9] Anlotinib is a small-molecule multi--target tyrosine kinase inhibitor that can block the downstream signalling pathway mediated by vascular endothelial growth factor receptor (VEGFR), thereby exerting anti-angiogenic effects. A phase II clinical study reported at ASCO 2022 showed that for MBC patients who failed to respond to anthracyclines and taxanes the combination of eribulin and anlotinib significantly improved mPFS (9.7 months *vs.* 3.7 months, p = 0.04) and DCR (100% *vs.* 66.7%, p = 0.007) compared with eribulin alone.[10]

Eribulin has the effect of inducing tumour vascular remodelling and increasing medicine perfusion, which theoretically can synergistically act with bevacizumab or anlotinib to inhibit angiogenesis. There is a possibility of synergistic efficacy. Single-arm and small-sample clinical studies have shown the anti-tumour efficacy of eribulin combined with bevacizumab and anlotinib.[10,11] This study was conducted to evaluate the efficacy and safety of eribulin plus anti-angiogenic medicine in MBC, and explore the potential biomarkers.

METHODOLOGY

A total of 40 patients diagnosed with MBC and treated with eribulin in Xi'an International Medical Center Hospital, Xi'an, China, from May 2022 to 2023 were retrospectively enrolled in this study. The patients included in the study had MBC and received treatment containing eribulin. All molecular subtypes were eligible for inclusion. However, patients with contraindications for anti-angiogenic therapy were excluded from the study. Patients' medical information was extracted from medical records, including patients' characteristics, treatment outcomes, treatment line, pretreated medicine history, and other combined treatments.

The specific regimen was determined based on guideline recommendations and the doctor's choice. A total of 40 patients received treatment including eribulin, with 22 patients receiving monotherapy with eribulin and 18 patients receiving eribulin in combination with anti-angiogenic medicine (bevacizumab or anlotinib). Combination therapy with anti-human epidermal growth factor receptor-2(HER-2) targeted treatment was allowed for HER-2-positive patients. The patient received 1.4 mg/m^2 of eribulin intravenous chemotherapy on the 1st and 8th day of each cycle, with bevacizumab (7.5 mg/kg, administered on the 1st day of each cycle) or anlotinib (12 mg once daily for 14 consecutive days followed by a 7-day break) as an anti-angiogenic agent. The treatment regimen consisted of a 21-day cycle and continued until the disease progressed or intolerable toxicity occurred. After every two treatment cycles, the efficacy of the anti-tumour treatment was evaluated according to the response evaluation criteria in solid tumours (RECIST) version 1.1.[12]

Ten clinical variables were recorded: Patient age, Eastern Cooperative Oncology Group (ECOG) performance status, hormone receptor (HR) (includes oestrogen receptor, ER, and / or progesterone receptor, PR) expression status, HER-2 expression status, Ki-67 levels, number of metastases, number of lines of eribulin treatment, whether combined with anti-angiogenic medicine therapy, history of taxane resistance, and the occurrence of grade 3-4 neutropenia after eribulin treatment.

Statistical analysis was performed using IBM SPSS 19.0 software. Qualitative variables were described by frequencies and percentages, continuous and ordinal variables by mean ± SD and median and interquartile ranges. The Kaplan-Meier method was used to calculate the median PFS (the time from the start of eribulin treatment to the time of disease progression) and the corresponding 95% confidence interval (CI). The log-rank test was used to compare differences in PFS between different groups. The Cox regression model was used for multivariate analysis. The Fisher exact probability test was used to compare the difference in adverse reactions between the two groups, with a level of significance set at p-value <0.05.

RESULTS

Patients' clinical pathological characteristics and correlation with PFS of eribulin are summarised in Table I. The ECOG score (p = 0.045), combination therapy with anti-angiogenic medicine (p <0.001), resistance to taxane (p <0.001), and the occurrence of grade 3-4 neutropenia after treatment (p <0.001) were significantly associated with PFS of eribulin Figure 1. Other variables were not significantly correlated with the PFS of eribulin Table I.

Table I: Univariate analysis of patient characteristics and correlation with PFS of eribulin.

Patient characteristics	n (%)	p-value
Age during eribulin treatment		0.065
18-55	18 (45%)	
≥56	22 (55%)	
HR (ER and/or PR) status		0.396
Negative	14 (35%)	
Positive	26 (65%)	
HER-2 status		0.325
Negative	29 (72.5%)	
Positive	11 (27.5%)	
Ki-67 level		0.067
1-30%	18 (45%)	
31-100%	22 (55%)	
Number of metastases		0.948
1-3	20 (50%)	
≥4	20 (50%)	
ECOG score		0.045
0-1	23 (57.5%)	
2	17 (42.5%)	
Resistance to taxanes		<0.001
No	26 (65%)	
Yes	14 (35%)	
Number of lines of eribulin treatment		0.80
1-5	22 (55%)	
≥6	18 (45%)	
Combined anti-angiogenic therapy		<0.001
No	22 (55%)	
Yes	18 (45%)	
Level of neutrophil reduction after treatment		<0.001
0-2	18 (45%)	
3-4	22 (55%)	

Kaplan-Meier analysis, log-rank test

Patients with ECOG scores of 0-1 had prolonged mPFS compared to those with ECOG scores of 2 [5.6 months (95% CI 3.115-8.085) *vs.* 3.6 months (95% CI 2.188-5.012), p = 0.045, Figure 1A]. Patients treated with eribulin plus anti-angiogenic therapy had significantly prolonged mPFS compared to those treated without anti-angiogenic therapy [7.0 months (95% CI 6.272-7.728) *vs.* 2.0 months (95% CI 1.655-2.345), p <0.001, Figure 1B)]. Patients without prior taxane-resistance had significantly prolonged mPFS compared to those with taxane-resistance [5.9 months (95% CI 4.401-7.399) *vs.* 2.0 months (95% CI 1.633-2.367), p <0.001, Figure 1C]. Patients who experienced grade 3-4 neutropenia after treatment had significantly prolonged mPFS compared to those who experienced grade 0-2 neutropenia after treatment [6.5 months (95% CI 5.213-7.787) *vs.* 1.9 months (95% CI 1.623-2.177), p <0.001, Figure 1D].

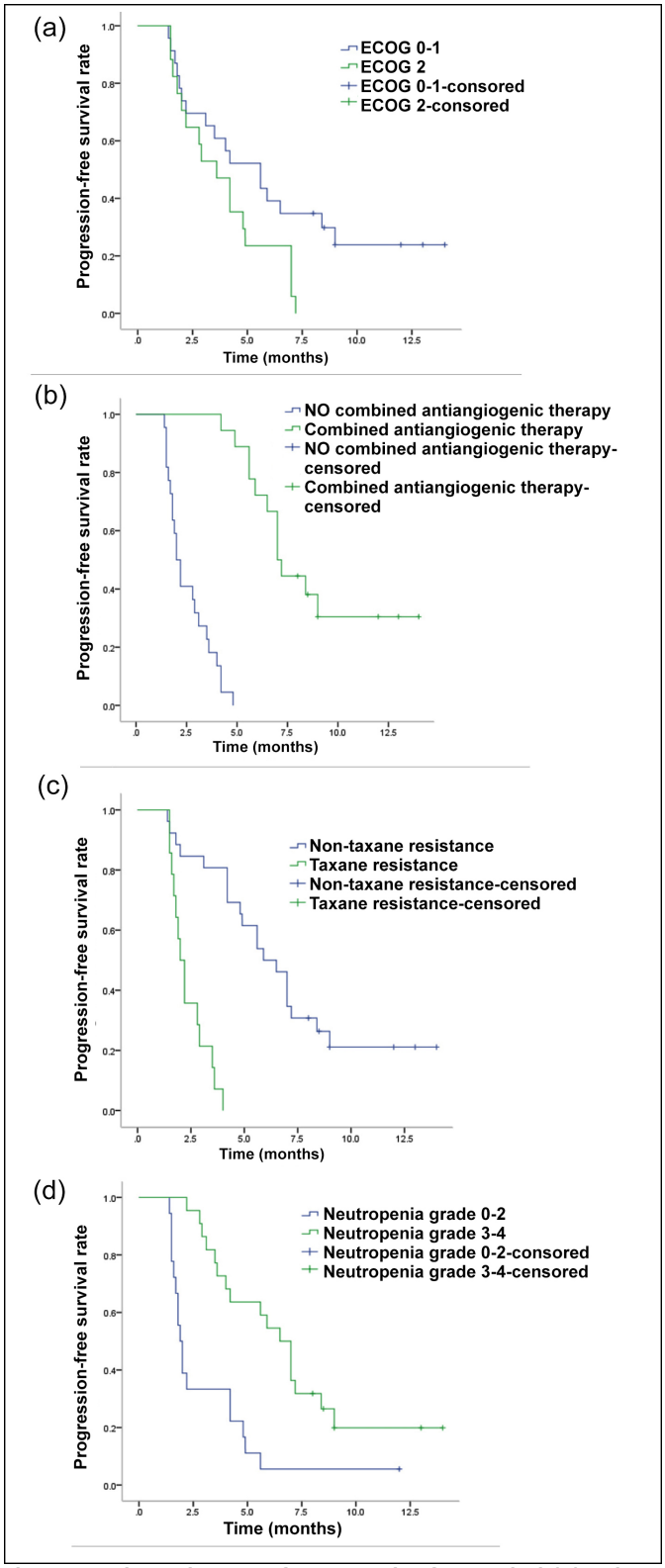

Figure 1: Kaplan-Meier curves for progression-free survival. (A) Patients with ECOG performance status of 0-1 *versus* patients with ECOG performance status of 2. (B) Patients treated with the combination of eribulin and anti-angiogenic medicine *versus* patients treated with eribulin only. (C) Patients with non-taxane resistance in the past *versus* patients with taxane resistance. (D) Grade 3-4 neutropenia after treatment *versus* grade 0-2 neutropenia after treatment.

The results of multivariate analysis showed that there are three statistically significant independent prognostic factors influencing PFS benefit of eribulin: The combination of anti-angiogenic medicine treatment (95% CI 0.005-0.369, HR = 0.043, p= 0.004), previous taxanes resistance (95% CI 1.283-16.363, HR = 4.583, p = 0.019), and grade 3-4 neutropenia after treatment (95% CI 0.138-0.754, HR = 0.322, p = 0.009). ECOG score could not serve as an independent prognostic factor for PFS benefit of eribulin (95% CI 0.702-3.462, HR = 1.559, p = 0.276).

The occurrence of adverse events was similar between the eribulin treatment group and the eribulin plus anti-angiogenic medicine group. There was no significant increase in treatment-related adverse events (all grades) after treatment combined with anti-angiogenic medicine. The Fisher exact probability test result indicated no statistically significant differences in the occurrence of neutropenia (63.6% *vs*. 83.3%), alopecia (50.0% *vs*. 55.6%), fatigue (40.9% *vs*. 27.8%), transaminase elevation (31.8% *vs*. 27.8%), peripheral neuropathy (27.3% *vs*. 27.8%), and thrombocytopenia (22.7% *vs*. 11.1%). It is worth noting that eribulin combined with anti-angiogenic medicine therapy may increase the occurrence of proteinuria and hypertension. However, the Fisher exact probability test showed no statistically significant differences in the occurrence of all-grade proteinuria (4.5% *vs*. 16.7%) and all-grade hypertension (4.5% *vs*. 22.2%). In the eribulin combined with anti-angiogenic medicine treatment group, one patient had Grade 3 proteinuria, which recovered to Grade 1 after reducing the anti-angiogenic medicine dose, and two patients had Grade 3 hypertension. By taking antihypertensive medicine alone, the hypertensions have been well controlled and patients continued to receive the original dose of anti-angiogenic medicine treatment Table II.

DISCUSSION

In this study, 40 patients with MBC received treatment with the eribulin regimen, with an average of five treatment lines. 45% of the patients had six or more treatment lines, and 50% of the patients had 4 or more metastatic lesions. Patients had an overall high tumour burden, worse disease prognosis, and received treatment in late lines. The efficacy of single-agent eribulin was found to be limited, with a mPFS of only 2.0 months. Consistent with this, previous large prospective clinical studies have reported mPFS of 2.8-4.1 months for MBC patients treated with single-agent eribulin. Anti-angiogenic treatment could improve PFS in MBC patients, but there is no OS benefit, so it is eliminated from the guidelines. Due to policy restrictions, anti-angiogenic medicine in China is not covered by medical insurance for MBC patients, thus most patients will not be treated with anti-angiogenic therapy in front-line treatment. Anti-angiogenic medicine may be combined with chemotherapy in later-line treatment to overcome medicine resistance. This study aims to utilise this treatment modality.

The study results revealed that patients who were treated with a combination of eribulin and anti-angiogenic therapy had a substantial increase in mPFS compared to those who did not receive anti-angiogenic therapy (7.0 months *vs*. 2.0 months, p <0.001).

Table II: Common treatment-related adverse events in two groups.

Adverse event	All Grades n (%)		p-value	Grade 3-4 n (%)		p-value
	Eribulin	Eribulin combination		Eribulin	Eribulin combination	
Neutropenia	14/22 (63.6)	15/18 (83.3)	0.286	10/22 (45.5)	10/18 (55.6)	0.751
Febrile neutropenia	1/22 (4.5)	0/18 (0)	>0.999	1/22 (4.5)	0/18 (0)	>0.999
Thrombocytopenia	5/22 (22.7)	2/18 (11.1)	0.427	1/22 (4.5)	0/18 (0)	>0.999
Anaemia	6/22 (27.3)	5/18 (27.8)	>0.999	2/22 (9.1)	0/18 (0)	0.492
Fatigue	9/22 (40.9)	5/18 (27.8)	0.510	1/22 (4.5)	1/18 (0)	>0.999
Nausea	4/22 (18.2)	2/18 (11.1)	0.673	0/22 (0)	0/18 (0)	-
Diarrhoea	2/22 (9.1)	3/18 (16.7)	0.642	0/22 (0)	0/18 (0)	-
Constipation	2/22 (9.1)	3/18 (16.7)	0.642	0/22 (0)	0/18 (0)	-
Oral mucositis	2/22 (9.1)	2/18 (11.1)	>0.999	0/22 (0)	0/18 (0)	-
Hair loss	11/22 (50)	10/18 (55.6)	0.761	NA	NA	-
Peripheral neuropathy	6/22 (27.3)	5/18 (27.8)	>0.999	0/22 (0)	1/18 (5.6)	0.450
Elevated Transaminase	7/22 (31.8)	5/18 (27.8)	>0.999	1/22 (4.5)	0/18 (0)	>0.999
Proteinuria	1/22 (4.5)	3/18 (16.7)	0.310	0/22 (0)	1/18 (5.6)	0.450
Hypertension	1/22 (4.5)	4/18 (22.2)	0.155	0/22 (0)	2/18 (11.1)	0.206
Joint pain	4/22 (18.2)	4/18 (22.2)	>0.999	0/22 (0)	0/18 (0)	-

Fisher's exact probability test. NA: This level does not exist. -: Since no adverse events of this level occurred in either group, Fisher's exact probability test cannot assess the difference in adverse reactions between the two groups.

This finding provides new insights into enhancing the efficacy of eribulin, suggesting that anti-angiogenic medicine may help overcome medicine resistance in later-line treatment of metastatic breast cancer patients. Furthermore, the combination of eribulin and anti-angiogenic medicine did not significantly increase treatment-related adverse events. Overall, patients have milder adverse reactions, thereby confirming the favourable tolerance of the combined treatment. Therefore, eribulin plus anti-angiogenic therapy can act as a viable treatment option for multi-line therapy and refractory MBC patients. Subsequent efficacy verification can be carried out in cell lines or animal models. The impact of the combined treatment regimen on inducing tumour vascular remodelling, tumour microenvironment, and other aspects can be analysed to further understand the intrinsic reasons for the synergistic effect of combination therapy.

In the exploratory analysis of the STUDY211 trial, a subgroup of patients with prior taxane resistance exhibited the lowest disease control rate (DCR) compared to patients with anthracycline, capecitabine, or gemcitabine resistance (55.8% *vs*. 55.7% *vs*. 51.2% *vs*. 48.9%) after receiving various chemotherapy regimens.[13] Moreover, the subgroup analysis of the STUDY301 trial indicated that MBC patients who experienced rapid progression after prior taxanes treatment had a worse OS when treated with eribulin chemotherapy compared to those without rapid progression (14.3 months *vs*. 18.6 months).[14] Furthermore, an analysis of the EMBRACE and STUDY301 trials demonstrated that eribulin had an inferior PFS in patients with taxanes resistance compared to those without taxanes resistance (3.5 months *vs*. 4.3 months).[15] The results of the STUDY304 trial were similar, as prior taxane resistance leading to a lower eribulin PFS (2.8 months *vs*. 4.1 months).[5]

Collectively, multiple studies have shown the limited efficacy of eribulin in patients who exhibited resistance to taxane-based therapies. Patients who are not resistant to taxane and receive eribulin treatment have better DCR, PFS, and OS outcomes. This can be attributed to the fact that both eribulin and taxanes are microtubule inhibitors and exert similar anti-tumour effects. The findings of the study align with these previous findings, indicating that non-resistance to taxane predicts a longer PFS with eribulin treatment. The adverse reactions of eribulin are slight. Eribulin has better tolerance than taxanes. Additionally, eribulin has also demonstrated positive results in the first-line treatment of MBC patients in advanced stages.[16,17] This suggests that eribulin can be utilised earlier in clinical practice to achieve more effective anti-tumour effects, rather than waiting for the development of taxane resistance before using it again.

Neutropenia is one of the prominent adverse reactions associated with eribulin. In this study, the incidence of grade 3-4 neutropenia in patients receiving eribulin-containing regimens was 50%. Both univariate and multivariate analyses demonstrated a significant association between the occurrence of grade 3-4 neutropenia following eribulin chemotherapy and longer PFS. The occurrence of severe bone marrow suppression after eribulin treatment suggests a strong cytotoxic effect of the chemotherapy drug on haematopoietic progenitor cells with proliferative and differentiation abilities, which also indicates a significant cytotoxic effect on rapidly proliferating tumour cells. The absolute lymphocyte count (ALC) in peripheral blood biomarkers often serves as a factor reflecting tumour immune regulation, while neutrophils are associated with tumour-related inflammation, inhibition of lymphocyte activity, and promotion of tumour progression.[18] Eribulin has been shown to possess immune regulatory activity within the tumour microenvironment. Post-hoc analysis based on the EMBRACE study and a retrospective study have both found that a low neutrophil-to-lymphocyte ratio (NLR) is linked to prolonged OS in eribulin therapy, serving as a predictive marker for eribulin efficacy.[19,20] In summary, a significant decrease in neutrophil levels following chemo-therapy may suggest that eribulin has a potent cytotoxicity against proliferating cells while regulating the immune activity of the tumour microenvironment. This effect may further reduce neutrophil-

related tumour invasion, and serve as a predictive factor for the eribulin efficacy.

The weakness of this study is that the sample size was small. The main reason is that antiangiogenic therapy is not covered by medical insurance, and eribulin has been approved for marketing for a short time in China. The study retrospectively analysed eribulin combined with antiangiogenic therapy and found that this treatment mode achieved good results in refractory MBC. At present, this centre is conducting a larger sample size, and prospective clinical study to verify the efficacy of the combination of chemotherapy and antiangiogenic therapy. Larger sample sizes, prospective clinical studies, and more comprehensive basic research are required to validate the above results and reveal the underlying mechanisms.

CONCLUSION

The combination of eribulin and anti-angiogenic therapy holds the potential for a theoretical synergistic effect, as demonstrated by this study, resulting in a significant prolongation of PFS in patients with MBC. Particularly for patients who are not resistant to taxanes, which are microtubule inhibitors, eribulin can achieve longer PFS. These findings have important implications for guiding clinical use of drugs. The combination of anti-angiogenic therapy, previous non-taxane resistance, and the occurrence of grade 3-4 neutropenia after chemotherapy can be used as predictive biomarkers for the efficacy of eribulin, further informing patient selection strategies.

ETHICAL APPROVAL:

This clinical study is a retrospective study, only collecting patients' clinical data without interfering with patients' treatment plan, which will not bring physiological risks to patients. The authors did not reveal personal privacy. Thus, this study was exempted by the Ethics Committee of Medical Centre Hospital.

PATIENTS' CONSENT:

The informed consent of the patients or their family members has been obtained prior to the publication of data related to this case.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

JZ, YX: Designed the research, analysed the data and drafted the manuscript.
JZ, YX, HD: Data collection and analysis.
All authors approved the final version of the manuscript to be published.

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