The Breast 57 (2021) 18–24

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Effectiveness and healthcare costs of eribulin versus capecitabine among metastatic breast cancer patients in Taiwan

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ARTICLE INFO

Article history:
Received 27 August 2020
Received in revised form
8 February 2021
Accepted 17 February 2021
Available online 23 February 2021

Keywords:
Real-world study
Claim database analysis
Metastatic breast cancer
Eribulin

ABSTRACT

Objective: To compare the real-world effectiveness and costs of eribulin to those of capecitabine in patients with metastatic breast cancer (MBC) pretreated with anthracyclines and taxanes.
Methods: This study extracted data from the Health and Welfare Database in Taiwan to identify MBC patients, and then eribulin and capecitabine users were matched at a 1:1 ratio by age, residential region, Charlson Comorbidity Index score, and molecular subtype of BC cell. The overall survival (OS) and time-to-treatment discontinuation (TTD) curves were plotted using the Kaplan–Meier method. Healthcare utilization and costs between the two groups were compared.
Results: A total of 24,550 MBC patients were identified, and 298 patients were enrolled in each group after matching. The median OS was 11.8 months for eribulin (95%CI: 11.5–13.5 months) and 15.2 months for capecitabine (95%CI: 15.3–17.9 months; HR = 1.7, $p < 0.0001$). The median TTD was 4.0 months for eribulin and 6.6 months for capecitabine (HR = 1.6; $p < 0.0001$). No significant difference was found between the two groups in patients with >4 prior chemotherapy agents (OS: HR 1.1, 95%CI 0.8–1.5; TTD: HR 1.2, 95%CI 0.9–1.7). The total healthcare costs per patient during the treatment period were NT$580,523.8 for eribulin versus NT$497,223.8 for capecitabine ($p < 0.0001$), and total medication costs were NT$438,335.8 and NT$348,438.4 ($p < 0.0001$), respectively.
Conclusion: Although eribulin showed an attenuated effect in the real-world setting in Taiwan, it may serve as an alternative for capecitabine in a heavy pretreated population. The total healthcare and medication costs were found to be higher with eribulin treatment.

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer, and the second most common cause of cancer-related death [1]. Despite considerable progress and advances over the years, metastatic breast cancer (MBC) remains treatable but incurable, with a 5-year survival rate greater than 25% [2,3]. There is no standard of care for patients pretreated with and resistant to anthracyclines and taxanes. Eribulin, capecitabine, and vinorelbine are the alternatives after patients become refractory to anthracyclines and taxanes. Additional options include gemcitabine, platinum agents, and liposomal anthracyclines [4,5].

Eribulin (Eribulin mesylate, Halaven®, E7389), a nontaxane microtubule dynamics inhibitor of antineoplastic drugs [6], has been proven to be an effective new chemotherapeutic agent based on the pivotal phase III randomized study EMBRACE [7]. Although another phase III trial, Study 301, failed to demonstrate the superiority of eribulin over capecitabine in terms of overall survival (OS) or progression-free survival (PFS) [8], a post hoc analysis reported a significant OS benefit for eribulin among MBC patients with human epidermal growth factor receptor 2 (HER2) negative tumors [9]. Since the U.S. Food and Drug Administration's (FDA) approval of eribulin in November 2010, real-world evidence of eribulin has been investigated in various countries and among different ethnicities [10–20]. However, there has been a paucity of real-world studies that included comparative agents in their study design. In addition to effectiveness analysis, cost study is also crucial, particularly for chemotherapeutic agents as they can lead to surging drug costs and toxicity, factors that increase overall costs of treatment

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https://doi.org/10.1016/j.breast.2021.02.011

and hinder the use of innovative medication [21]. At present, there is little published data regarding the costs associated with eribulin in treating MBC patients; an exception is a cost analysis in France that assessed the one-year health care costs of a monocentric MBC cohort [14]. The total per-patient (PP) costs were estimated at €18,694, and it was found that eribulin and its associated administration costs contributed to 79% of PP costs.

In December 2014, Taiwan FDA approved eribulin for the treatment of refractory MBC patients who have previously received an anthracycline and a taxane. A real-world study of eribulin in Taiwan appeared to show a 1-year survival rate similar to that in the EMBRACE trial [17]. However, it was not conducted nationwide, no comparative agent was included, and OS was not examined. Also, there has been no study assessing the cost of eribulin treatment in Taiwan. Since capecitabine has been commonly used as a salvage or maintenance therapy for MBC after anthracyclines or taxanes in Taiwan, and it has been used as a comparison to eribulin in previous studies, this study aimed to compare the clinical outcomes and healthcare costs of eribulin to those of capecitabine in MBC patients and to provide more insight into real-world clinical practice in Taiwan.

2. Methods

2.1. Data source

Data were extracted from the Health and Welfare Data (HWD) Science Center, Ministry of Health and Welfare, a large data repository site that preserves, manages, and analyzes health data. This study examined health data in the National Health Insurance Research Database (NHIRD), the National Cancer Registry (NCRD), and the Cause of Death Registry Database, which were all included in the HWD. The databases can be interlinked with each other using keys and encrypted personal identification numbers. The NHIRD comprises the claims data of national health insurance beneficiaries, which encompass 99.6% of the 23 million residents in Taiwan. Patient-level information such as demographic characteristics, diagnoses, medical assessments, procedures and treatments, and costs of treatments were recorded in the databases. The accuracy of NHIRD data input is ensured by a peer-review committee with a disciplinary system. The NCRD accounts for the registration of 90% of all cancers in Taiwan and preserves clinical data associated with all newly diagnosed malignant neoplasms, including date of initial diagnosis, primary cancer site, American Joint Committee on Cancer (AJCC) staging, and clinical and pathological tumor, node, metastasis staging. Data is recorded and standardized into a report by trained cancer registrars and passes through a computerized logic check to conserve fidelity and quality. The Cause of Death Registry Database preserves all causes of death (encoded by ICD-10) in Taiwan by collecting death certificates transferred from the household registration system. Patient survival and the date of expiration in the study population were confirmed by examining this database. These three national health insurance-related databases collect patients' information until they die. As such, no patients were lost to follow up.

2.2. Study design and patients

This retrospective observational real-world study was approved by the Taipei Medical University-Joint Institutional Review Board (approval number: N201709052). Patients were enrolled from January 1, 2015 to December 31, 2016 (i.e., enrollment period), then followed until any cause of death occurred or December 31, 2017, the date of administrative censoring (i.e., follow-up period). The inclusion criteria were females aged 20 years or older, diagnosed with MBC, and who had received at least one anthracycline and one taxane. During the screening process, MBC patients were identified in both the NHIRD and the NCRD. In the NHIRD, MBC patients were selected by a diagnosis of BC (ICD-9-CM: code 174. XX or ICD-10-CM: C.50. xxx) in either an inpatient or outpatient claim along with a prescription record of chemotherapy such as vinorelbine, capecitabine, gemcitabine, and eribulin. In the NCRD, however, newly diagnosed patients were identified with a histologically or cytologically confirmed diagnosis of BC (ICD-*O*-3: C50. xxx) at AJCC stage IV. The MBC patients identified in the two databases between 2015 and 2016 were combined into the preliminary study cohort for further selection.

Eribulin and capecitabine users were identified based on the chemotherapeutic agent that the patient used after the treatment failure of both anthracyclines and taxanes. The index date was defined as the first date with a prescription of eribulin or capecitabine during the enrollment period. Data were traced back to January 1, 2010 and patients who were not taking eribulin or capecitabine as a single agent and those with prior use of the comparative chemotherapy agent were excluded.

2.3. Outcome measures

The primary outcome of this study is OS, defined as the time from the index date to any cause of death or last follow-up. The secondary outcomes were: (1) time to treatment discontinuation (TTD); (2) rate of use of granulocyte-colony stimulating factor (G-CSF); and (3) healthcare utilization and costs. TTD was defined as the time from the index date until the date of treatment discontinuation for any reason, including progressive disease, treatment toxicity, and death. TTD was also referred to as the treatment period in this study. The rate of G-CSF use during the treatment period was measured to elicit the rate of severe neutropenia. Healthcare utilization under assessment included the number of outpatient oncology visits, inpatient admissions, and emergency room (ER) visits during the treatment period, while the calculation of healthcare costs included costs incurred for inpatient services, outpatient services, ER visits, and medications during the treatment period.

2.4. Statistical analysis and matching

Patients' characteristics were summarized using descriptive statistics (means or median and standard deviations [SD]) and compared between groups using the Student's t-test for continuous data while categorical variables were summarized by frequencies and compared between groups using the Chi-square test. The OS and TTD curves were plotted using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Healthcare costs and utilization were summarized using descriptive statistics and measured per-patient (PP) and per-patient-per-month (PPPM) during the treatment period. Healthcare utilization and various types of costs between the groups were compared using the Mann-Whitney *U* test. In the NHIRD, medical expenditures data were coded in point values due to the implementation of the global budget system. For ease of calculation, the points were converted to monetary values by assigning NT $1 for each point.

To control for confounding factors and minimize differences between eribulin and capecitabine users, patients in the two groups were matched at a 1:1 ratio based on age within ± one year, Charlson Comorbidity Index (CCI) score [22] within ± one point, residential area, and molecular subtype of BC cell. The matched patients (i.e., the eribulin group and the capecitabine group) were included in the subsequent analysis of this study.

Subgroup analysis was performed to investigate the outcomes of interest between eribulin and capecitabine while controlling for the line of chemotherapy treatment. First, the number of previous chemotherapy agents was calculated for identified eribulin and capecitabine users, and the two groups were matched at a 1:1 ratio based on age within ± one year, CCI score within ± one point, residential area, molecular subtype of BC cell, and early or late therapeutic line depending on whether the patients had received ≤4 previous chemotherapies or more than four (i.e., fifth- or earlier-line vs. sixth- or later-line). The variables used for matching were selected according to the EMBRACE trial and previous real-world studies [7,14,17,23]. The matching of groups was done using a macro that performs a greedy match algorithm with SAS® software, as defined elsewhere [24].

3. Results

3.1. Patients' characteristics

From Jan 1, 2015 to Dec 31, 2016, 24,550 MBC patients were identified in the NHIRD and the NCRD. Among them, 567 patients used eribulin after treatment failure with anthracyclines and taxanes, and 1674 patients used capecitabine. After excluding patients with prior or concurrent use of the comparative chemotherapy agent and 1:1 matching, 298 patients were assigned to the eribulin and capecitabine groups, respectively.

Patients' baseline characteristics were comparable between the two treatment groups (Table 1). Most of the patients were ages 51–60 years, with a mean of 54.3 years in both groups. Half of the patients were from the northern district (51.7%), approximately 85% of the patients had a CCI score of eight or greater, more than half of the patients were with hormone receptor expression (87.6%), and most of the patients had received at least four chemotherapy (CT) agents.

3.2. Effectiveness and the use of G-CSF

Until the date of administrative censoring (i.e. 31st December 2017), there were 214 (71.8%) deaths in the eribulin group and 157 (52.7%) deaths in the capecitabine group. The 1-year survival rate was 49.0% (deaths = 152) in the eribulin group and 65.1% (deaths = 104) in the capecitabine group. Median OS was 11.8 months (95%CI, 11.5–13.5 months) for eribulin compared to 15.2 months (95%CI, 15.3–17.9 months) for capecitabine, resulting in an HR of 1.7 (95%CI, 1.4 to 2.1; $p < 0.0001$). The Kaplan-Meier graph of OS is presented in Fig. 1A.

Median TTD was 4.0 months (95%CI 5.5–6.9) in the eribulin group and 6.6 months (95%CI 9.0–11.1) in the capecitabine group (HR 1.6; 95%CI 1.3–1.9; $p < 0.0001$). Until the date of administrative censoring, there were 280 and 261 (94.0% and 87.6%, respectively) treatment discontinuations in the eribulin and capecitabine groups, respectively, with a median TTD of 3.8 months and 4.7 months, respectively. The Kaplan-Meier graph of TTD is plotted in Fig. 1B.

Subgroup analysis (Fig. 2) demonstrated that when capecitabine and eribulin were initiated in patients with >4 prior chemotherapy agents (i.e., the study treatment was at least a sixth- or later-line treatment), there was no significant difference between the two groups' median OS or TTD (OS: HR 1.1, 95%CI 0.8–1.5; TTD: HR 1.2, 95%CI 0.9–1.7). However, capecitabine performed better than eribulin when each was initiated as a fifth-line or earlier chemotherapy treatment (OS: HR 1.7, 95%CI 1.2–2.4; TTD: HR 1.4, 95%CI 1.1–1.9).

Among patients receiving eribulin, 135 (45.3%) received G-CSF during the treatment period. In comparison, 41 (13.8%) patients taking capecitabine received with the same. A univariate logistic regression analysis suggested the odds ratio to be 5.2 (95%CI 3.5–7.8, $p < 0.0001$).

Table 1
Baseline characteristics of study patients after matching.

Characteristic	Eribulin (n = 298)		Capecitabine (n = 298)	
	n	%	N	%
Age				
20–30	0	0.0	0	0.0
31–40	12	4.0	11	3.7
41–50	82	27.5	85	28.5
51–60	129	43.3	135	45.3
61–70	71	23.8	64	21.5
71–80	4	1.3	3	1.0
>=81	0	0.0	0	0.0
Mean (SD) [Median], years	54.3 (7.9) [55]		54.3 (7.9) [55]	
P value			0.97	
Geographical region				
North	154	51.7	154	51.7
South	93	31.2	93	31.2
Central	51	17.1	51	17.1
East	0	0	0	0
P value				1
CCI score				
2	22	7.4	28	9.4
3	20	6.7	15	5.0
4	4	1.3	3	1.0
8	124	41.6	129	43.3
9	80	26.8	79	26.5
10	33	11.1	37	12.4
>=11	15	5.0	7	2.3
Mean (SD) [Median], points	7.8 (2.4) [8]		7.7 (2.4) [8]	
P value			0.68	
Cancer cell type (phenotype)				
ER/PR positive	261	87.6	261	87.6
HER2 positive	90	30.2	90	30.2
ER/PR and HER2 positive	74	24.8	74	24.8
ER/PR and HER2 negative	21	7.0	21	7.0
P value				1
Number of previous CT agents				
2	3	1.0	5	1.7
3	54	18.1	102	34.2
4	67	22.5	87	29.2
5	78	26.2	55	18.5
6	52	17.4	25	8.4
7	36	12.1	20	6.7
>=8	8	2.7	4	1.3
Mean (SD) [Median]	4.9 (1.4) [5]		4.2 (1.3) [4]	
P value				<0.0001
History of chemotherapy agents				
Doxorubicin/liposomal doxorubicin	135	45.3	110	36.9
Epirubicin	189	63.4	204	68.5
Docetaxel	243	81.5	249	83.6
Paclitaxel	190	63.8	129	43.3
Cyclophosphamide	258	86.6	279	93.6
Cisplatin	99	33.2	71	23.8
Carboplatin	16	5.4	5	1.7
Gemcitabine	146	49.0	83	27.9
Vinorelbine	164	55.0	115	38.6
Methotrexate	15	5.0	17	5.7
P value				0.29

CCI Charlson Comorbidity Index, ER Estrogen receptor, HER2 Human epidermal receptor 2, PR Progesterone receptor, SD Standard deviation.

3.3. Healthcare utilization and costs

Healthcare utilization and costs PP as well as PPPM during the treatment period were calculated and are summarized in Tables 2

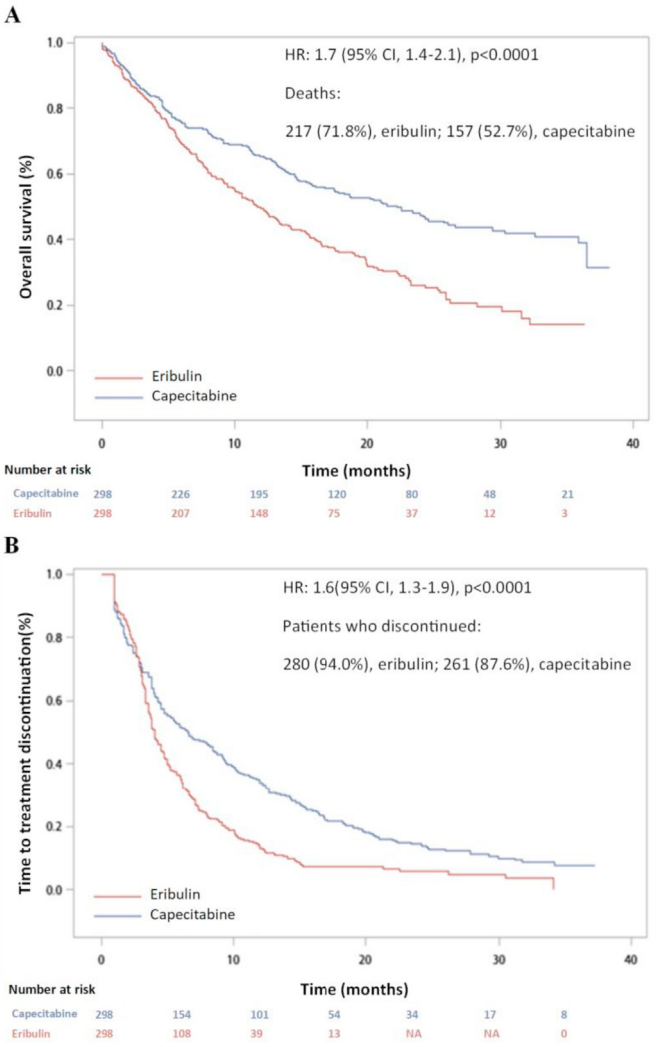

Fig. 1. Kaplan-Meier graph of (A) OS and (B) TTD.

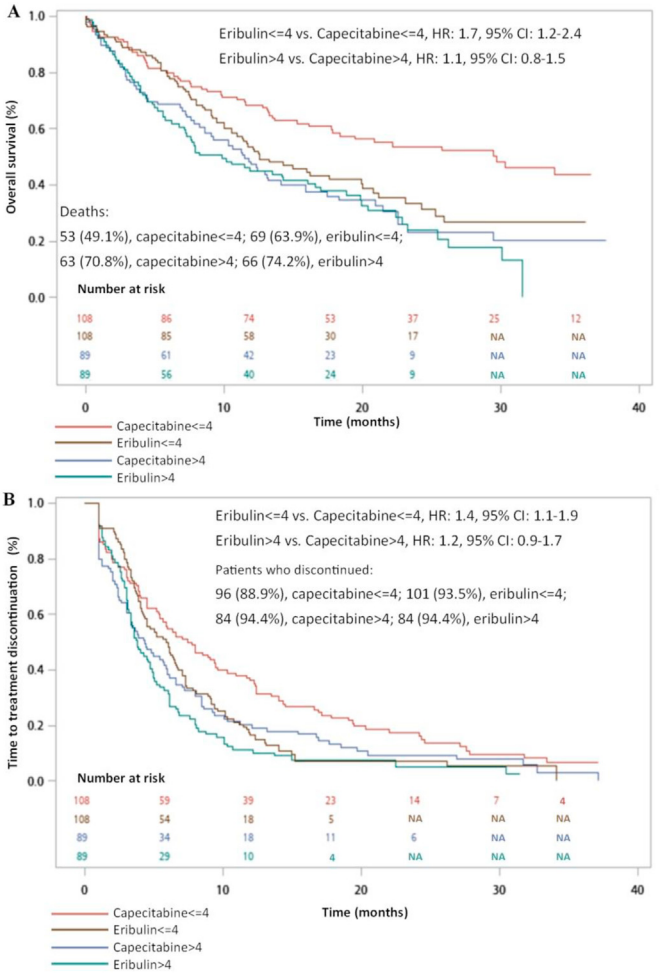

Fig. 2. Subgroup analysis of (A) OS and (B) TTD by the number of previous chemotherapy agents.

and 3, respectively. As shown in Table 2, although patients receiving eribulin treatment tended to visit an outpatient oncologist less frequently ($p = 0.049$), the mean PP medical cost of outpatient oncology visits was higher than that for patients receiving capecitabine (NT$405,654.1 vs. NT$371,177.7; $p = 0.003$). As for the emergency room and hospitalization costs, no difference was found between the two groups. The mean total PP medical costs for eribulin and capecitabine were NT$ 580,523.8 and NT$ 497,223.8, respectively ($p < 0.0001$). Outpatient costs contributed to approximately 70% of the total medical costs of both eribulin and capecitabine while drug costs contributed to a greater proportion of total medical costs for eribulin than for capecitabine (60.4% vs. 15.3%).

As presented in Table 3, the mean PPPM medical cost of oncology visits for eribulin was NT$88,442.7, which doubled that of capecitabine (NT$42,246.9). Similar to PP costs, the PPPM emergency room costs were comparable between the two groups, albeit eribulin patients' utilization was higher. The mean PPPM total medical cost of eribulin was NT$ 148,984.3 (95%CI, NT$134,563.9-NT$163,404.8), with around 60% of it resulting from eribulin's drug cost and the cost of outpatient oncology visits. In contrast, the mean PPPM total medical cost of capecitabine (NT$ 103,521.6; 95% CI, NT$ 65,821.9-NT$141,221.4) was mainly driven by hospitalizations (58.3%).

Overall, compared to capecitabine, eribulin had both higher total medical costs and higher total medication costs PP and PPPM.

4. Discussion

This is the first real-world study investigating the effectiveness and cost of eribulin in Taiwan. Also, to the best of our knowledge, it is the first observational study that included capecitabine as a comparator to eribulin.

Patient characteristics in this study moderately mirror those in previous studies. The average age of our study sample was 54 years old, which is the same as that in the EMBRACE trial and Study 301, and the proportion of study patients with estrogen receptor positive or HER2 positive receptor was also comparable [7,8]. However, compared to those two clinical trials, patients in the present study were receiving MBC treatment for a worse baseline health condition, as indicated by higher CCI scores and a greater number of previous lines of chemotherapy. These characteristics were instead similar to those in the eribulin real-world study by Hurtaud et al. where study patients were closer to routine clinical practice, with 19.5% of patients having received more than six previous chemotherapy regimens [14].

Compared to Study 301, the only clinical trial to compare eribulin and capecitabine, a shorter OS of eribulin was observed in the present study (15.9 months vs. 11.8 months). The discrepancy may

Table 2
Healthcare utilization and costs per-patient (eribulin vs. capecitabine).

	Eribulin				Capecitabine				p value
	N	Median	Mean	95%CI	N	Median	Mean	95%CI	
Healthcare utilization									
Outpatient oncology visits (n)	278	17.0	28.4	24.8–32.0	281	23.0	38.8	33.6–43.9	0.049
Emergency room visits (n)	85	1.0	2.0	1.6–2.4	73	1.0	2.3	1.8–2.8	0.68
Hospitalizations (n)	160	2.0	4.3	3.3–5.3	157	2.0	3.6	2.8–4.4	0.40
Days of hospitalization (n)	160	13.0	32.8	23.0–42.6	157	14.0	36.8	10.6–63.0	0.64
Medication cost									
Cost of eribulin/capecitabine	298	254,300.0	350,458.6	312,554.0–388,363.2	298	46,144.0	76,247.7	66,776.6–85,718.8	<0.0001
Cost of G-CSF	298	0.0	16,899.6	12,897.0–20,902.3	298	0.0	2313.8	1217.3–3410.3	<0.0001
Total medication cost	298	305,335.0	438,335.8	388,488.1–488,183.5	298	154,731.0	348,438.4	294,184.5–402,692.3	<0.0001
Medical cost									
Cost of outpatient oncology visits	298	262,319.0	405,654.1	353,578.1–457,730.1	298	181,910.5	371,177.7	313,071.4–429,284.0	0.003
Cost of emergency room visits	298	0.0	2880.2	2055.9–3704.5	298	0.0	2865.3	1490.8–4239.9	0.18
Cost of hospitalizations	298	25,524.5	171,989.5	125,334.7–218,644.3	298	11,733.5	123,180.8	95,876.9–150,484.7	0.45
Total medical cost	298	367,653.0	580,523.8	514,217.1–646,830.4	298	282,622.5	497,223.8	431,400.1–563,047.6	<0.0001

G-CSF granulocyte-colony stimulating factor.

Table 3
Healthcare utilization and costs per-patient-per-month (eribulin vs. capecitabine).

	Eribulin				Capecitabine				p value
	N	Median	Mean	95%CI	N	Median	Mean	95%CI	
Healthcare utilization									
Outpatient oncology visits (n)	278	5.1	5.6	5.2–5.9	281	4.0	4.7	4.3–5.1	<0.0001
Emergency room visits (n)	85	0.4	0.7	0.5–0.9	73	0.2	0.7	0.3–1.0	0.002
Hospitalizations (n)	160	0.9	1.5	1.1–2.0	157	0.4	1.2	0.8–1.6	0.0006
Days of hospitalization (n)	160	5.2	11.6	9.1–14.0	157	2.1	14.8	7.5–22.1	0.01
Medication cost									
Cost of eribulin/capecitabine	298	75,493.8	88,414.2	80,803.2–96,025.3	298	9471.2	12,137.8	10,273.6–14,002.1	<0.0001
Cost of G-CSF	298	0.0	5293.9	3515.5–7072.3	298	0.0	974.0	100.1–1848.0	<0.0001
Total medication cost	298	89,062.4	107,366.5	98,030.6–116,702.4	298	34,673.4	47,438.6	41,168.5–53,708.7	<0.0001
Medical cost									
Cost of outpatient oncology visits	298	87,487.4	88,442.7	81,706.4–95,179.0	298	35,212.1	42,246.9	38,072.7–46,421.0	<0.0001
Cost of emergency room visits	298	0.0	967.1	593.8–1340.5	298	0.0	913.2	232.0–1594.5	0.09
Cost of hospitalizations	298	3425.2	59,574.5	45,350.4–73,798.7	298	748.5	60,361.6	23,910.6–96,812.5	0.10
Total medical cost	298	114,335.0	148,984.3	134,563.9–163,404.8	298	51,706.4	103,521.6	65,821.9–141,221.4	<0.0001

G-CSF granulocyte-colony stimulating factor.

be explained by the differences between clinical trials and real-world studies and also by the fact that 99.3% of patients in Study 301 had received no more than two previous CT regimens for advanced disease. With regards to HR status, among the HR- population in the Study 301, although the OS and PFS of the Eribulin group were longer than those of the capecitabine group, the difference did not reach statistical significance ($p = 0.05$ and 0.82, respectively) [25]. Moreover, in two other clinical trials (eribulin vs. physician choice in one; eribulin vs. vinorelbine in the other), the efficacy of eribulin in patients with positive hormone receptor is similar to that in patients with negative hormone receptor status [26,27]. In a further analysis, we explored the potential effect of HR and HER2 status using multiple regression analysis, but no statistical significance was observed. Although there is no real-world study comparing eribulin and capecitabine to serve as a reference, the median OS of eribulin observed in this study is slightly longer than those of other real-world studies involving eribulin in Denmark, Italy, and Japan [11,12,15]. Also, the 1-year survival of patients on eribulin observed in the present study mirrors the result published by Hurtaud et al. in France (42%) [14]. Therefore, even though the effectiveness of eribulin was not as good as that of capecitabine, the performance of eribulin in this study is comparable to and even better than that reported in other real-world studies. Moreover, in the subgroup analysis, we discovered that eribulin exhibited the same benefits as capecitabine when both were administered in chemotherapy lines greater than five. Our findings provided a better understanding of the effectiveness of eribulin since few published studies have inspected the impact of the line of treatment.

The rate of G-CSF use in this study indicates that the rate of severe neutropenia in eribulin users observed in Taiwan was higher than those in Europe and the U.S [7,8,10,12]. It has been suggested that severe neutropenia could be more pronounced in east Asian populations, which is particularly reflected in the use of eribulin as a late-line treatment [28]. Indeed, an incidence rate of 57.4% for grade 4 neutropenia was observed in eribulin users in South Korea, and up to two-thirds of eribulin users had neutropenia in Japan [16,18].

The cost items included in this analysis were comprehensive and consisted of all healthcare products and services reimbursed by the NHI. Although the estimated treatment costs cannot be compared with other studies directly due to different health care policies and systems among countries and variations in study methods, previous cost and cost-effectiveness studies conducted in the US, the UK, and the Southeast Netherlands also concluded that eribulin was expensive and not cost-effective when compared to other chemotherapies [23,29,30].

At an advanced stage of MBC, whether to continue with chemotherapy is a tough decision, as the benefits are debatable [31]. Since November 2010 when eribulin received approval from the US FDA, studies have been conducted to examine its real-world effectiveness and costs. However, no study has compared the

benefit of eribulin with another chemotherapy agent. Moreover, although capecitabine is effective and commonly prescribed, its adverse events of hand-foot syndrome occurred in 50–60% of its users [32], and some of the cases were extreme, leaving physicians with no choice but to discontinue the treatment. In this study, eribulin was found to show comparable benefits to capecitabine in patients who had received more than four chemotherapy agents; therefore, eribulin may serve as an alternative for patients who have been heavily pretreated and for whom capecitabine is contraindicated. The costs analysis in this study discovered that the high treatment cost of eribulin was mainly driven by the high drug acquisition cost. Although the price of eribulin has dropped 9.7% since being approved by the Taiwan FDA, additional price negotiation is warranted. Moreover, as eribulin was found to be less effective and costlier than its comparator, further comprehensive health technology assessments of eribulin should be performed using real-world data. To further minimize selection bias and the imbalance in the line of chemotherapy between eribulin and capecitabine, future research aiming to evaluate eribulin as used in various lines of chemotherapy is warranted. In addition, the best sequential use of eribulin after the failure of anthracyclines and taxanes also needs to be examined.

The major limitation to this study resulted from the use of the HWD, which makes the study subject to potential data coding errors and missing data. Also, we were unable to know whether the assigned treatment was actually administered. Nevertheless, considering the high drug cost and the administration setting (i.e., in hospitals), the chance of not being administered is quite low. In addition, the absence of information about lab tests and biomedical images in the study databases prevented us from evaluating PFS. Although TTD was designed as a surrogate for PFS to demonstrate the effectiveness of comparators, care should be taken when comparing our TTD to PFS reported in other studies. Similarly, a G-CSF prescription was used as a proxy for the occurrence of severe neutropenia, which may have overestimated the rate of adverse events since prophylactic treatment may have also been included. Also, only reimbursed medications were recorded in the HWD so patients' treatment history may not be complete, particularly for late-line therapies. Moreover, although great efforts were made to alleviate potential confounding, the effects of selection bias and unequal disease burden/spread may still have existed. Finally, the follow-up period was limited by data availability (the last date of available data in the HWD was Dec 31, 2017).

5. Conclusions

This population-based real-world study provides a better understanding of the effectiveness of eribulin in refractory MBC patients who had failed to respond to anthracyclines and taxanes in Taiwan. Despite the potential biases, our study results suggest that eribulin has shorter OS and TTD when compared to capecitabine; however, that difference no longer exists when the drugs are both initiated as sixth- or later-lines of chemotherapy. Therefore, eribulin may serve as an alternative for those heavily pretreated patients and those for whom capecitabine is contraindicated. In addition, the rate of G-CSF use and the total medical and medication costs were found to be higher with eribulin treatment.

Funding

This study was funded by a research grant provided by Taipei Medical University (TMU104-AE1-B16).

Ethical approval

The study was approved by Taipei Medical University- Joint Institutional Review Board (Approval number: N201709052).

Declaration of competing interest

All author declare that they have no conflict of interest.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA: Canc J Clin 2019;69(1):7–34. 2019.
[2] Dawood S, Broglio K, Ensor J, Hortobagyi G, Giordano SH. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010;21(11):2169–74.
[3] Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast 2017;31:46–50.
[4] Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, Harbeck N, Aguilar Lopez B, Barrios CH, Bergh J, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4)††These guidelines were developed by the European school of oncology (ESO) and the European society for medical oncology (ESMO). Ann Oncol 2018;29(8):1634–57.
[5] Giordano SH, Elias AD, Gradishar WJ. NCCN guidelines updates: breast cancer. J Natl Compr Canc Netw : J Natl Compr Canc Netw 2018;16(5s):605–10.
[6] Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Canc Therapeut 2005;4(7):1086–95.
[7] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Dieras V, Delozier T, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377(9769):914–23.
[8] Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, Olivo MS, He Y, Dutcus CE, Cortes J. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol : Off J Am Soc Clin Oncol. 2015;33(6):594–601.
[9] Pivot X, Im SA, Guo M, Marme F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting from a phase 3, open-label, randomized study of eribulin mesilate versus capecitabine. Breast Canc 2018;25(3):370–4.
[10] Aftimos P, Polastro L, Ameye L, Jungels C, Vakili J, Paesmans M, van den Eerenbeemt J, Buttice A, Gombos A, de Valeriola D, et al. Results of the Belgian expanded access program of eribulin in the treatment of metastatic breast cancer closely mirror those of the pivotal phase III trial. Eur J Canc (Oxford, England : 1990 2016;60:117–24.
[11] Barni S, Livraghi L, Morritti M, Vici P, Michelotti A, Cinieri S, Fontanella C, Porcu L, Del Mastro L, Puglisi F. Eribulin in the treatment of advanced breast cancer: real-world scenario from 39 Italian centers - ESEMPiO study. Future Oncol 2019;15(1):33–44.
[12] Brems-Eskildsen AS, Kristoffersen KB, Linnet S, Lorincz T, Langkjer ST. Efficacy and toxicity of eribulin treatment in metastatic breast cancer patients. Acta Oncol 2019;58(1):119–21.
[13] Jacot W, Heudel PE, Fraisse J, Gourgou S, Guiu S, Dalenc F, Pistilli B, Campone M, Levy C, Debled M, et al. Real-life activity of eribulin mesylate among metastatic breast cancer patients in the multicenter national observational ESME program. Int J Canc 2019;145(12):3359–69.
[14] Hurtaud A, Donnadieu A, Escalup L, Cottu PH, Baffert S. Costs associated with Eribulin treatment for patients with metastatic breast cancer in a comprehensive cancer center in France. Breast 2016;30:73–9.
[15] Iizumi S, Shimoi T, Tsushita N, Bun S, Shimomura A, Noguchi E, Kodaira M, Yunokawa M, Yonemori K, Shimizu C, et al. Efficacy and safety of eribulin in patients with locally advanced or metastatic breast cancer not meeting trial eligibility criteria: a retrospective study. BMC Canc 2017;17(1):819.
[16] Park YH, Kim TY, Im YH, Lee KS, Park IH, Sohn J, Lee SH, Im SA, Kim JH, Kim SH, et al. Feasibility and efficacy of eribulin mesilate in Korean patients with metastatic breast cancer: Korean multi-center phase IV clinical study results. Canc Res Treat: Off J Kor Canc Assoc 2017;49(2):423–9.
[17] Rau KM, Ou-Yang F, Chao TC, Kuo YL, Cheng TF, Chao TY, Chen DR, Tzeng YD, Wang BW, Liu CY, et al. Effect of eribulin on patients with metastatic breast cancer: multicenter retrospective observational study in Taiwan. Breast Canc Res Treat 2018;170(3):583–91.
[18] Sakata Y, Matsuoka T, Ohashi S, Koga T, Toyoda T, Ishii M. Use of a healthcare claims database for post-marketing safety assessments of eribulin in Japan: a comparative assessment with a prospective post-marketing surveillance study. Drugs - Real World Outc 2019;6(1):27–35.
[19] Tanaka N, Ogura K, Hattori A, Inoue H, Yukawa H, Sakaguchi S, Matsuoka A, Kodera A, Naritaka Y, Hirano A. [Treatment out come of eribulin in patients with advanced or metastatic breast cancer who resistant to anthracycline and taxane]. Gan to kagaku ryoho Canc Chemother 2017;44(12):1200–2.

[20] Tanaka T, Ueno M, Nakashima Y, Chinen S, Sato E, Masaki M, Mogi A, Sasaki H, Tamura K, Takamatsu Y. Retrospective analysis of the efficacy and safety of eribulin therapy for metastatic breast cancer in daily practice. Thorac Canc 2017;8(5):523–9.
[21] Niraula S, Amir E, Vera-Badillo F, Seruga B, Ocana A, Tannock IF. Risk of incremental toxicities and associated costs of new anticancer drugs: a meta-analysis. J Clin Oncol : Off J Am Soc Clin Oncol. 2014;32(32):3634–42.
[22] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43(11):1130–9.
[23] Lopes G, Gluck S, Avancha K, Montero AJ. A cost effectiveness study of eribulin versus standard single-agent cytotoxic chemotherapy for women with previously treated metastatic breast cancer. Breast Canc Res Treat 2013;137(1):187–93.
[24] The PSMATCH Procedure [https://documentation.sas.com/?docsetId=statug&docsetTarget=statug_psmatch_examples04.htm&docsetVersion=14.3&locale=en].
[25] Twelves C, Awada A, Cortes J, Yelle L, Velikova G, Olivo MS, Song J, Dutcus CE, Kaufman PA. Subgroup Analyses from a phase 3, open-label, randomized study of eribulin mesylate versus capecitabine in pretreated patients with advanced or metastatic breast cancer. Breast Canc Basic Clin Res 2016;10:77–84.
[26] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Diéras V, Delozier T, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377(9769):914–23.
[27] Yuan P, Hu X, Sun T, Li W, Zhang Q, Cui S, Cheng Y, Ouyang Q, Wang X, Chen Z, et al. Eribulin mesilate versus vinorelbine in women with locally recurrent or metastatic breast cancer: a randomised clinical trial. Eur J Canc (Oxford, England : 1990 2019;112:57–65.
[28] Kok VC. Eribulin in the management of advanced breast cancer: implications of current research findings. Breast Canc Basic Clin Res 2015;9:109–15.
[29] Greenhalgh J, Bagust A, Boland A, Oyee J, Trevor N, Beale S, Dundar Y, Hockenhull J, Proudlove C, O'Reilly S. Eribulin for the treatment of advanced or metastatic breast cancer: a NICE single technology appraisal. Pharmacoeconomics 2015;33(2):137–48.
[30] Pouwels X, Ramaekers BLT, Geurts SME, Erdkamp F, Vriens B, Aaldering KNA, van de Wouw AJ, Dercksen MW, Smilde TJ, Peters N, et al. An economic evaluation of eribulin for advanced breast cancer treatment based on the Southeast Netherlands advanced breast cancer registry. Acta Oncol 2020:1–8.
[31] Bonotto M, Gerratana L, Iacono D, Minisini AM, Rihawi K, Fasola G, Puglisi F. Treatment of metastatic breast cancer in a real-world scenario: is progression-free survival with first line predictive of benefit from second and later lines? Oncol 2015;20(7):719–24.
[32] Degen A, Alter M, Schenck F, Satzger I, Völker B, Kapp A, Gutzmer R. The hand-foot-syndrome associated with medical tumor therapy – classification and management. JDDG J der Deutschen Dermatol Gesellschaft 2010;8(9):652–61.