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Eribulin in Heavily Pretreated Metastatic Breast Cancer Patients in the Real World: A Retrospective Study

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Eribulin · Metastatic breast cancer · Real-world practice · Progression-free survival · Overall survival · Safety

Abstract
Objectives: The aim of this study was to investigate efficacy and safety of eribulin in heavily pretreated patients with advanced breast cancer (BC) in a real-life setting. ***Methods:*** This retrospective monocentric study included patients with HER-2-negative metastatic BC, pretreated with anthracyclines and taxanes, who were referred to the Oncology Department of Spedali Civili of Brescia from May 2012 to April 2017. Patients received the same dose of eribulin as that used in the EMBRACE trial: 1.4 mg/m^2 on days 1 and 8 every 21 days. ***Results:*** In a total of 53 patients, 32% obtained a partial response, 11% a stable disease, and 43% a clinical benefit (CB). After a median follow-up of 36 months, median progression-free survival (PFS) was 4.7 months and median overall survival (OS) 13.53 months. Median PFS was significantly longer in patients who reported a CB compared to those with no CB, while survival outcomes (PFS and OS) were better in patients who received >6 cycles of eribulin. Eribulin showed a good tolerability profile with acceptable toxicities, similar to those reported in EMBRACE. ***Conclusions:*** Our experience in a real-world setting confirms the activity, efficacy, and good tolerability profile of eribulin in heavily pretreated BC patients.

Introduction

In Italy, breast cancer (BC) represents 29% of all female cancers; it is the leading cause of neoplastic death in women, and long-term survival of patients with advanced BC (ABC) has only minimally improved despite the availability of several active agents [1–3].

Anthracyclines and/or taxanes are the most commonly used drugs in first-line metastatic settings, in patients with human epidermal growth factor 2 (HER2)-negative BCs. Other drugs such as vinorelbine, gemcitabine, nab-paclitaxel, capecitabine, and liposomal anthracyclines are used in this setting; however, no standard of care exists [4–8]. Eribulin mesylate is a structurally simplified synthetic analogue of halichondrin B (a natural product isolated from the marine sponge *Halichondria okadai*), which inhibits the growth phase of microtubule dynamics

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and sequesters tubulin into nonproductive aggregates. This results in the inhibition of microtubule polymerization, without affecting depolymerization, and inducing an irreversible mitotic block at G2-M phases and consequent apoptosis [9–11]. Three phase II trials evaluated the efficacy and safety of eribulin in ABC patients, showing encouraging results in terms of activity and tolerability [12–14]. A randomized phase III trial (EMBRACE) demonstrated overall survival (OS) advantage of eribulin compared to treatment of physician's choice in patients with heavily pretreated BC, with manageable toxicity [15]. The results observed in the pivotal EMBRACE study led to the regulatory approval of eribulin as treatment in metastatic BC patients who had progressed after at least 2 chemotherapy lines, including anthracyclines and taxanes in either an adjuvant or metastatic setting.

This drug is now being widely employed outside of clinical trials in Italy, including our center, as third or further line of treatment. On this basis, we conducted a real-life retrospective study investigating the efficacy and safety of eribulin in heavily pretreated ABC patients treated at our center.

Patients and Methods

This monocentric study was conducted at the Oncology Department of Spedali Civili of Brescia from May 2012 to April 2017.

Our analysis included metastatic BC patients, with a HER-2-negative status, pretreated with anthracyclines and taxanes, and with 2 or more previous chemotherapy lines for advanced disease; patients with HER2 overexpression or amplification were excluded. Inclusion criteria also comprised Eastern Cooperative Oncology Group (ECOG) grade 2 or less, a life expectancy of more than 12 weeks, and adequate organ and hematological functions.

Treatment schedule was the same as that used in the registered trial, namely eribulin mesilate 1.4 mg/m^2 administered intravenously during 2–5 min on days 1 and 8 of a 21-day cycle. Treatment continued until disease progression, unacceptable toxicity, and patient's or physician's request to discontinue.

Adverse events (AE) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4), and treatment efficacy was evaluated by conventional RECIST criteria every 3 weeks or whenever clinically indicated.

All clinical and histopathological information as well as all AEs, and their correlation with eribulin treatment, were recorded.

Statistical Analysis

A retrospective review of clinical and treatment data for all the patients was carried out, and data were entered into a database for data collection. The standard descriptive statistics was used for both continuous and discrete variables. The purpose of the study was to evaluate the clinical outcomes of the treated patients in terms of objective response rate (ORR) and progression-free survival (PFS), and the correlation with biological features, safety, and OS. Response rate included complete response (CR) and partial response (PR); clinical benefit (CB) was defined as CR + PR + disease stabilization lasting at least 24 weeks. PFS was defined as the interval from the start of therapy with eribulin to the date of progression. Patients without progression were censored. OS was calculated as the interval from the start of therapy with eribulin to the date of death or the date of last follow-up evaluation. PFS and OS were calculated by the Kaplan-Meier method.

Table 1. Patient and tumor characteristics (n = 53)

Median age, years	62 (range 30–79)
Median ECOG	
PS 0–1	41 (77%)
PS 2	12 (13%)
Dominant disease site	
Viscera	52 (98%)
Bone alone	1 (2%)
Sites of metastases	
Liver	30 (55%)
Lung	11 (21%)
Bone	9 (17%)
Others	3 (7%)
Histology	
ER- and PgR-positive	45 (85%)
Triple negative	8 (15%)
Median prior lines of chemotherapy for advanced disease	4 (range 2–7)
Number of prior chemotherapies for advanced disease	
1–3	17 (32%)
>3	36 (68%)
Previous chemotherapy for advanced disease	
Taxanes	54 (100%)
Vinorelbine	28 (52%)
Eribulin cycles administered	5 (range 2–15)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; PS, performance status.

Results

Our analysis included 53 metastatic and pretreated BC patients referred to our center, who received at least 2 eribulin cycles.

The baseline characteristics of the patients are reported in Table 1. Median age was 61 years (range 39–81) and 77% of patients had an ECOG of 0–1. In terms of BC subtypes, 45 patients (85%) had endocrine-sensitive disease and 8 patients (15%) had a triple-negative BC. Fifty-two (98%) patients had visceral metastases, 1 patient (2%) had only bone involvement, and 7 patients (14%) presented

Table 2. Toxicity according to National Cancer Institute Common Terminology Criteria version 4.0

Toxicity	G1–2, *n* (%)	G3–4, *n* (%)
Neutropenia	2 (4)	2 (4)
Anemia	1 (2)	–
Fatigue	8 (15)	–
Neurotoxicity	2 (4)	–
Dermatological toxicity	1 (2)	–
Hypertransaminasemia	2 (4)	–

Table 3. Objective response in 53 evaluable patients

Responses	Patients, *n* (%)	95% CI
Partial response	17 (32)	±12.6
Stable disease	6 (11)	–
Progressive disease	30 (57)	–
Clinical benefit (SD+PR)	23 (43)	±13.3

CI, confidence interval; PR, partial response; SD, stable disease.

Table 4. Clinical benefit according to other variables

Variable	Disease progression	Clinical benefit	*p*
Histology			
Hormone receptor positive	25	20	0.715
Triple negative	5	3	
Sites of metastases			
Liver	17	13	0.139
Lung	9	2	
Bone	3	6	
Others	1	2	
Previous therapies			
1–3	10	7	0.083
>3	20	16	

Table 5. Survival outcome

Outcome	Mean (95% CI)	Median (95% CI)
PFS	6.8 (4.95–8.64)	4.7 (3.32–6.14)
OS	14.97 (11.79)	13.53 (9.39–17.67)

OS, overall survival; PFS, progression-free survival.

metastases of the central nervous system. Patients had received a median of 4 (range 2–7) prior lines of chemotherapy for advanced disease. Seventeen patients (32%) had been treated with less than 3 lines of chemotherapy, while the remaining 36 patients (68%) had received more than 3 and up to 7 previous chemotherapy lines, excluding the adjuvant setting. All patients had received previous anthracycline and taxane treatment, and vinorelbine had been used in 52% of the population.

Patients received a median of 5 cycles of eribulin (range, 2–11), with 15 patients (28%) receiving more than 6 cycles, and the remaining 38 patients (72%) 6 cycles or less. Regarding eribulin dose, 43 patients (81%) started treatment at a lower dose (75%), and 22% started and continued treatment at 50% of the standard dose.

Hematological and other toxicities are reported in Table 2. Grade 4 (G4) neutropenia occurred in 2 patients, grade 2 (G2) neutropenia occurred in 2 patients, and G2 anemia was reported in 1 patient. Regarding nonhematological toxicities, 8 patients (15%) experienced G2 asthenia, 2 patients (4%) experienced G2 peripheral neuropathy, and 2 patients (4%) reported increase in transaminases. None of the patients suffered from mucositis. Of note, the toxicity profile was similar in patients aged 70 years or more (8 patients, 14%) as compared to the younger population.

All the 53 patients enrolled in the study were evaluated for response (Table 3). No patient achieved a CR, and 17 patients obtained a PR, with an ORR of 32%. Stable disease was observed in 6 patients (11%) and CB was reported in 23 patients (43%). No difference in CB rate was observed in our cohort of unselected patients according to prognostic factors such as tumor histology, site of metastasis, or number of previous therapies (Table 4).

Table 5 summarizes median PFS and OS recorded in the study. At the time of the present analysis, 16 patients (30%) are still alive. After a median follow-up of 36 months, median PFS was 4.7 months (95% confidence interval [CI] 3.32–6.14 months) (Table 5; Fig. 1a), and median OS was 13.53 months (95% CI 9.39–17.67 months) (Table 5; Fig. 1b).

Table 6 reports survival outcomes according to different patients' prognostic features such as BC subtype, location of metastases, CB, number of previous therapies, and number of eribulin cycles. Median PFS was significantly longer in patients who reported CB, compared to those who did not obtain a CB (7.8 vs. 3 months, $p = 0.0001$), and in patients who received more than 6 cycles of eribulin compared to those who received 6 cycles or less (8.73 vs. 3.06 months, $p = 0.001$). Median OS was longer in pa-

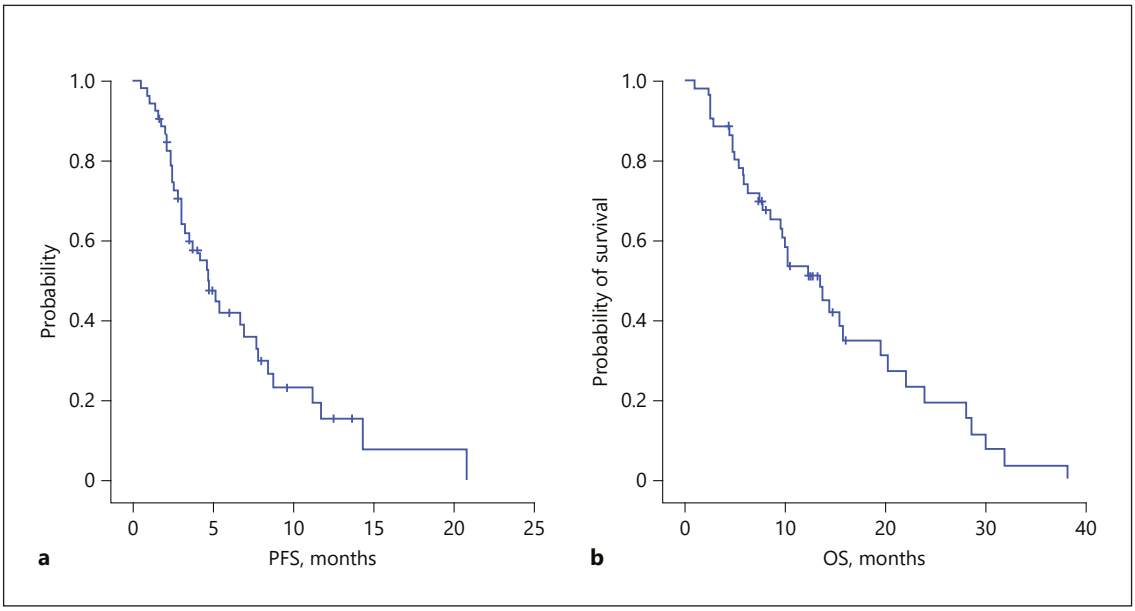

Fig. 1. Median progression-free survival (PFS; **a**) and median overall survival (OS; **b**).

tients who received more than 6 cycles of eribulin compared to those who received 6 cycles or less (20.3 vs. 9.5 months, $p = 0.034$) (Fig. 1b).

Discussion

Despite the advances obtained over the last 2 decades in the treatment of BC, both in terms of efficacy and tolerability, the prognosis for ABC patients remains poor. Until now, treatment guidelines have not clearly identified a specific regimen or single agent to be used in the advanced setting after the first-chemotherapy line. Recent retrospective studies have suggested that administration of chemotherapy beyond the third line can lead to a potential gain in terms of outcome, since each line can contribute to survival prolongation [16–21]. It should be noted, however, that patients that receive several chemotherapy lines might be identified as having a better prognosis independently from the treatment administered.

Our experience in the use of eribulin in the real-world practice confirms the activity and efficacy of this drug in heavily pretreated patients. In fact, PR and disease stabilization were observed in 32 and 11% of the patients, respectively, and CB was obtained in 43% of the study population. The median PFS and OS registered during the study were 4.7 and 13.5 months, respectively, an interesting result, especially considering the heavily pretreated status of our patients and their poor prognostic features. As expected, PFS was longer in subjects obtaining a CB as compared to those who did not, and survival outcomes were better in patients who received more than 6 cycles of eribulin chemotherapy.

The results of the EMBRACE trial, in which eribulin was compared with the best treatment strategy chosen by the investigator, were encouraging, as they showed a survival advantage that had never been previously reported with a single agent in a cohort of very heavily pretreated patients [15]. Interestingly, a pooled analysis of 2 phase III studies on eribulin revealed that the OS benefit was consistent in all BC molecular subtypes, with triple-negative patients obtaining the largest benefit [22]. Eribulin activity in heavily pretreated patients in terms of ORR, CB, PFS, and OS has been further confirmed in other retrospective analyses conducted in different countries in a clinical practice setting [23–29]. In our experience on the use of eribulin in a real world heavily pretreated population, we observed similar outcomes to those reported in the EMBRACE trial (OS 13.5 months). Similarly the ORR and OS obtained with eribulin were comparable between triple-negative and hormone-positive subtypes, in line with the results reported by other colleagues [23, 30]. The results of our study, in agreement with other experiences, confirm that eribulin can be active regardless of chemo-

Table 6. Survival outcome and other variables

Variable	Median PFS (95% CI)	Median OS (95% CI)
Histology		
Hormone receptor positive	4.6 (2.70–6.63)	13.5 (9.39–17.67)
Triple negative	4.7 (0.0–11.56)	7.43 (3.39–11.47)
p	0.29	0.488
Sites of metastases		
Liver	4.66 (2.16–7.16)	9.6 (7.56–11.77)
Lung	3.7 (3.20–4.19)	12.3 (0.0–24.81)
Bone	2.52 (2.84–12.7)	15.5 (1.89–29.1)
Others	1.87 (3.25–10.61)	19.5 (9.95–29)
p	0.86	0.35
CB		
SD+RP	3 (2.24–3.76)	9.56 (6.43–12.69)
PD	7.8 (5.86–9.73)	19.5 (12.56–26.44)
p	0.000	0.119
Previous therapy		
1–3	4.73 (0.55–8.91)	13.5 (5.15–21.9)
>3	3.7 (1.47–5.92)	10.3 (4.93–15.66)
p	0.26	0.683
Cycles, *n*		
≤6	3.06 (2.30–3.83)	9.5 (6.67–12.46)
>6	8.73 (7.10–10.35)	20.3 (14–26.5)
p	0.001	0.034

therapy line [24, 25] and seems to be more active in patients who received chemotherapy until progression (more than 6 cycles).

In our population, eribulin showed a good tolerability profile, and patient's toxicities were acceptable and lower compared to those registered in the EMBRACE trial and in other studies [23–29]. This aspect deserves further consideration, as one possible reason for this lower toxicity is that eribulin chemotherapy was started at a lower dose (75%) and that 22% of the patients maintained during the whole study a reduced dosage treatment with 50% of the standard dose. The most common G3 and G4 AE was neutropenia; alopecia was the most frequent AE (85%), and patients also suffered from fatigue (15%) and neurosensory toxicity (4%). Of note, 52% of the patients had already received vinorelbine, and all the subjects had been previously treated with a taxane-based chemotherapy, agents known for causing peripheral neuropathy [31]. These findings could suggest that eribulin may not aggravate peripheral neuropathy toxicity in patients pretreated with neurotoxic drugs, as reported by Fabi et al. [26]. Moreover, no differences in toxicity were observed between young and elderly patients, considering that 36% of the patients were 65 years or older.

Despite all the limitations implicit in a retrospective, real-life design, our study of eribulin treatment in an unselected highly pretreated patient population achieved similar results to those reported in clinical studies in terms of both activity and toxicity. Further, prospective studies investigating the effects of eribulin treatment in metastatic BC patients are warranted.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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