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ORIGINAL RESEARCH

Prognostic and predictive factors of eribulin efficacy in heavily pretreated patients affected by metastatic breast cancer: correlation with tumor biology and previous therapies

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Abstract

Background: Eribulin mesylate is currently approved in the United States and Europe for the treatment of metastatic breast cancer (MBC).

Scope: The objective of this retrospective study is to find specific predictive criteria related to patient or tumor characteristics in order to select patients that might benefit the most from eribulin and define the correct treatment sequence.

Findings: Forty-four patients with MBC who received eribulin in third or subsequent lines of therapy in a single Italian center were considered eligible. Patients were stratified by body mass index, hormonal/HER2 status, and previous therapies. Primary endpoint was progression free survival (PFS), whereas secondary endpoint was disease control rate (DCR).

A longer PFS was found in patients with hormone-positive tumors (p=0.0051), in HER2-negative cases (p=0.037), and in overweight patients (p=0.0015). No difference in efficacy was observed when eribulin was administered in third or subsequent lines of therapy. Significantly longer PFS (p<0.0001) and higher DCR (p=0.035) were achieved by patients previously treated with paclitaxel-bevacizumab in comparison to those pretreated with other drug combinations or with anthracyclines. Prior treatment with nab-paclitaxel seems to have a detrimental effect on PFS (p=0.0008).

Conclusion: Hormone and HER2 status seems a good predictive and prognostic indicator of response to eribulin. Efficacy seems independent from the number of prior therapies, and it is not influenced by prior endocrine treatments and anthracyclines-containing regimens. On the other hand, sensitivity to a prior treatment with paclitaxel-bevacizumab might be predictive of response to eribulin.

Keywords: breast neoplasms, neoplasm metastasis, body mass index, obesity receptors, progesterone, receptors, estrogen, triple negative breast neoplasms, bevacizumab, paclitaxel, taxoids.

Citation

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Introduction

Despite several treatments that are available, long-term prognosis of patients affected by metastatic breast cancer (MBC) remains poor; in this phase of disease, the primary objectives of therapy are disease control and symptoms relief, meanwhile attempting to prolong patients' survival. Chemotherapy plays an important role both in triple negative and in HER2-positive tumors in association with targeted agents, as well as in hormone-positive patients who developed a resistance to endocrine treatments or in symptomatic cases with extensive visceral metastases. Actually, there is no agent accepted as a standard of care after failure of anthracycline and taxane therapy; the choice of second-line treatment depends on the tumor subtype, site of metastases, disease burden, and prior therapies. However, no clear guidelines or predefined treatment sequence exists.

Eribulin mesylate is a non-taxane microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents; in Europe, it was approved as monotherapy for patients with MBC who have received at least one chemotherapy regimen for advanced disease (in the United States, the indication refers to two chemotherapy regimens) and who

have been previously treated with an anthracycline and a taxane in either the adjuvant or metastatic setting [1,2]. Briefly, eribulin binds to the plus ends of microtubules, suppressing the microtubule growth in the interphase cells and leading to the storage of tubulin into nonproductive aggregates, cell cycle block in G2/M, and finally to apoptosis following prolonged mitotic blockage [3]. Differently from other microtubule inhibitors such as vinca alkaloids and taxanes, which affect both the shortening and growing phases of cell cycle, mitotic blockade with eribulin is irreversible. Probably owing to this difference, eribulin exhibits a lower frequency of treatment discontinuation due to peripheral neuropathy when compared to other microtubules-targeted agents [4]. Moreover, eribulin binds either at the interface between the alfa and beta subunits of the microtubule or at the beta subunit alone, in a concentration-dependent manner; thus far, the mechanisms responsible for resistance to eribulin are unknown. Vinca alkaloids bind at both the ends (alfa and beta); whereas, taxanes bind only at the beta end, particularly on the inner side of the microtubule; in fact, beta tubulin mutation is one of the mechanisms of resistance to taxanes [5].

In heavily pretreated patients, the primary unsatisfied need is to find the clinical or biological criteria that are able to predict the response to individual drugs, allowing selection of patients that might benefit the most from specific therapies. The objective of the present study is to identify patient or tumor-specific characteristics as predictive factors of response to eribulin and, then, to define a correct treatment sequence.

Patients and methods

Patients selection

The study was designed as a retrospective analysis of 44 patients (aged≥18 years) with histologically proven MBC treated at Agostino Gemelli Hospital Foundation (Italy) between 2010 and 2014. Demographic information, patients characteristics (including height and weight), histologic features, details about previous treatments and clinical outcomes were extracted from the clinical records. Body mass index (BMI) was calculated as weight in kilograms divided by square height in meters (kg/m^2) and defined according to the World Health Organization (WHO). Eribulin administration details, including actual administered doses, dose reductions, and delays, were extracted from the computerized chemotherapy prescription platform. Criteria for selection were the following: (a) third or subsequent line of therapy with eribulin; (b) imaging assessment (bone scan, computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography based on clinical judgment) performed at regular intervals (no longer than 3 months); (c) complete information on tumor prognostic factors, previous or subsequent lines of therapy. Patients were excluded in case of prior malignancy within 5 years from starting treatment for MBC and double breast tumor with different prognostic factors. Patients starting eribulin treatment after November 2014 were excluded in order to assure a minimum follow-up of at least 1 year. Finally, patients treated within clinical trials with any not approved drug were also excluded.

The study was conducted in accordance with the rules of the local Ethics Committee and the Declaration of Helsinki. All patients provided a written consent for the use of their clinical and biological data.

Treatments

All patients received a treatment with eribulin at the recommended dose of 1.23 mg/m^2 on days 1 and 8 of a 21-day cycle in third or subsequent lines. The treatment was continued until disease progression, unacceptable toxicity, or patient's withdrawal. The clinical response to treatment was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the response evaluation criteria in solid tumors (RECIST) 1.1 criteria [6]. Provided the retrospective nature of the study, previous and subsequent treatments have been administered according to approved standard of care.

Statistical analyses

Progression free survival (PFS) was established as primary endpoint; disease control rate (DCR) was considered a secondary endpoint. PFS was calculated from the beginning of eribulin therapy until radiologically assessed disease progression. DCR is defined as the proportion of patients obtaining a complete/partial response in addition to those achieving a stable disease. The outcome was censored if a patient had not progressed at the time of last follow-up. The Kaplan-Meier method and the log-rank test were used to estimate PFS. Multivariate Cox regression models were used to identify the predictive effect of different variables on PFS. Exact Fisher test and Chi-squared test were used for establishing the significance of the association between DCR and other variables. All reported *p*-values are two-tailed, and a level of 0.05 or less was considered statistically significant.

Results

Patients characteristics

Forty-four out of 54 patients with histologically proven diagnosis of MBC treated in a single Italian center between December 2010 and November 2014 were considered eligible. Median age at the first diagnosis of MBC was 50 years (range 36–63 years). Sixteen out of 44 patients were overweight (36%). Most patients (64%) had ductal histology, 23% had lobular subtype, 11% a poorly differentiated not otherwise specified MBC and only one patient (2%) a medullary subtype. Twelve patients (27%) had a triple-negative disease, 8 patients (18%) had human epidermal growth factor receptor 2 (HER2)-positive disease, and, in 28 patients (64%), the hormone receptor status

was positive (estrogen receptor [ER]/progesterone receptor [PR]/both of them). Eight patients (18%) were metastatic since first diagnosis; 36 patients (82%) received a neoadjuvant or adjuvant treatment. Among hormone-positive cases, 6 out of 28 patients (21%) had not received a hormonal treatment in metastatic setting, 8 patients (29%) received only one endocrine treatment, 14 (50%) received two or more lines of endocrine therapy. Twenty out of 44 patients (45%) received eribulin as third-line treatment, the remaining 24 (55%) were treated with eribulin in fourth or subsequent lines of therapy. Twenty-six patients (59%) received bevacizumab before eribulin therapy (10 mg/kg on days 1–15 of a 28-day cycle in association with paclitaxel and 7.5 mg/kg on day 1 of a 21-day cycle as maintenance treatment), 26 (59%) and 12 (27%) patients were pretreated in metastatic setting with anthracyclines (doxorubicin or liposomal doxorubicin 75 mg/m^2 on day 1 of a 21-day cycle/epirubicin 90 mg/m^2 on day 1 of a 21-day cycle) or nab-paclitaxel (260 mg/m^2 on day 1 of a 21-day cycle), respectively. The patients' characteristics are summarized in Table 1.

Table 1. Patients' characteristics.

Patients' characteristics	***n* (%)**
Median age at diagnosis of MBC	50 (36–63)
Obesity (BMI≥25)	16/44 (36%)
Patients metastatic at first diagnosis	8/44 (18%)
Patients receiving neoadjuvant/adjuvant therapy	36/44 (82%)
Histologic subtype	
Ductal	28/44 (64%)
Lobular	10/44 (23%)
Medullary	1/44 (2%)
Poorly differentiated	5/44 (11%)
Prognostic factors	
Triple negative	12/44 (27%)
Her2 positive	8/44 (18%)
ER/PR positive	28/44 (64%)
Hormonal treatment in ER/PR positive MBC	
0	6/28 (21%)
1 line of therapy	8/28 (29%)
≥2 lines of therapy	14/28 (50%)
Eribulin treatment	
3rd line	20/44 (45%)
4th or subsequent lines	24/44 (55%)
Previous treatments	
Previous bevacizumab	26/44 (59%)
Previous anthracyclines	26/44 (59%)
Previous nab-paclitaxel	12/44 (27%)

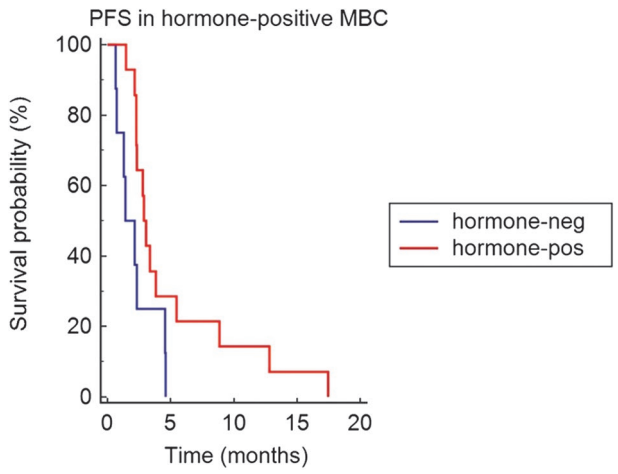
At a median follow-up of 2 years, 34 deaths (77%) had occurred, and all patients (100%) experienced progressive disease during or after eribulin treatment. Median PFS was 2.33 months (95% confidence interval [CI]: 2.267–3.367). Toxicity events of grade 1–2 were recorded in 23 patients (52.2%); no serious adverse events were recorded.

Efficacy of eribulin according to patients' and tumor characteristics

Body weight: According to the WHO classification, two groups were identified: those with normal weight including BMI from 18.5 to 24.9 and those overweight or obese including patients with BMI equal to or greater than 25 for overweight and obesity. Sixteen out of 44 patients were overweight; median PFS was 2.1 months in normal weight subgroup and 2.8 months in overweight patients (hazard ratio [HR] 0.42; 95% CI: 0.23–0.77; p=0.0015). DCR was not statistically different. However, a trend was observed in favor of overweight group (50 *vs* 36%; p=0.52).

Hormone receptor status: Twenty-eight out of 44 patients had a hormone-positive disease (ER+/PR+/both of them). Median PFS resulted doubled in patients affected by hormone-positive disease when compared to those with ER and PR negative (2.9 *vs* 1.4 months; HR 0.45; 95% CI: 0.21–0.93; p=0.0051) (Figure 1). In agreement with this result, DCR was also higher in hormone-positive cases (50 *vs* 25%), although not statistically significant (p=0.12). The efficacy of eribulin in hormone-positive patients was independent from previous endocrine treatment received in metastatic setting. In fact, comparing hormone-positive patients who received no previous endocrine treatment in metastatic setting (six patients) to those who received 1 or ≥2 lines of previous hormonal therapy (8 and 14 patients, respectively), no difference in eribulin efficacy was surprisingly found in terms of PFS (p=0.96), although DCR was better in previously untreated patients (p=0.01).

Figure 1. Median PFS in hormone-positive *vs* hormone-negative MBC.



HER2-positive and triple-negative patients: Only eight patients (18.2%) had HER2-positive disease but, when compared to HER2-negative group, median PFS resulted significantly longer in the last one (1.4 *vs* 2.8 months; HR 0.47; 95% CI: 0.17–1.29; *p*=0.037) (Figure 2). Only two patients in HER2-positive group achieved a stable disease as best response to eribulin (25%); DCR in patients affected by HER2-negative disease was higher (44%) but the difference was not statistically significant (*p*=0.44). On the other hand, 12 out of 44 patients had a triple-negative disease. No differences in eribulin efficacy were observed between triple-negative tumors and HER2 positive and/or hormone-positive tumors with a median PFS of 2.1 and 2.8 months, respectively (*p*=0.13; 95% CI: 0.29–1.32). DCR was 33% in triple-negative cases and 44% in the control arm (*p*=0.73).

Efficacy according to previous treatments

In this study, the efficacy of eribulin was evaluated in heavily pretreated patients, but no difference in PFS was found when patients treated with third-line eribulin were compared to those who received eribulin in more advanced lines (*p*=0.50; 95% CI: 0.46–1.50); conversely, DCR was higher in patients receiving eribulin in third line (60 *vs* 25%; *p*=0.03).

Prior treatments or mechanisms of acquired resistance to other drugs might affect eribulin efficacy; thus, we stratified patients by previous therapy (paclitaxel-bevacizumab, nab-paclitaxel, or anthracyclines). Twenty-four out of 44 patients received paclitaxel-bevacizumab as previous treatment and seven of them received bevacizumab also as maintenance. PFS was significantly higher in patients pretreated with paclitaxel-bevacizumab (3.8 *vs* 1.4 months; HR 0.30; 95% CI: 0.14–0.63; *p*<0.0001) (Figure 3A). DCR was 61% in patients pretreated with paclitaxel-bevacizumab and 11% in the other patients (*p*=0.001). Median PFS of patients previously treated with paclitaxel-bevacizumab was 8.0 months in our population;

Figure 2. Median PFS in HER2-positive *vs* HER2-negative MBC.

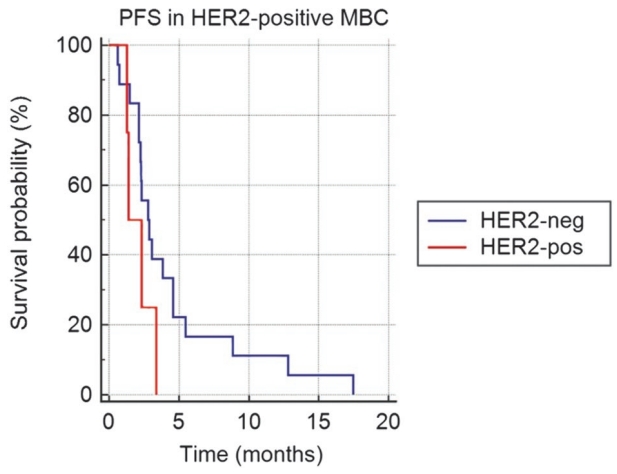


Figure 3A. Median PFS in patients pretreated with paclitaxel-bevacizumab.

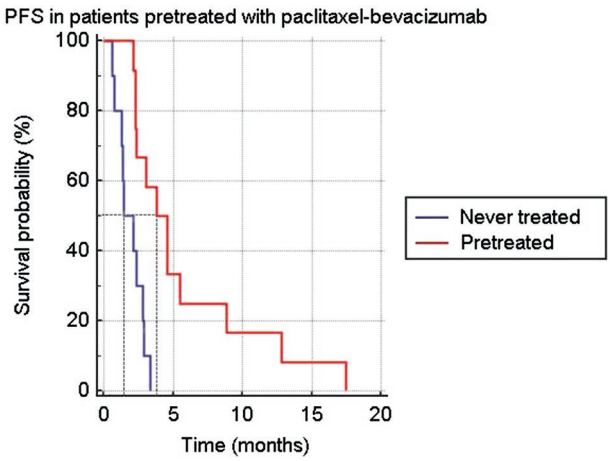
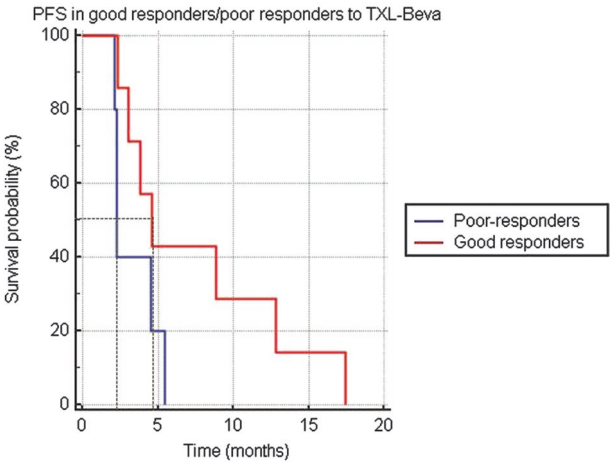


Figure 3B. Median PFS in good responders *vs* poor responders to paclitaxel-bevacizumab.



we considered good responders to this regimen those reaching a PFS >8 months (n. 14) and poor responders those achieving a PFS ≤8 months (n. 10). Efficacy of eribulin therapy was greater in good responders to paclitaxel-bevacizumab than in poor responders (PFS 4.6 *vs* 2.3 months; HR 0.39; 95% CI: 0.15–1.03; *p*=0.0095) (Figure 3B).

In 18 out of 44 cases, no anthracycline was administered in the metastatic setting. Median PFS resulted slightly longer in patients who did not receive anthracyclines when compared to those who received anthracyclines (3.4 *vs* 2.3 months; HR 0.69; 95% CI: 0.38–1.24; *p*=0.18). DCR resulted significantly lower in patients pretreated with anthracyclines (23 *vs* 66%; *p*=0.006).

Only 12 patients received nab-paclitaxel in previous lines of therapy; none of these patients was pretreated with paclitaxel-bevacizumab. Eribulin seems detrimental in these patients. Median PFS was 1.5 months in comparison to 3.1 months

Figure 4. Median PFS in patients pretreated with nab-paclitaxel.

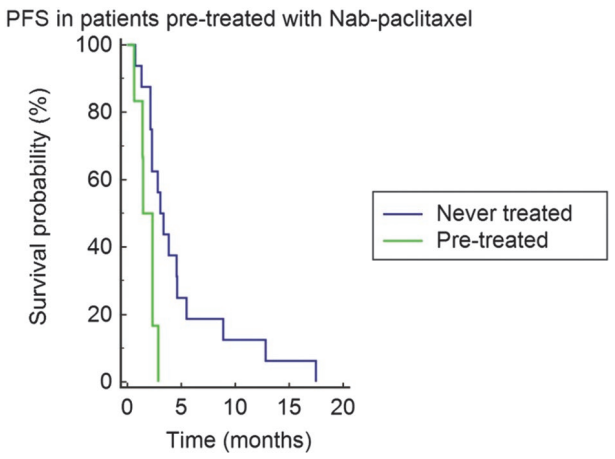
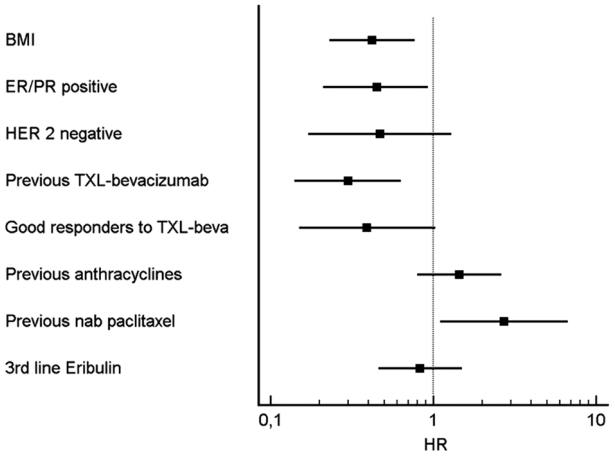


Figure 5. Eribulin efficacy in all subgroups analyzed.



of patients not pretreated with nab-paclitaxel, including those pretreated with paclitaxel-bevacizumab (HR 0.36; 95% CI: 0.15–0.91; p=0.0008) (Figure 4). Similarly, DCR was 8% in patients pretreated with nab-paclitaxel and 56% in those who did not receive previous nab-paclitaxel (p=0.006).

The efficacy of eribulin treatment in all subgroups analyzed is summarized in Figure 5.

Discussion

In the present observational study, we evaluated patients and tumor characteristics as well as prior treatments received in order to identify a population of patients more likely to benefit from eribulin in MBC. The potential impact of obesity in patients under active treatment for breast cancer (neoadjuvant, adjuvant, or metastatic setting) is still a matter of debate. Recently, Barba and colleagues have evaluated the role of obesity as a predictive factor of response to chemotherapy in a retrospective series of 101 patients with MBC treated with eribulin in six different Italian oncologic centers [7]. Lower BMI, ER-positive status, and third-line treatment resulted associated with a greater clinical benefit from eribulin, even if it was not statistically significant. In our series, 36% of women were overweight (*vs* 42.6% of the cited study), and a significantly longer PFS was revealed in this subgroup of patients. Sample size in both studies is considerably small to draw definitive conclusions and data available are discordant, not allowing any hypothesis in favor of an association between BMI and treatment outcome.

In the first multicenter, randomized, open-label phase III trial comparing eribulin to treatment of physician's choice (EMBRACE), exploratory subgroup analysis of overall survival did not show any survival advantage based either on HER2 status or previous therapy with capecitabine, but no comment on hormone-positive cases was made [8]. In another phase III randomized trial (study 301), eribulin was compared to capecitabine as first-, second-, and third-line treatment in 1102 patients with advanced MBC; most patients had HER2-negative tumors (70%), and 25% had triple-negative disease [9]. In this study, a trend toward a better overall survival (OS) was found in HER2-negative cases and in ER-negative disease as well as in triple-negative disease. Nonetheless, in a pooled analysis of the above cited studies, the authors showed that the OS benefit in the eribulin arm was consistent in all molecular subtypes, with triple-negative patients obtaining a larger benefit, while clinical benefit rate resulted significantly improved only in patients with ER-positive and in HER2-negative/hormone-positive tumors [10]. In our population, PFS was significantly longer in hormone-positive patients with a trend toward a higher DCR, even if not statistically significant. The better outcome observed in patients with hormone-positive tumors does not seem driven by previous endocrine treatments, although eribulin seems to induce a larger DCR in patients previously not exposed to antiestrogen therapy. In addition, HER2-negative tumors seem to have longer PFS than HER2-positive disease with eribulin therapy. Furthermore, the outcomes resulted similar in triple-negative and in non-triple negative patients.

Many other studies have evaluated the efficacy of eribulin in relation to hormonal and HER2 status. In a retrospective series of 133 patients, Gamucci et al. suggested a clinical benefit in HER2-negative cases. Moreover, when eribulin was administered as third-line therapy, the response rate to eribulin in triple-negative or HER2 and/or hormone-positive subtype was substantially identical, even though the significance was affected by the small sample size [11]. In a phase II trial including 56 HER2-negative patients, eribulin was administered as first-line treatment; the authors observed a greater clinical benefit in ER-positive patients compared to triple-negative cases [12]. A retrospective Swedish study investigated the efficacy of eribulin in a subgroup of 48 patients defined on the basis of hormonal status, HER2 positivity, and Ki67 index; no statistically significant difference in objective response and

survival was found [13]. In another retrospective, multicenter study, Dell'Ova et al. evaluated prognostic and predictive factors in a series of 258 patients affected by MBC treated with eribulin. HER2-positive cases had a higher clinical benefit rate, probably owing to the combination of trastuzumab with eribulin in the study population. Time to progression was longer in hormone-positive tumors, but also triple-negative status was predictive of response to eribulin even if it was an adverse prognostic factor because OS and time to progression were significantly lower in this subgroup of patients [14]. Taken together, these data suggest that both ER-positive and HER2-negative status might have a favorable impact on eribulin efficacy, whereas effects in triple-negative patients are divergent and mostly poorer.

In our group of heavily pretreated patients, no difference in PFS was found by comparing patients treated with eribulin in third or subsequent lines; only DCR—as expected—was higher when eribulin was administered as a third line. In a Japanese retrospective study including 293 women with ER-positive/HER2-negative MBC, no significant difference in OS was observed among patients receiving eribulin as first-, second-, third-line treatment, or beyond [15]. In the same study, eribulin demonstrated a significant survival benefit in patients pretreated with an anthracycline-based regimen. The influence of previous treatments on eribulin activity was evaluated in other studies. In the pooled analysis of Twelve et al., taxane refractory patients obtained no survival advantage from eribulin treatment as opposed to nonrefractory patients [12]. Similar results were observed in the ERIBEX retrospective study where taxane-resistant patients were found to have a shorter time to progression [14]. In our study population, a previous treatment containing anthracyclines does not seem to influence eribulin outcome. The same finding has been reported in two phase 2, multicenter, single arm studies with first-line eribulin alone or combined with trastuzumab in HER2-negative and HER2-positive MBC, respectively [14,16]. Both these studies confirmed eribulin efficacy regardless of prior neoadjuvant/adjuvant anthracycline/taxane treatment [17]. In Study 206, overall response rate (ORR) and median PFS were similar in patients who had received prior anthracycline, in those pretreated with taxanes, and in those treated with both anthracycline and taxane; ORR and PFS were slightly but not significantly higher only in anthracyclines/taxanes naïve patients. In Study 208, these data were confirmed, but anthracyclines/taxanes naïve patients derived most benefit from eribulin plus trastuzumab therapy. Interestingly, our data suggest a possible association between a previous treatment with paclitaxel-bevacizumab and a better outcome of eribulin therapy; in fact, PFS and DCR resulted significantly improved in patients pretreated with paclitaxel-bevacizumab. As taxanes and eribulin share the same cellular site of action, sensitivity to prior treatment with paclitaxel-bevacizumab may represent an important aspect to consider in predicting eribulin sensitivity. As in our series many patients pretreated with paclitaxel-bevacizumab received maintenance bevacizumab as well, it might be assumed that the interval from exposure to paclitaxel-bevacizumab combination might have been sufficiently long to allow regrowth of clones sensitive to microtubule inhibition. On the other hand, the patients pretreated with nab-paclitaxel but not receiving prior paclitaxel-bevacizumab combination had the worst outcome from eribulin therapy, both in terms of PFS and DCR. The preclinical data suggest that taxanes induce mobilization of endothelial progenitor cells whose expansion is responsible for the development of drug resistance; this effect might be enhanced by nano-albumin binding of paclitaxel; whereas, addition of antiangiogenic drugs to taxanes could block the mobilization of the progenitor cells, improving response to microtubule inhibitors [18–20]. It might be challenging in the future to evaluate the role of bevacizumab in association with other microtubule inhibitors beyond progression.

Conclusions

In summary, in this retrospective analysis, eribulin appears to be an effective treatment in hormone-positive tumors, as well as in other previous studies. However, to the best of our knowledge, this is the first study that suggests a possible treatment sequence where eribulin seems to be effective in good responders to a previous line with paclitaxel-bevacizumab, but not after prior treatment with nab-paclitaxel. Nevertheless, our study has some limitations owing to its retrospective nature, the small number size, possible changes of the basal biomolecular profile, and inclusion criteria not as strict as in prospective clinical trials. Despite these biases, some results might be useful in the clinical practice, allowing detection of specific biomarkers of response.

Contributions: All authors contributed to the collection, analysis, and interpretation of data and participated in the revision and editing of the final manuscript.

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