Real-world effect of bevacizumab and eribulin on metastatic breast cancer using a propensity score matching analysis

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Abstract. Bevacizumab and eribulin are novel agents for the treatment of HER2-negative metastatic breast cancer (MBC); however, the choice between bevacizumab and eribulin for MBC can be difficult. The present study aimed to compare two treatment strategies, eribulin followed by bevacizumab and paclitaxel (BEV + PTX) versus BEV + PTX followed by eribulin, to determine whether the order of administration affects the outcome of MBC in the real world. A total of 180 patients who started BEV + PTX and eribulin treatment for HER2-negative MBC from August 2011 to June 2018 were selected. Of these, 84 patients were treated with both BEV + PTX and eribulin sequentially. To evaluate the influence of the sequential order, the efficacy of BEV + PTX followed by eribulin (B-E arm) was compared to treatment with the reverse sequence (E-B arm). The propensity score matching method (PSMA) was used to improve the robustness of the findings from the present study. A total of 60 cases analyzed received BEV + PTX or eribulin as either first- or second-line treatment. In the entire cohort, the median time to failure of strategy (TFS) was 16.8 and 9.9 months in the B-E and E-B arms, respectively [hazard ratio (HR)=0.515, 95% CI 0.298-0.889, P=0.017). A similar HR was derived from PSMA for TFS. Using PSMA, TFS was 16.9 and 9.9 months in the B-E and E-B arms, respectively (HR=0.491, 95% CI 0.253-0.952, P=0.031). These results suggested that when both bevacizumab and eribulin are administered, bevacizumab should be administered first and eribulin should be administered later to ensure the most effective use of each drug.

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Introduction

Bevacizumab and eribulin are novel agents for the treatment of HER2-negative metastatic breast cancer. Eribulin improved overall survival in the EMBRACE trials (1). Eribulin has been shown to improve survival in patients with advanced recurrent breast cancer previously treated with anthracycline or taxane chemotherapy. It may be effective in the early treatment of recurrent breast cancer after surgery, but this has not been reported at this time. On the other hand, bevacizumab has improved progression-free survival but not overall survival in several clinical studies (2,3,4). However, there are many reports that have denied the effectiveness of bevacizumab for OS, even though it has been suggested to be effective in improving outcomes in metastatic disease from several tumor types (5-7). Recently, real-world data have been reported from ESME in France, and the efficacy of BEV in improving overall survival was shown (8). Its excellent tumor reduction effect is expected to improve symptoms and complications associated with recurrent tumors, and the lack of a difference in the incidence of serious adverse events suggests that bevacizumab is a drug that preserves patients' quality of life and inhibits rapid tumor progression.

At present, there is no standard for treatment with these drugs. Making a clinical decision about which treatment option to choose can be difficult. Clinical data on this question are lacking. Although there are some reports about an improved prognosis and fewer adverse events in other cancers by changes in the sequence of treatment (9,10), there have been no reports of differences in the effectiveness of BEV+PTX and eribulin according to their order of administration.

The purpose of this study was to compare two treatment strategies, eribulin followed by BEV + PTX versus BEV + PTX followed by eribulin, to determine whether the order of administration affects patient outcomes in the real world.

Patients and methods

Patients. The database of the TBCRG, a multicenter study group, was established to centralize real-world data on metastatic breast cancer from 14 institutions in Toyama. We used this database to evaluate the survival benefit in patients who were treated with bevacizumab + paclitaxel (BEV + PTX) and eribulin. All patients who started BEV + PTX and eribulin treatment for MBC from August 2011 to June 2018 were selected. Among the 264 patients recorded in the TBCRG database, 180 patients who started BEV + PTX and eribulin treatment for HER2-negative MBC were selected. Of these, 84 patients were treated with both BEV + PTX and eribulin sequentially regardless of the treatment line. The following data were collected from each institution: age, PS, estrogen receptor (ER) status, progesterone receptor (PgR) status, adjuvant chemotherapy, most common metastatic sites, number of metastatic sites, and treatment line.

We retrospectively reviewed the medical records of 60 cases within the 2nd line and analyzed the following items: overall survival, time to failure of the strategy, efficacy of treatment, and adverse events. Computed tomography (CT) was performed after 2 or 3 months of treatment with eribulin or BEV + PTX to assess the efficacy. Disease status was assessed according to the response evaluation criteria in solid tumors (RECIST), and adverse events were assessed by CTCAE version 4.0. TFS was calculated as the duration of BEV+PTX and eribulin administration.

In all institutions, BEV+PTX and eribulin were continued until progression or unacceptable toxicity. Bevacizumab (10 mg/kg) was administered biweekly, and paclitaxel (80 mg/m^2) was administered 3 weeks on/1 week off. Eribulin (1.4 mg/m^2) was administered 2 weeks on/1 week off.

To evaluate the influence of the order of treatment, we compared the efficacy of eribulin followed by BEV + PTX (arm E-B) with the efficacy of treatment with the reverse treatment sequence (arm B-E).

Statistical analysis. Arms E-B and B-E were compared with adjustment for imbalances in patient background factors using a propensity score matching analysis (PSMA) (11,12). The PSMA method was used to examine the consistency between the analysis results, thereby making the clinical findings as robust as possible. The propensity scores were estimated using a logistic regression model with treatment line, age, performance status, number of metastatic sites, recurrence, liver metastasis, and triple negative status. OS and TFS were analyzed using the Kaplan-Meier method and compared using the log-rank test. In addition, univariate Cox regression analysis with the treatment arm as a covariate was used to estimate the hazard ratio and its confidence interval. When survival curves crossed over during the follow-up time, resulting in violation of the proportional hazards assumption, the two-stage test proposed by Qiu and Sheng (13) was used to compare survival curves between treatment arms.

Patient background factors were compared between arms using Pearson's χ^2 test or unpaired Student's t-test, where appropriate. $P<0.05$ was considered to indicate statistical significance. Statistical analyses were performed with JMP software version 14.0 and SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

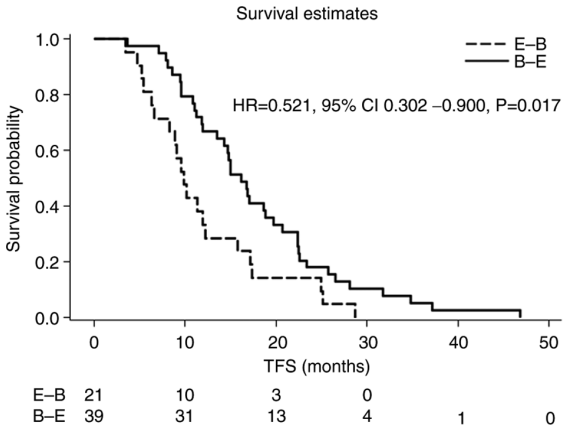

Figure 1. Kaplan-Meier curves for TFS in the entire cohort. TFS, time to failure of strategy.

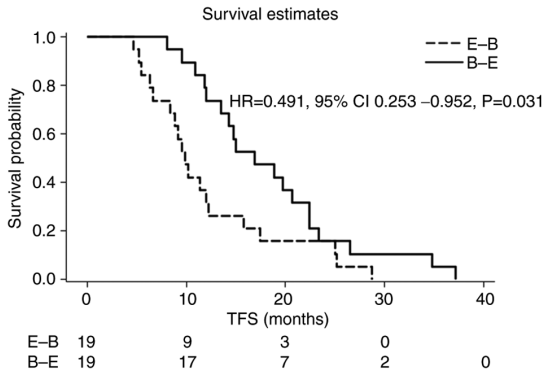

Figure 2. Kaplan-Meier curves for TFS after PMSA. PMSA, propensity score matching analysis; TFS, time to failure of strategy.

Results

Baseline patient demographics and tumor characteristics. The baseline patient characteristics are summarized in Table I. Thirty-nine patients were treated with the B-E sequence, and 21 patients were treated with the E-B sequence; the median ages were 54.4 (range, 30-77) and 54 (range, 34-73) years, respectively. The ER- or PgR-positive rates were 84.6 and 52.4% for the B-E and E-B groups, respectively. Five patients in the B-E group and seven patients in the E-B group had triple-negative breast cancer. Significantly more patients in the B-E arm than in the E-B arm received it as first line treatment (32 vs. 9, P=0.0019). Twelve patients in the E-B arm had received capecitabine or S-1 previously.

Safety. Neutropenia was the most frequent grade ≥3 adverse event and had a similar incidence in both arms. There was one case of grade 3/4 hypertension as a result of treatment with BEV + PTX in each of the arms. There was only one case of grade 3/4 proteinuria in the B-E arm (Table IIA and B). There were no differences in adverse events between the two arms, and there were no deaths.

Efficacy. The overall response rates (ORRs) to eribulin treatment were 28.9 and 33.3% in the B-E and E-B groups,

Table I. Characteristics of the patients.

Characteristics	Number of patients (%)		P-value
	B-E arm (n=39)	E-B arm (n=21)	
Age, median (range)	54.4 (30-77)	54.0 (34-73)	ns[a]
PS			ns[b]
0	29 (74.3)	14 (66.7)	
1	9 (23.1)	5 (23.8)	
2	1 (2.6)	2 (9.5)	
De novo metastatic disease	34 (87.2)	19 (90.5)	ns[b]
ER status			0.008[b]
Positive	33 (84.6)	11 (52.4)	
Negative	6 (15.4)	10 (47.6)	
PgR status			ns[b]
Positive	26 (66.7)	9 (42.9)	
Negative	13 (33.3)	12 (57.1)	
Triple negative	5 (18.5)	7 (25.0)	ns[b]
Neo/adjuvant chemotherapy			ns[b]
Taxane	25 (64.1)	14 (66.7)	
Anthracycline	27 (69.2)	12 (57.1)	
Metastatic sites			
Bone	21 (53.9)	8 (38.1)	ns[b]
Liver	18 (46.2)	6 (28.6)	
Lung	17 (43.6)	12 (57.1)	
CNS	1 (2.6)	1 (4.8)	
Number of metastatic sites			ns [b]
Within 2	23 (59.0)	13 (61.9)	
3 or more	16 (41.0)	8 (38.1)	
Treatment line			0.0019[b]
1	32 (82.0)	9 (42.9)	
2	7 (18.0)	12 (57.1)	

B-E arm, BEV + PTX followed by eribulin; E-B arm, eribulin followed by BEV + PTX; BEV, bevacizumab; PTX, paclitaxel. P-values were obtained by using [a]Student's t-test or [b]Pearson's χ^2 test for comparisons between B-E and E-B groups.

respectively, and the difference was not statistically significant (Table III). In contrast, the ORRs for BEV + PTX treatment were 66.6 and 23.9% in the B-E and E-B groups, respectively, and the difference was statistically significant (P=0.0147) (Table III). In the entire cohort, the median TFS was 16.8 and 9.9 months in the B-E and E-B arms, respectively (HR=0.515, 95% CI 0.298-0.889, P=0.017) (Fig. 1). Using PSMA with the caliper of 1.0, 19 pairs (38 patients) were identified, and their patient characteristics are summarized in Table IV. TFS was 16.9 and 9.9 months in the B-E and E-B arms, respectively (HR=0.491, 95% CI 0.253-0.952, P=0.031) (Fig. 2). The results (12 pairs, 24 patients) of PSMA with the caliper of 0.2, which was conducted as a sensitivity analysis (Fig. S1). Despite matching for treatment line, age, PS, triple-negative status, liver metastasis, and number of metastatic sites, the E-B and B-E arms showed significant differences in TFS.

Discussion

Patients who received BEV + PTX before eribulin (the B-E arm) had a significantly longer TFS than patients who received eribulin before BEV + PTX (the E-B arm) (16.8 vs. 9.0 months). Overall survival was also longer with the B-E treatment than with the E-B treatment (28.0 vs. 17.2 months). With regard to progression-free survival, while our result in the B-E arm was in line with that reported in E2100, RIBBON-1, AVADO, and JO19901, which were phase 2 and 3 trials of first-line therapies, our patients in the E-B arm had a shorter progression-free survival than obtained in those trials (2,3,4,14). On the other hand, progression-free survival with eribulin treatment was 3.7 and 4.1 months in the E-B and B-E arms, respectively, and the difference was not statistically significant. Thus, a significant difference appeared during the time to second progression. With regard to progression-free

Table II. Adverse events.

A, Adverse events of eribulin

	B-E arm (n=39)		E-B arm (n=21)	
Toxicity	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
Leucopenia	11 (28.2)	4 (10.3)	12 (57.1)	1 (4.8)
Neutropenia	5 (12.8)	4 (25.6)	7 (33.3)	5 (23.8)
Hypertrans-aminasemia	3 (7.7)	0 (0)	6 (28.6)	0 (0)
Asthenia/fatigue	17 (43.6)	1 (2.6)	8 (38.1)	0 (0)
Peripheral neuropathy	21 (53.8)	0 (0)	7 (33.3)	0 (0)
Nausea/vomiting	6 (15.4)	0 (0)	3 (14.3)	0 (0)
Stomatitis	7 (17.9)	0 (0)	3 (14.3)	0 (0)
Dysgeusia	10 (25.6)	0 (0)	6 (28.6)	0 (0)

B, Adverse events of BEV + PTX

	B-E arm (n=39)		E-B arm (n=21)	
Toxicities	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)
Leucopenia	13 (33.3)	5 (12.8)	7 (33.3)	1 (4.8)
Neutropenia	10 (25.6)	7 (17.9)	3 (14.3)	3 (14.3)
Hypertrans-aminasemia	6 (15.4)	0 (0)	5 (23.8)	0 (0)
Asthenia/fatigue	18 (46.2)	1 (2.6)	10 (47.6)	1 (4.8)
Peripheral neuropathy	30 (76.9)	1 (2.6)	9 (42.9)	0 (0)
Nausea/vomiting	9 (23.1)	1 (2.6)	4 (19.0)	0 (0)
Stomatitis	12 (30.8)	0 (0)	4 (19.0)	0 (0)
Dysgeusia	11 (28.2)	0 (0)	5 (23.8)	0 (0)
Hypertension	5 (12.8)	1 (2.6)	3 (14.3)	1 (4.8)
Proteinuria	9 (23.1)	1 (2.6)	1 (4.8)	0 (0)

B-E arm, BEV + PTX followed by eribulin; E-B arm, eribulin followed by BEV + PTX; BEV, bevacizumab; PTX, paclitaxel.

survival with eribulin, our results in both the E-B and B-E arms were in line with those reported in the EMBRACE trial and the 301 trials, which were phase 3 trials (1,15). When a regimen of BEV + PTX is administered late, progression-free survival is significantly decreased compared with initial eribulin treatment. The BEV + PTX regimen was the second-line treatment in the RIBBON-2 trial (16), in which the median progression-free survival was 9.1 months. In the present study, progression-free survival in the B-E arm was better than in the RIBBON-2 trial (11.5 months), a phase 3 trial designed to assess second-line bevacizumab-containing therapy, but it was significantly decreased in the E-B arm compared to the RIBBON-2 trial (6.2 months). It is supposed that BEV + PTX was administered after 2 regimens in 57.1% of the E-B arm. Therefore, we performed PSMA to minimize any imbalances in the background factors between the two arms. The PSMA analysis yielded results consistent with those in the overall analysis. Therefore, eribulin treatment is recommended after BEV + PTX treatment. A similar tendency for TFS was seen as a result of OS analysis by PSMA. However, a further follow-up survey is necessary because there were few observation events.

In regards to the mechanism, there is a difference in tumor vessel remodelling and reoxygenation between BEV + PTX and eribulin. Eribulin increases the density of tiny blood vessels and the supply of oxygenated blood to breast cancer tissue (17). Eribulin may improve the state of hypoxia relative to bevacizumab treatment. Furthermore, eribulin stabilizes the microenvironment and may improve the treatment effect. From these results, it is suggested that the administration of eribulin after BEV + PTX is most effective.

In the present study, BEV + PTX treatment and eribulin treatment were generally well tolerated. The incidence of adverse events with BEV + PTX was similar to that in previous clinical trials (2-4,14,16). Eribulin had a manageable profile of adverse events, consistent with those in previous clinical trials; neutropenia, alopecia, leukopenia, and peripheral neuropathy were the most common (1,18-22). The incidence of grade ≥3 neutropenia was 17.9% in the B-E arm, which was higher than that in the E-B arm. Therefore, considering the adverse events of subsequent treatments, we must administer BEV + PTX carefully. It is considered that the prognosis can be effectively improved by reducing adverse events by dose reduction, with-

Table III. Efficacy.

Tumor response	Number of patients (%) B-E arm (n=39)	E-B arm (n=21)	P-value
Eribulin			ns
CR	1 (2.6)	0 (0)	
PR	10 (26.3)	7 (33.3)	
SD	11 (29.0)	6 (28.6)	
PD	12 (31.6)	6 (28.6)	
Not evaluable	1 (2.6)	2 (9.5)	
BEV+PTX			0.0147
CR	2 (5.1)	1 (4.8)	
PR	24 (61.5)	4 (19.1)	
SD	10 (25.6)	9 (42.9)	
PD	3 (7.7)	6 (28.6)	
Not evaluable	0 (0)	1 (4.8)	

B-E arm, BEV + PTX followed by eribulin; E-B Arm, eribulin followed by BEV + PTX; BEV, bevacizumab; PTX, paclitaxel. P-values are obtained by using Pearson's χ^2 test for comparisons between B-E and E-B groups.

Table IV. Characteristics of the patients after performing PSMA.

Characteristics	Number of patients (%) B-E arm (n=19)	E-B arm (n=19)
Treatment line		
1	12 (63.2)	9 (47.4)
2	7 (36.8)	10 (52.6)
Age		
≤50 years	5 (26.3)	6 (31.6)
51-60 years	7 (36.8)	5 (26.3)
≥61 years	7 (36.8)	8 (42.1)
PS		
0	14 (73.7)	13 (68.4)
1	4 (21.1)	4 (21.1)
2	1 (5.3)	2 (10.5)
Triple negative	5 (26.3)	8 (42.1)
Liver metastasis	6 (31.6)	5 (26.3)
Number of metastatic sites		
≤2	13 (68.4)	11 (57.9)
≥3	6 (31.6)	8 (42.1)

B-E arm, BEV + PTX followed by eribulin; E-B arm, eribulin followed by BEV + PTX; BEV, bevacizumab; PTX, paclitaxel.

drawal or maintenance therapies. Indeed, recent data suggest that maintenance therapy has a positive effect on overall survival (23,24).

There are more ER+ in the B-E group. If TFS (and OS) is longer in the ER+ group, then the B-E group would be better for this reason (if ER were a confounding factor). Therefore, we examined whether ER is associated with TFS (and OS) using multivariate Cox regression. We found that ER was not associated with TFS. For reference, TFS group comparisons were performed separately for ER+ and ER-, and it was confirmed that TFS was longer in groups B-E in both subgroups. As we examined the proportional hazards assumption using the two-stage test proposed by Qiu and Sheng (13), the violation of the assumption was not indicated (P =0.337 for OS and 0.766 for TFS) (Figs. S2 and S3; Table SI). Based on the above discussion, we believe that the B-E arm can be recommended regardless of ER status in TFS prolongation.

To our knowledge, this is the first report of the impact of the sequential treatment of HER2-negative metastatic breast cancer with BEV + PTX and eribulin. This study has some limitations. An important limitation is that although it is a multicenter database, the study design is retrospective and observational, and the number of cases is small. Although consistent results were obtained using the PSMA method to reduce selection bias, it is necessary to confirm the findings in a large, prospective study.

In conclusion, despite the retrospective nature of the present analysis and its inherent limitations, the data presented show that when BEV+PTX and eribulin are administered sequentially, the prognosis is better if BEV+PTX is administered first.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KM and TF designed the study concepts and confirm the authenticity of all the raw data. KM, ME, AY, WF, ZN, KO, KK and KM collected the data. SM and AN performed statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted according to the guidelines of The Declaration of Helsinki. However, ethics approval was not applicable because this was a retrospective study that did not include procedures outside of common and correct clinical practice.

Patient consent for publication

Not applicable.

Competing interests

SM received honoraria from Chugai Pharmaceutical Co., Ltd., and Eisai Co., Ltd., and received research funding (institution) from Eisai Co., Ltd., outside the submitted work.

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