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ORIGINAL ARTICLE

Is eribulin treatment prognostic factor in patients with metastatic breast cancer treated with this drug? Retrospective analysis of a multicentre study

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Summary

Purpose: *This study aimed to analyze prognostic factors for survival and the reliability and the effectiveness of eribulin therapy in metastatic breast cancer (MBC) patients.*

Methods: *A total of 80 patients treated with eribulin in 12 medical oncology centers in Turkey between 2013-2017 were retrospectively evaluated. Sixteen potential prognostic variables were assessed for analysis.*

Results: *The patients had received a median of 5 prior chemotherapy regimens and a median of 3 eribulin cycles for MBC. Median progression-free survival (PFS) was 5.5 months (95% Cl: 4.1-7.8) and median overall survival (OS) was 11 months (95 % Cl: 6-15). Multivariate analysis showed that eribulin treatment line was shown to have independent prognostic significance for PFS. PFS difference was demostrated in patients who received 3 chemotherapy lines for advanced disease compared to those who had more than 3 chemotherapy lines [median PFS; 3 lines: 8.6 months (6.2-11) and >3 lines: 4.6 months (3.7-4.6) p=0.00]. The clinical benefit rate (CBR) was 52.5 and 35% in patients treated with three lines and with >3 previous chemotherapeutic regimens. Most common toxicities were neutropenia (62.5%), fatigue (52.5%), alopecia (50%) and nausea (37.5%).*

Conclusions: *Eribulin treatment line was identified as indepedent prognostic factor for PFS in MBC patients.*

Key words: *metastatic breast cancer, eribulin, chemotherapy, prognostic factors, breast cancer*

Introduction

Metastatic breast cancer (MBC) is an incurable disease and optimal palliation and prolongation of life are the main goals of treatment [1, 2]. Meaningful improvements in survival have been seen with the introduction of newer systemic therapies [3]. Very few effective treatment options are available in MBC, particularly in HER2 negative and triple negative breast cancer. Anthracyclines and taxa-

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nes are the standard chemotherapeutics employed for MBC but many patients present with disease resistant to both drugs. Sequential use of single agent chemotherapy is recommended for patients with anthracycline and taxane resistant or refractory MBC and include capecitabine, gemcitabine and vinorelbine [4, 5]. Eribulin is a non-taxane microtubule inhibitor. This drug induces mitotic catastrophe leading to cell death but has also other important antitumor effects, including reversal of epithelial-mesenchymal transition (EMT) and remodeling of the tumor vasculature [6].

Eribulin is approved for the treatment of locally advanced or MBC in patients who have progressed following prior chemotherapy for advanced disease. Previous treat¬ment should include an anthracycline and a taxane in either the adjuvant or metastatic setting. Approval was based on the results of two large, randomized phase III clinical trials - EMBRACE and the 301 study [6].

EMRACE trial demonstrated OS advantage of eribulin compared to treatment of physician's choice in patients with heavily pretreated breast cancer with manageable toxicity [7]. In the study 301, eribulin showed a favorable improvement in overall survival (OS) compared with capecitabine; however, this improvement did not reach statistical significance [8].

Many factors are important in the management and prognosis of breast cancer. These factors include patient characteristics (age, performance status and menopausal status), tumor characteristics (grade, tumor size, hormone receptor status and expression of the human epidermal growth factor receptor 2 (HER2), biological subtypes) and disease characteristics (stage, localization and disease-free interval) [9].

Prior studies have demostrated that survival in breast cancer depends on several factors, such as the number and location of metastases, estrogen receptor status and performance status [10, 11]. Other factors also have a prognostic impact such as the stage of the primary disease, prior adjuvant chemotherapy, a short disease-free interval and advancing age [10-12].

Many randomized trialsshowed efficacy and safety of eribulin [13-15]. Here, the aim of the present study was to identify prognostic risk factors and to analyze the reliability and effectiveness of eribulin treatment in patients with MBC.

Methods

The medical records of patients with MBC receiving eribulin in 12 medical oncology centers in Turkey between 2013-2017 were retrospectively evaluated. All patients were previously treated with anthracyclines and taxanes for MBC.

Included in the analysis were women with histologically confirmed adenocarcinoma of the breast with distant metastases. All patients had measurable disease and adequate hematological, hepatic and renal functions and an Eastern Cooperative Oncology Group performance status of 0-2. Patient age, sex, menopausal status, histopathological features, tumor size, lymph node involvement, hormone receptor and HER2 status and treatment details were recorded.

The patients received 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) administered i.v. over 2-5 min on days 1 and 8 of a 21-day cycle. Dose reductions were made for grade 3 or 4 toxicities according to the treating physician's judgment. The treatment continued every 3 weeks until disease progression or unacceptable toxicity. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors after every third cycle of treatment.

Sixteen clinical variables were evaluated on the basis of previously published clinical trials. The variables were patient age, histology, nodal status, stage, metastatic disease at diagnosis, grade, ER, PR status, HR status, menopausal status, presence of adjuvant chemotherapy and radiotherapy, adjuvant hormonal therapy, region of recurrence, metastasis-free interval, and eribulin treatment line.

Statistics

PFS was defined as the period from the beginning of treatment until documented progression or death. OS was defined as the period from the first day of treatment until the date of last follow-up or death. 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, SD maintained for at least 3 months. The parameters identified as prognostic factors for breast cancer in previous studies were included in the model.

SPSS 18.0 software was used for statistical analyses. Univariate analysis was performed with independent samples using t-test, chi-square test and Fisher's exact test. For survival analysis, Kaplan-Meier method was used and log-rank test was performed to evaluate differences between groups. Multivariate analysis was performed using the Cox model. The parameters identified as prognostic factors for breast cancer in the univariate analysis were entered in the Cox model. P value <0.05 was considered as statistically significant.

Results

A total of 80 patients were retrospectively evaluated in 12 centers between 2013-2017. All patients (n=80) treated with eribulin were previously treated with anthracyclines and taxanes for MBC.The main patient and tumor characteristics are reported in Table 1. The median patient age was 49 years and median ECOG PS 1. All of the patients

were female and 55% (44/80) were premenopausal at the time of diagnosis.

Invasive ductal carcinoma was the most common histologic subtype (90%, n=72/80). Grade 3 tumors were observed in 40% (n=32/80) of the patients. Estrogen receptor (ER) and progesterone receptor (PR) positivity was 77.5% (n=62) and 65% (n=52), respectively (Table 1). HER2 receptor positivity and triple negative disease were 27.5% (22/80) and 12.5% (10/80), respectively.

Prior surgery and prior radiotherapy were performed in 90% (72/80) and 52.5% (42/80) patients, respectively. The proportion of patients receiving neoadjuvant chemotherapy was 67.5% (54/80). Median number of previous chemotherapy for advanced disease was 5 (3-10). The patients had received a median of 4 eribulin cycles for MBC (3-15). With regard to previous chemotherapy, all patients had received previous anthracycline and

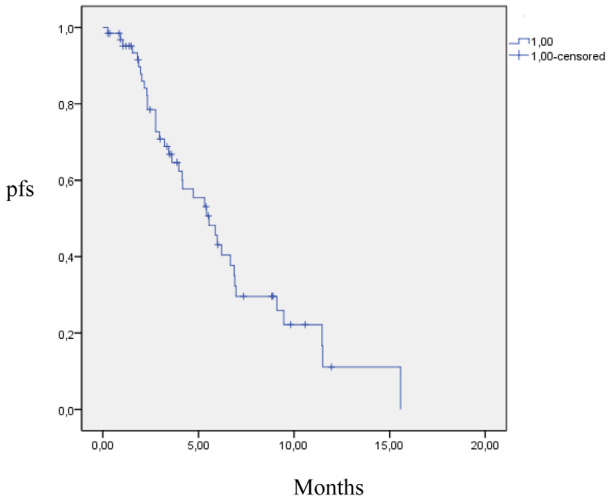

Figure 1. Progression free survival curve (PFS) in MBC patients receiving eribulin.

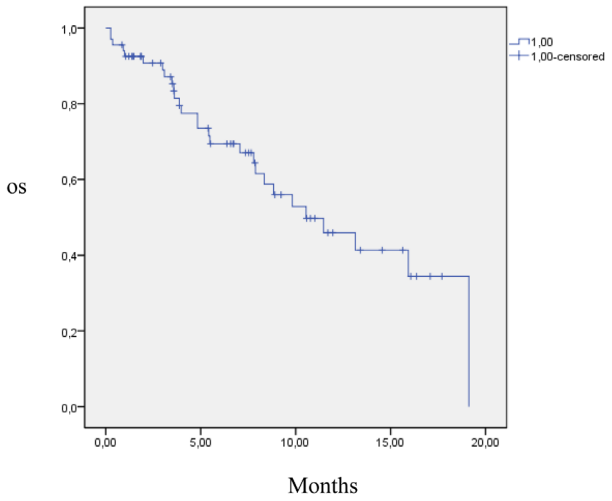

Figure 2. Overall survival curve (OS) in MBC patients receiving eribulin.

Table 1. Baseline patient characteristics

Characteristics	*Patients n (%)*
Median age	49 (26-75)
ECOG PS (median)	1
Histology	
Invasive ductal	90 (72)
Lobuler	5 (4)
Other	5 (4)
Menopausal status	
Pre	55 (44)
Post	45 (36)
Grade	
1	10 (8)
2	50 (40)
3	40 (32)
Nodal status	
N1	17.3 (9)
N2	44.3 (23)
N3	38.4 (20)
ER status	
Positive	77.5 (62)
Negative	22.5 (18)
PR status	
Positive	65 (52)
Negative	35 (28)
HER2 status	
Positive	27.5 (22)
Negative	72.5 (58)
Triple negative	12.5 (10)
Neoadjuvant chemotherapy	
Yes	67.5 (54)
No	32.5 (26)
Prior surgery	90 (72)
Prior radiotherapy	52.5 (42)
Treatment line for eribulin	
3	7.5 (6)
4	15 (12)
5	26.2 (21)
6	25 (20)
7	13.7 (11)
Other	12.5 (10)
Median prior lines of chemotherapy for MBC, median (range)	5 (2-10)
Median cycles administered, median (range)	3 (1-18)
Previous chemotherapy regimens	
Anthracyclines	65 (52)
Taxanes	75 (60)
Capecitabine	68.7 (55)
Vinorelbine	45 (36)
Gemcitabine	41.2 (33)

ER:estrogen receptor, PR:progestrone receptor, HER2:human epidermal growth factor receptor 2

taxane treatment, 65% and 75% of the patients as treatment for advanced disease, respectively. Ninety-five patients (68.7%) had also received previous capecitabine (Table1).

The median follow up time was 11 months (range 6-19). Median PFS was 5.5 months (95% Cl:4.1-7.8), median OS was 11 months (95 % Cl:6-15) (Figure 1 and 2). Median OS was 13.1 and 10 months in patients who received three lines of chemotherapy and in patients who received >3 previous lines of chemotherapy for MBC, respectively (p=0.147).PFS difference was demostrated in patients who received 3 chemotherapy lines for advanced disease compared to those who had more than 3 chemotherapy lines [median PFS; 3 lines: 8.6 months (6.2-11) and >3 lines:4.6 months (3.7-4.6) p=0.008](Figure 3). Twenty-six patients (32.5%) responded to treatment with PR and 16 (20%) had SD. CR was 0%. Thirty-eight (47.5%) patients were diagnosed with disease progression.The ORR was 32.5% and CBR was 52.5%, respectively. ORR did not differ between patients that had previously received up to three or more previous chemotherapy lines for MBC (32.5% in both groups). The CBR was 52.5% and 35% in patients treated with three lines and with >3 previous chemotherapeutic regimens.

Table 2. Multivariate analysis

Prognostic factors	*OR*	*95% Cl*	*p value*
Age	0.98	0.95-1	0.29
Histology	0.3	0.06-1.5	0.15
Nodal status	0.78	0.52-1.1	0.25
Stage	0.63	0.41-0.99	0.45
Metastatic disease at diagnosis	1.8	0.4-7.4	0.37
Grade	1.1	0.36-3.3	0.86
ER	0.48	0.19-1.2	0.13
PR	1.0	0.45-2.3	0.93
HER2	0.7	0.38-1.6	0.48
Menopausal status	0.79	0.07-8.6	0.8
Adjuvant radiotherapy	1.4	0.66-3.3	0.33
Adjuvant chemotherapy	2.1	0.79-5.7	0.13
Adjuvant hormonal therapy	1.7	0.74-4.1	0.19
Region of recurrence	2.4	0.32-17.6	0.39
Disease-free interval	1.6	0.72-3.7	0.23
Eribulin treatment line	5.0	1.8-14.1	0.002

OR: odds ratio

Table 3. Most common adverse events occurring during therapy

Adverse events	*All grades Total (n=80) n (%)*	*grade 3-4 n (%)*
Neutropenia	62.5 (50)	30 (24)
Thrombocytopenia	20 (16)	10 (8)
Anemia	32.5 (26)	6.2 (5)
Febrile neutropenia	15 (12)	5 (4)
Fatigue	52.5 (42)	12.5 (10)
Nausea	37.5 (30)	8.7 (7)
Vomiting	30 (24)	10 (8)
Diarrhea	11.2 (9)	3.7 (3)
Stomatitis	22.5 (18)	10 (8)
Alopecia	50 (40)	20 (16)
Renal toxicity	6.2 (5)	0 (0)
Elevated aminotransferase level	12.5 (10)	3.7 (3)
Neuropathy	31.2 (25)	3.7 (3)
Allergic reaction	11.2 (9)	1.2 (1)
Arthralgias	25 (20)	2.5 (2)

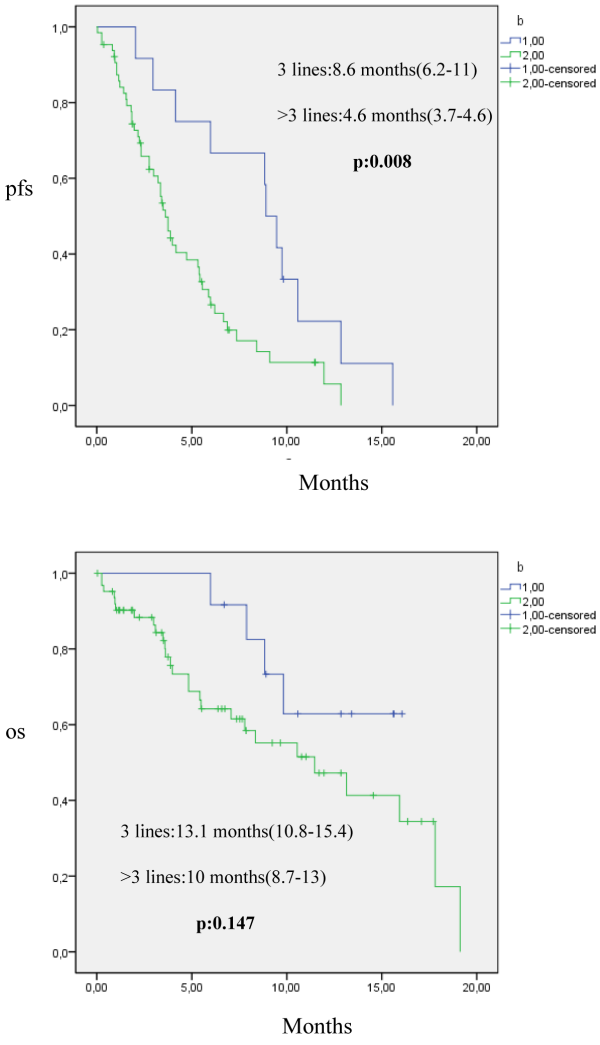

Figure 3. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) in 80 patients with metastatic breast cancer who received three versus >3 previous chemotherapies before treatment with eribulin.

The prognostic factors defined by patient age, histology, nodal status, stage, metastatic disease at diagnosis, grade, ER, PR status, HR status, menopausal status, presence of adjuvant chemotherapy and radiotherapy, adjuvant hormonal therapy, region of recurrence, disease-free interval, eribulin treatment line were analyzed using multivariate analysis. The results of the analyses are summarized in Table 2. Multivariate analysis showed eribulin treatment line was independent prognostic factor for PFS [eribulin treatment line (OR:5.95%Cl 1.8-14.1, p=0.002]. The other variables of multivariate analysis did not reach prognostic significance for PFS (Table 2).

Most common toxicities were neutropenia (62.5%), fatigue (52.5%), alopecia (50%), nausea (37.5%), anemia (32.5%) and periph¬eral neuropathy (31.2%). Toxic effects reported are shown in Table 3.The most frequent treatment-related grade 3/4 adverse events was neutropenia (30%) and alopecia (20%). Peripheral neuropathy was observed in 31.2% of the patients. Grade 3/4 peripheral neuropathy occurred in 3.7% of the patients. Neutropenic fever developed in 15% of the patients. Dose reduction was necessary for 32.5% (26/80) of the patients due to grade 3/4 toxicity. Delays of chemotherapy administration were needed in 36.2% (29/80) of the patients. No chemotherapy related toxic deaths occurred.

Discussion

Anthracyclines and taxanes are substantial chemotherapeutic agents in breast cancer, both in the adjuvant and metastatic settings. No standard therapy has been established for patients with MBC requiring third or fourth line therapy. The results of EMBRACE study showed that eribulin prolongs survival in patients with heavily treated MBC. Eribulin is effective for both prolonging life and improving the quality of life, which are the main goals in the treatment of metastatic or recurrent cancer [6].

We retrospectively performed a multicenter analysis of prognostic factors for survival and efficacy of eribulin in 80 metastatic breast cancer patients treated with eribulin. The median OS and PFS for eribulin-treated MBC was 11 and 5.5 months respectively (Figures 1 and 2). The results were slightly lower compared with the EMBRACE study (median OS=13.1 months).

Prognostic factors are important for the planning of systemic treatment and for predicting survival from therapy in breast cancer patients.This retrospective multicenter study tried to identify whether tumor, host or treatment characteristics might be of prognostic importance for survival in patients with MBC treated with eribulin. Only one independent significant prognostic factor was found in multivariate analysis: eribulin treatment line.

In this study age and stage were not found as independent prognostic factor for PFS. It is generally accepted that young age at diagnosis is associated with more aggressive disease and relative poor survival [16]. The stage at diagnosis does not reliably indicate prognosis after relapse [17]. Intrinsic biology of the primary tumor plays a critical role in determining outcome following recurrence [18]. But in our analysis, ER, PR, HER2, grade and histologywere not found as prognostic factors for PFS.

Some studies have considered adjuvant chemotherapy or axillary lymph node involvement at first diagnosis as prognostic factors for survival following first recurrence [1, 9, 17]. The results showed differences. Adjuvant chemotherapy appears to be an unfavorable independent prognostic factor for survival. It should also be considered that adjuvant chemotherapy is given to patients with high risk characteristics [18]. In this analysis, adjuvant radiotherapy, chemoterapy, hormonal therapy and nodal status were not found as prognostic factor for PFS.

As previously known, multiple or visceral site of metastasis seems to be predictor of poor specific survival with a median survival not exceeding 22 months, while nonvisceral sites such as metastatic bone disease are associated with better specific survival with a median survival of >33 months [19, 20]. In a retrospective analysis including 1038 MBC patients, it was shown that age at initial diagnosis, hormonal receptor status, site of metastasis, presence of chemotherapy, high grade and large tumor size are the most relevant prognostic factors for predicting survival from the time of metastatic occurence. In contrast, metastatic diagnosis period and metastasis-free interval appeared to have no influence on survival after recurrence [21].

In many countries, eribulin has been approved for the treatment of patients with MBC who were previously treated with at least two chemotherapy regimens, including anthracycline- and taxane-based regimens; however, in some countries such as Japan, eribulin has been approved for patients with inoperable or recurrent breast cancer, irrespective of their previous treatment history [22].

Our analysis found that eribulin treatment line is predictive for survival in patients treated with eribulin for MBC. In this analysis, patients that had received three previous chemotherapy lines compared to those who had more than 3 chemotherapy lines for MBC had a clear trend to better OS, better PFS and CBR. PFS was statistically significant

(p=0.008) (Figure 3). Gamucci et al reported a significant difference in clinical benefit in patients exposed to eribulin as third line in comparison with more advanced lines (in early line 27.3% response and 48.5% clinical benefit; in subsequent lines 15.2% response and 28.8% clinical benefit, respectively) [13]. Kessler et al reported OS difference in patients who received from one to three and in patients who received ≥4 previous lines of chemotherapy prior to eribulin for MBC (median OS 12.8 and 6.5 months, respectively p=0.06) [14]. These results support the administration of eribulin at earlier steps in MBC. However, in a retrospective study performed by Ates et al, 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, p=0.19) [23].

In a Japanese study, the efficacy of eribulin in thoσe who received the drug as a third or beyond third line treatment was comparable to those who received eribulin as first- or second-line treatment. The study showed that the survival benefit of eribulin was independent of the organs involved, previous treatment regimens or line of treatment. Eribulin might be beneficial and effective not only as a late-line but also as a front-line treatment for MBC [22]. Our analysis showed that early use of eribulin can obtain more favorable results compared with subsequent lines. Moreover, as an early-line treatment, patients can tolerate eribulin better owing to fewer treatment-related adverse effects.

Three large retrospective studies related to eribulin in MBC have been published. In these three studies, 504 patients with advanced breast cancer received eribulin. Treatment responses and adverse events were consistent with outcomes reported from pro¬spective randomized phase III trials. The pooled incidence of the most common toxicities (all grades) was fatigue (59%), neutropenia (35%), and periph¬eral neuropathy (34%); grade 3/4 neuropathy was reported in 16/504 patients (3%) [13, 15, 24]. In our analysis, eribulin-related toxicities were manageable. Grade 3/4 neutropenia and thrombocytopenia were observed in 30% and 10% patients, respectively. Hematologic side effects were acceptable and similar with other studies. Nausea and vomiting were frequently seen as non-hematologic toxicities.Febrile neutropenia was higher in our analysis, occuring in 12 (15%) patients. The most common adverse events reported in EMBRACE and 301 study were hematologic toxicities, including grade 3/4 neutropenia in 45% of the patients, but the reported incidence of febrile neutropenia across both studies was low (3%). Other common adverse events included alopecia, anemia, nausea and fatigue. Peripheral neuropathy (all grades) was reported in 31% of the patients, with grade 3/4 peripheral neuropathy in 8% of the cases [6]. In our analysis, peripheral neuropathy similarly occurred in 31.2% of the patients, with grade 3/4 3.7%.

Our analysis has some limitations. It is a retrospective multicenter study with a small sample size, which limited a strong assessment of prognostic factors.

In summary, this study shows that among the prognostic factors for MBC, eribulin treatment line is associated with survival. Moreover, this retrospective analysis confirms the efficacy and tolerability of eribulin in MBC. Therefore, this regimen should be considered during the early stages of MBC treatment.

Authors' contributions

Zeynep Oruc and M.Ali Kaplan: conception and design of study, writing of the article. Caglayan Geredeli: data analysis and interpretation.

Nilgun Yildirim Sari: Ersin Ozaslan, Aydin Aytekin, Emin Tamer Elkiran, Sinan Koca, Mutlu Dogan, Nedim Turan, Ozlem Yuce, Alper Sevinc, Ozlem Ercelep, Abdurrahman Isikdogan: data analysis and interpretation.

Conflict of interests

The authors declare no conflict of interests.

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