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ORIGINAL ARTICLE

Efficacy and safety of eribulin monotherapy in patients with heavily pretreated metastatic breast cancer

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Summary

Purpose: *Eribulin is a non-taxane microtubule inhibitor, which can be used after anthracycline and taxane treatment in patients with metastatic breast cancer (MBC). The purpose of this study was to investigate the efficacy and safety of eribulin monotherapy in heavily pretreated MBC patients.*

Methods: *In this single-center trial, a total of 66 MBC patients who received eribulin monotherapy in Hacettepe University Cancer Institute between 2013 and 2015 were retrospectively analyzed. Kaplan-Meier survival analysis was carried out for progression free survival (PFS) and for overall survival (OS). Two-sided p values <0.05 were considered as statistically significant.*

Results: *Sixty-six patients who received at least one cycle of eribulin were registered. Most patients were heavily pretreated with a median of 4 (range 2-7) previous chemotherapy lines prior to eribulin. Median patient age was 50 years (range 28-67). Most patients were treated with eribulin at 4th or 5th line (33.3 and 27.3%, respectively). Brain metastases were present in 19 (28.8%) patients at the time of initial eribulin administration. Median PFS was 5 (95% CI 4.1-5.8) and median OS was 8 (95% CI 6-9.9) months. Fifteen patients (22.7%) responded to treatment with partial remission (PR) and 36 (54%) had stable disease (SD). No hypersensitivity reactions and no toxic deaths were observed. Three (5%) patients experienced grade 4 neurotoxicity. Fourteen (21.5%) patients developed grade 3-4 neutropenia.*

Conclusion: *Eribulin monotherapy is an effective and safe regimen for MBC patients. Its low toxicity profile compared to other intravenous cytotoxic agents and the ease in its intravenous administration make this agent a preferable option for both physicians and patients.*

Key words: *efficacy, eribulin, metastatic breast cancer, subtypes, survival, toxicity*

Introduction

MBC is still accepted as an incurable disease despite recent improvement in treatment strategies [1]. Cytotoxic chemotherapy, human epidermal growth factor receptor 2 (HER2) targeted therapy and hormonal therapy are considered as treatment options in MBC, depending on the tumor biology, presence of symptoms, disease free intervals and previous treatments [2]. Systemic chemotherapy is the cornerstone of the treatment in this setting and aims to control symptoms, prevent serious complications, maintain quality of life and prolong survival [3].

Anthracyclines and taxanes are the most effective agents currently used in the treatment of breast cancer. These agents are administered frequently as adjuvant treatment for patients with

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early-stage cancers as well as for those who present with metastatic disease [4]. However, there are some limitations with their use in patients with MBC. There is no single accepted standard regimen after failure of anthracycline and taxane therapy; capecitabine, gemcitabine, vinorelbine, and ixabepilone have demonstrated activity in this setting and are commonly used [5-8].

Eribulin mesylate is a non-taxane microtubule inhibitor which is a structurally synthetic halichondrin B analogue. Eribulin shows its cytotoxic effect by inhibiting microtubule growth and sequestering tubulin, finally causing G_2-M cell cycle arrest and cell death through apoptosis [9]. Phase II-III studies showed that eribulin has an antitumor activity and safety profile even in heavily pretreated MBC [10,11]. The phase 3 EMBRACE study [12] has also demonstrated that eribulin provided a survival benefit in women with MBC who had previously received at least two chemotherapeutic regimens including anthracycline and taxanes. In that study eribulin was well tolerated and mostly grade 1-2 toxicities were observed [12]. Based on the EMBRACE study eribulin was approved by Food and Drug Administration (FDA) for MBC.

The aim of this study was to evaluate the activity and tolerability of eribulin in advanced breast cancer patients who were pretreated with ≥ 2 chemotherapy lines for metastatic disease.

Methods

This study was performed at Hacettepe University Cancer Institute and the patients treated between September 2013 and February 2015 were registered. Patients who were metastatic at the initial presentation or became metastatic after adjuvant treatment with or without loco-regional recurrence were included in this study. Eribulin was administered in a 3-week treatment cycle of eribulin mesylate (1.4 mg/m^2 i.v. equivalent to 1.23 mg/m^2 eribulin expressed as free base) on days 1 and 8. HER2-negative tumors were scored as 0 or +1 by immunohistochemistry, while HER2-positive cases were +2 or +3 by immunohistochemistry and amplified by fluorescence *in situ* hybridization. In HER2-positive patients, eribulin was given in combination with trastuzumab 6-8 mg/kg every 3 weeks. Patients with bone metastases received bisphosphonate therapy as well. Endocrine therapy was not given concomitantly with eribulin treatment. Primary granulocyte colony-stimulating factor (G-CSF) was not given routinely except for patients who developed grade 3-4 neutropenia. Dose reduction was performed depending on patients' grade 3-4 toxicity.

The demographic features of patients, tumor pathologic characteristics, site of metastases, administration of hormonal therapy prior to eribulin treatment, type of previous chemotherapy treatments lines, duration of eribulin treatment, eribulin adverse effects, response rate, PFS, and OS were recorded. Radiological and clinical assessments were used for efficacy evaluation. Imaging assessment was done in 2-3 monthly intervals. Adverse events were registered retrospectively according to the common terminology criteria for adverse events, version 4.0. The evaluation of tumor response was performed in accordance with RECIST criteria, version 1.1.

Statistics

Standard descriptive statistics were used to characterize the sample dataset. OS and PFS were the endpoints of this study. OS and PFS were defined as the time from the start of eribulin therapy to the progression or death due to any cause. Statistical significance of the differences in Kaplan-Meier estimates was assessed using the log-rank test. Univariate and multivariable Cox proportional hazards model was used to evaluate the influence of all potential predictive and prognostic factors on the survival measurements. Model optimization was performed using analysis of deviance and model residuals. Objective response rate (ORR) was defined as the sum of PR and complete response (CR). Clinical benefit rate (CBR) was defined as the sum of PR, CR and SD. We defined clinical benefit rate as the duration of response for 3 months or longer.

In all assessments, a p value < 0.05 was considered as statistically significant.

Results

Sixty-six patients who received at least one cycle of eribulin were registered. The median patient age was 50 years (range 28-67). The majority of patients had previously received adjuvant (N=38, 57.6%) or neoadjuvant (N=9, 13.6%) chemotherapy before they were diagnosed with metastases. Patient demographic and baseline clinical characteristics are given in Table 1. Most patients were heavily pretreated with a median of 4 (range 2-7) metastatic chemotherapy lines prior to eribulin treatment. Fourth, fifth and sixth line of eribulin treatments were 33.3, 27.3 and 15.2%, respectively. In 36 patients (54.5%) metastatic disease involved 3 or more sites (Table 1). Brain metastases were present in 27% (N=19) of the patients. At the end of the follow-up period (February 2015), all patients had already received a median of 3 courses of eribulin (range 1-8) while 32 patients were still on eribulin. Median PFS was 5 (95% CI: 4.1-5.8) months and median OS was 8 (95% CI: 6.0-9.9) months. Fifteen patients (22.7%) responded to

Table 1. Patient demographic and baseline clinical characteristics

Characteristics	*N (%)*
Age, years, median (range)	50 (28-67)
Menopausal status	
Pre	43 (65.2)
Post	23 (34.8)
Histology	
IDC	52 (78.8)
ILC	3 (4.5)
Mixed IDC and ILC	4 (6.1)
Other	7 (10.6)
Site of metastasis	
Bone	58 (87.9)
Lung	51 (77.3)
Brain	19 (28.8)
Liver	38 (57.6)
Local recurrence	7(10.6)
Receptors status	
ER positive	52 (78.8)
PR positive	46 (69.7)
Triple negative	7 (10.6)
HER-2 status	
Positive	11 (16.7)
Negative	55 (83.3)
ECOG PS	
0	29 (43.9)
1	30 (45.4)
2	7 (10.6)
Adjuvant hormonotherapy	
Yes	52 (78.8)
No	13 (19.7)
Adjuvant radiotherapy	
Yes	48 (72.7)
No	18 (27.3)
Metastatic treatments	
Taxane	63 (95.5)
Gemcitabine	57 (86.4)
Capecitabine	51 (77.3)
Vinorelbin	27 (40.3)
Other (CMF, etc)	8 (12.1)
Metastatic line chemotherapy	
2 line	5 (7.6)
3 line	22 (33.3)
4 line	18 (27.3)
5 line	10 (15.2)
6 line	9 (13.2)
7 line	2 (3)
Adjuvant chemotherapy	38 (57.6)
Anthracycline only	11 (28)
Anthracycline plus taxane	18 (48)
Other (CMF..)	9 (25)

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ER: estrogen receptor, PR: progesterone receptor, ECOG PS: Eastern Cooperative Oncology Group performance status

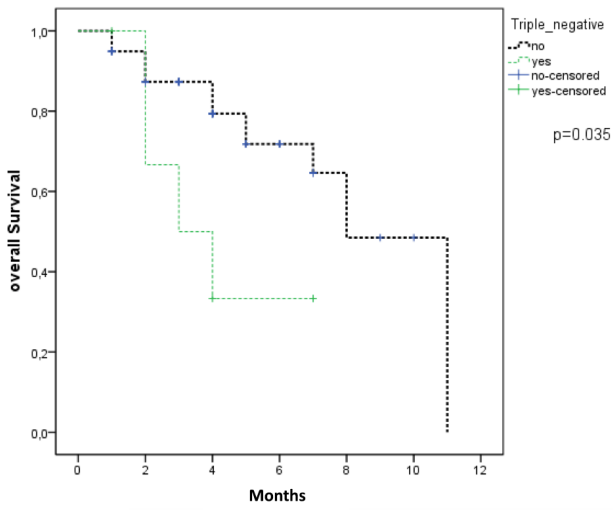

Figure 1. Kaplan-Meier curves for overall survival of triple negative patients.

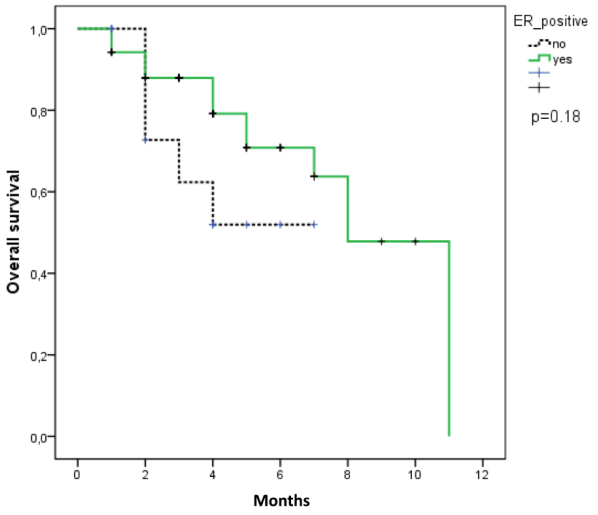

Figure 2. Kaplan-Meier curves for overall survival of estrogen receptor positive patients..

treatment with PR and 36 (54%) had SD. No OS difference was demonstrated in patients who received 1-3 chemotherapy lines compared to those who had more than 3 chemotherapy lines (median OS: 8 months for both groups, range: 5.7-10.2 months, p= 0.19). HER2-positive groups' PFS i n HER2-positive group was 5 months and OS couldn't be reached (Table 2). In cases where 2 or more organs were involved, response rates were also poor (median OS: 8 months, range 6.1-9.8 months) (Table 3). The triple negative group had significantly worse OS (Figure 1) and PFS (3 and 3 months, p=0.03; Figure 2). Median OS in HER2-negative group was 8 months (95% CI 6.2-9.7) which was also similar in other groups.

Table 2. Outcomes of the study groups according to ER positivity and HER2 status

Outcomes	*All 66 (100%) N (%)*	*HER2 (-) (N=55) N (%)*	*HER2 (+) (N=11) N (%)*	*ER (+) (N=52) N (%)*	*Triple-negative (N= 7) N (%)*
ORR	15(22.7)	12(21.8)	3(27.3)	12(23.1)	1(14.3)
CR	0	0	0	0	0
PR	15(22.7)	12(21.8)	3(27.3)	12(23.1)	1(14.3)
SD	36(54)	28(50.9)	8(72.7)	29(55.8)	2(28.6)
PD	15(22.7)	15(27.3)	0	11(21.2)	4(57.1)

CR: complete response, PR: partial response, ORR: objective response rate defined as CR + PR, SD: stable disease, PD: progressive disease, ER: estrogen receptor

In general, treatment was well tolerated. No hypersensitivity reactions and no toxic deaths were seen. None of the patients discontinued eribulin treatment due to toxicity. The most common adverse events were grade 3-4 neutropenia and grade 1-2 neuropathy. Six patients were admitted to hospital during the eribulin treatment. Three of them had dyspnea due to pulmonary metastases and the fourth had grade 4 neutropenia (Table 4). Dose reductions were necessary in only 3 patients. Three (5%) patients experienced grade 4 neurotoxicity. Grade 3-4 neutropenia and subsequent granulocyte colony-stimulating factor (G-CSF) administration was recorded in 14 (21.5%) patients.

Discussion

Eribulin has recently shown to exert antitumor activity in the challenging setting of lateline treatment of locally advanced or MBC cases. It can be received as monotherapy after anthracycline and taxane treatment [12]. Several phase II studies demonstrated that eribulin has a substantial activity and manageable toxicity profile in MBC with a reported ORR of 9.3-21.3% and a CBR of 17.1-27.5%, with a PFS of 2.6 months and an OS of 10.4 months [11,14-16]. In these studies, anticancer activity was reported across all molecular subgroups, although responses were higher in less refractory patients and in those who were hormone receptor positive and HER2-negative, and lower in patients who were triple-negative.

On the basis of the activity and manageable toxicity profile observed in phase II trials, 2 randomized phase III studies in patients with locally advanced breast cancer or MBC were conducted [13,14]. When eribulin was administered as monotherapy the reported ORR and median OS were 10-20% and 9-15 months, respectively [10-13]. Median PFS and OS were calculated as 5 and 8 months respectively in our study group and a total of 22.7% of the patients responded to treatment with PR and 54% of patients had SD. While our results with eribulin appeared to be partially effective in most subgroups, this was not the case for triple-negative patients for whom both the median PFS and median OS were calculated as 3 months. The ORR in our study was 22.7%. Also the response rates in HER2-positive and triple-negative groups of our study were 27.3 and 14.3%, respectively. This was higher compared to 12 and 11% of ORR reported in the 2 phase III trials [12,13]. This was probably due to the fact that the response evaluation in the current study was based on the assessment of the treating physician and therefore was less strict than the RECIST criteria applied in the randomized trials.

The first reported study was the EMBRACE study [12] which showed a benefit in OS in heavily pretreated patients with MBC. In that study patients were randomized either for eribulin or received a treatment of physician's choice (TPC). Median OS was 13.1 months in the eribulin-treated patients compared with 10.6 months in the TPC-treated group (HR 0.81, 95% CI 0.66–0.99; p=0.041). Despite of the improvement in OS, median PFS was not significantly better (p=0.137) with eribulin (3.7 months) compared to that of TPC (2.2 months). ORR were significantly more frequent in patients treated with eribulin than with TPC (12 vs 5%; p=0.002). In our study, the median OS was substantially lower compared with the EMBRACE study (8 months compared to 13.1 months) presumably owing to the fact that our patients were not preselected as in randomized trials. Another possible reason for this might be that in our study most patients were already heavily pretreated with a median of 4 (range 2-7) metastatic chemotherapy lines prior to eribulin. However our study's PFS was higher than in the EMBRACE

Table 3. Efficacy analysis in selected subgroups of patients

	OS				*PFS*			
	N	*Events*	*Median, months (95% CI)*	*p value*	*N*	*Events*	*Median, months (95% CI)*	*p value*
All groups	66	19	8 (6-9.9)		66	29	5 (4.1-5.8)	
HER2 (-)	55	18	8 (6.2-9.7)	0.38	55	27	5 (4.0-5.9)	0.45
HER2 (+)	11	1	Not reached		11	2	5 (3.4-6.6)	0.37
ER(+)	52	14	8 (6.0-9.8)	0.18	52	14	5 (3.4-6.6)	0.16
TNBC	7	4	3 (0.6-5.4)	0.035	7	4	3 (1-4.9)	0.02
NOM								
1-2	30		Not reached	0.19	30	12	5 (3.8-6.1)	0.23
>2	36	12	8 (6.1-9.8)		30	17	5 (3.8-6.1)	
Liver	38	12	7 (4.6-9.3)		38	18	5 (4.1-5.8)	
Brain	19	5	8 (0-16.4)	0.87	19	10	5 (3.2-6.7)	0.44
Visceral								
1	60	18	Not reached	0.53	60	26	5 (4.2-5.7)	0.64
0	6	1	8 (6.2-9.7)		6	3	4 (1-6.9)	

OS: overall survival, PFS: progression free survival, Her-2: human epidermal growth factor 2 receptor, ER: estrogen receptor, TNBC: triple negative breast cancer, NOM: number of metastatic organs

Table 4. Eribulin treatment-related adverse events

Events	*Grade 1-2 N (%)*	*Grade 3-4 N (%)*	*Total*
Neutropenia	9 (13.6)	16 (24.2)	25 (37.6)
Thrombocytopenia	1 (1.5)	2 (3)	3 (4.5)
Transaminase elevation	4 (6.1)	0	4 (6.1)
Neuropathy	4 (6.1)	3 (4.5)	7 (10.6)
Dose reduction	NA	NA	3 (4.5)
Hospitalization	NA	NA	6 (9.1)
Infection	NA	NA	3 (4.5)
GCSF usage	NA	NA	14 (21,5)
Treatment discontinuation	NA	NA	NA

Scaled according to National Cancer Institute-Common Toxicity Criteria for Adverse Events v 4.0
NA: not applicable

study (5 vs 3.7 months).

The second phase III study [13] compared eribulin mesylate with capecitabine in patients who had previously received treatment with anthracyclines and taxanes. The patients included in that study had received mostly 2 or fewer (maximum of 3) prior chemotherapy regimens for advanced disease. However, this phase III study failed to show any favorable outcomes that eribulin was not superior to capecitabine with regard to OS or PFS. Although there was a trend towards improvement in OS for patients treated with eribulin (15.9 vs 14.5 months, p=0.056), this was not statistically significant. PFS was similar in both arms at 4.1 and 4.2 months (p=0.736).

In order to provide more information on the efficacy of eribulin in patients with HER2-negative or HER2-positive breast cancer, the European Medicines Agency requested a pooled analysis of the EMBRACE and another phase III trial [17]. This pooled analysis showed that women with HER2-negative or triple-negative disease gained a particular benefit, however the effects in patients with HER2-negative but hormone receptor-positive disease were somewhat less beneficial. This analysis also showed that patients with more than 2 organs involved might gain an additional survival benefit. In our study, however, we did not observe such benefit; in cases where 2 or more organs were involved the response rates were also

poor (median OS: 8 months, range 6.1-9.8; p=0.19). Also in the present study, further-line eribulin treatment for MBC was proven to be slightly beneficial, particularly in ER-positive and HER2 negative groups of patients compared to triple-negative group with median PFS of 5 months and median OS of 8 months compared to 3 months of PFS and OS, respectively. This was much lower compared to that of the EMBRACE study which reported 12.9 months. One factor of our poor results in the triple-negative group might be due to the fact that our patients received eribulin at a much later phase when they had already been heavily pretreated with other lines of chemotherapy regimens. While the number of triple-negative patients represents a small percentage in our study group (7 patients, 11%), it still can be argued that eribulin was not effective in such terminal stage patients and its use needs to be reevaluated in terms of cost effectiveness.

A recent phase II study assessed the antitumor activity and safety of eribulin in combination with trastuzumab as first-line therapy for patients with locally recurrent or metastatic HER2 breast cancer [18]. The results of this study suggested that the combination of eribulin with trastuzumab had a considerable activity with acceptable toxicity profile as first-line therapy for HER2-positive MBC. In our study we had 11 HER2-positive patients who were treated with eribulin and trastuzumab and we indeed have achieved a better response rate in this group (PR=27.3%) the OS of which could not yet be reached. PFS in this group was 5 (range 3.4-6.6) months.

Eribulin's adverse effects are in general well tolerated and manageable. Fatigue, myelosuppression and peripheral neuropathy are characteristic and the most common side effects of eribulin, which usually do not require hospitalization. In the EMBRACE study, the most common grade 3 or 4 adverse event was neutropenia, however febrile neutropenia was uncommon in both arms and the incidence of all treatment-related fatal adverse events were the same [12]. Grade 3 or 4 asthenia or fatigue occurred with very similar frequency with eribulin and TPC. Peripheral neuropathy was observed in 174 of 503 (35%) patients with eribulin, but among those patients, grade 3 or 4 neuropathy was only in 41 (8%) cases, and discontinuation occurred in 24 (5%) patients. In our study the most common adverse event was grade 3-4 neutropenia which was observed in 16 (24.2%) cases and grade 1-2 neuropathy occurred in 4 (6.1%) patients (Table 2). There were 6 patients requiring hospitalization due to neutropenia and dyspnea. In this study eribulin discontinuation was not observed. We had only 2 patients who required treatment delay due to grade 4 myelosuppression and pneumonia.

Our study has some limitations that need to be acknowledged. The main weakness was that it provided data from a cohort of patients outside of clinical trials, the study groups were heterogeneous and the patients were representing the general population profile. Secondly, while we have registered the adverse events of our patients, we did not assess quality of life parameters. Finally, our study was of retrospective nature and the patient number was not sufficient to evaluate the effectiveness of eribulin in terms of some variables such as the type of molecular subtypes of breast cancer.

In conclusion, this study was the first to evaluate the efficacy and safety of eribulin in further-line chemotherapy received by MBC patients in Turkish population. We revealed that eribulin for the treatment of MBC was slightly valuable, particularly in ER-positive and HER2-positive patients, but it may not be as effective especially in triple-negative groups receiving this as late-line treatment. Its low toxicity profile compared to other intravenous cytotoxic agents and its short intravenous administration duration which does not require premedication make eribulin a preferable alternative for both physicians and patients.

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