JBUON 2020; 25(6): 2562-2569
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy and safety evaluation of eribulin-trastuzumab combination therapy with heavily pretreated HER2-positive metastatic breast cancer

Furkan Sarici[1], Kadri Altundag[2]

[1]Istinye University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey. [2]MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey.

Summary

Purpose: *Eribulin mesylate is a non-taxane microtubule inhibitor which is a synthetic holichondrin B analog that can be used after anthracycline and taxane treatment in patients with metastatic breast cancer. We aimed to analyze the results of eribulin-trastuzumab combination in aggressively pretreated metastatic HER2-positive breast cancer patients.*

Methods: *In this single-center study, the records of 36 patients with HER-2-positive metastatic breast cancer who received at least one cycle of eribulin-trastuzumab in our clinic between 2015 and 2018 were analyzed retrospectively. Kaplan-Meier survival analysis was used for progression-free survival (PFS), and overall survival (OS) analyzes. Two-sided p values <0.05 were considered statistically significant.*

Results: *A total of 36 patients with metastatic breast cancer were eligible and included in this study. The median age of the patients was 41 years (range 20-60). Most patients were heavily pretreated with a median of 5 (range 3-8) previous chemotherapy lines before eribulin. At the end of the follow up period (February 2018) all patients received a median of 5.5 cycles of eribulin-trastuzumab. Partial response (PR) was achieved in 9 patients (25%) and stable disease (SD) in 17 patients (47%). Median PFS was 4 months (95% CI: 3.8-6.1), and median OS was 10 months (95% CI: 7.5-12.4). The most common adverse events were grade 1-2 anemia (n=12, 33%), neutropenia (n=12, 33%) and grade 3-4 neuropathy (n=4, 11.1%).*

Conclusion: *Eribulin-trastuzumab combination is an effective and safe treatment option with a low toxicity profile for aggressively pre-treated patients with metastatic breast cancer.*

Key words: *Eribulin, trastuzumab, metastatic breast cancer, efficacy, survival, HER2-positive*

Introduction

Metastatic breast cancer (MBC) is an incurable disease, with a 5-year survival rate of approximately 23% [1]. In the United States, almost 5% to 10% of women have MBC at the time of diagnosis [2]. Although the prognosis is poor overall survival (OS) for women with MBC has improved over the recent years [2,3]. A great need for treatments exists that improve OS for women with advanced or recurrent MBC [4]. Anthracycline or taxane-based chemotherapy regimens are commonly used to treat breast cancer in the neoadjuvant, adjuvant, and metastatic settings [5]. However, many patients either do not respond or become refractory to anthracyclines and taxanes during treatment [6]. There is no single standard option after the failure of these agents, but capecitabine is often used in this setting [7]. In addition, the frequency of HER2 receptor overexpression is increased among patients with metastatic disease [8].

Eribulin mesylate is a halichondrin B analogue which acts by destabilizing microtubules and inhibiting microtubule dynamics [9,10]. Antitumor

Corresponding author: Kadri Altundag, MD. MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.
Tel and Fax: +90 3122854685, Email: altundag66@yahoo.com
Received: 29/08/2020; Accepted: 25/09/2020

activity and survival benefit with eribulin had previously been demonstrated in patients with MBC who had previously received at least two chemotherapy regimens, including an anthracycline and a taxane. Eribulin is approved by the United States Food and Drug Administration (FDA) for these patients [11,12].

Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of HER2, is an essential part of the treatment for HER2-positive breast cancer [13]. A combination of trastuzumab with chemotherapeutic agents such as carboplatin, docetaxel, paclitaxel, vinorelbine, or capecitabine is effective for MBC as demonstrated by multiple clinical trials [14-17]. The efficacy of eribulin with trastuzumab was demonstrated in the first-line setting in a multicenter, phase II, single-arm study among 52 patients with recurrent or metastatic HER2-positive breast cancer . The objective response rate (ORR) was 71.2% with a median time to response (TTR) of 1.3 months, and progression-free survival (PFS) was 11.6 months. Combination of eribulin with trastuzumab resulted in a substantial tumor response with an acceptable safety profile in this study [18].

Our aim was to analyze the results of eribulin/trastuzumab combination in heavily pre-treated metastatic HER2-positive breast cancer patients.

Methods

Patients who applied to our clinic between December 2015 and December 2018 were included in the study. Patients were in the metastatic or in the recurrence processes developed after adjuvant therapy at the time of diagnosis. Patients with HER2 positive (immunohistochemically 3+ or 2+ and fluorescence in situ hybridization positive histology), and with at least three lines of chemotherapy in the metastatic process, and subsequently treated with eribulin-trastuzumab were included in the study. Eribulin mesylate was administered in a 3-week treatment cycle (1.4 mg/m^2 equivalent to 1.23 mg/m^2 eribulin) on days 1 and 8 and trastuzumab was administered at 8 mg/kg every three weeks. Patients with bone metastases continued bisphosphonate or denosumab as well. Endocrine treatment was not given concomitantly with an eribulin-trastuzumab combination. Primary granulocyte colony-stimulating factor (G-CSF) was applied only to patients with grade 3-4 neutropenia. Dose reduction was performed depending on patients' grade 3 or 4 toxicity according to National Cancer Institute-Common Toxicity Criteria for Adverse Events v 4.0.

The demographic features of patients, tumor histopathologic characteristics, previous chemotherapy lines, previous radiotherapy, site of metastases, administration of hormonal therapy before eribulin-trastuzumab treatment, treatment-related adverse effects, overall response rates (ORR), progression-free survival (PFS), and overall

Table 1. Patient demographic and baseline clinical features

Clinical feautures	*n (%)*
Age (mean)	43.3+9.9 (20-60)
Menopausal status	
Premenopausal	27 (75)
Postmenopausal	9 (25)
Histology	
IDC	29 (80.5)
ILC	2 (5.6)
Mikst IDC and ILC	4 (11.1)
Invasive micropapiller	1 (2.8)
Recertor status	
ER positive	19 (52.8)
PR positive	17 (47.2)
ER and PR negative	14 (38.9)
HER-2 positivity status	
IHC 3+	33 (91.7)
IHC 2+ and FISH(+)	3 (8.3)
ECOG PS	
ECOG 0	12 (33.3)
ECOG 1	18 (50.0)
ECOG 2	6 (16.7)
Adjuvant hormonotherapy	
Yes	20 (55.6)
No	16 (44.4)
Adjuvant radiotherapy	
Yes	25 (69.4)
No	11 (30.6)
Adjuvant chemotherapy	
Anthracycline only	9 (25.0)
Anthracycline plus Taxane	21 (58.3)
Other (CMF, etc)	6 (16.7)
Neoadjuvant chemotherapy	
Yes	5 (13.9)
No	31 (86.1)
Site of metastases	
Bone	25 (69.4)
Lung	22 (61.1)
Liver	20 (55.6)
Brain	16 (44.4)
Scin	2 (5.6)
Metastatic chemotherapy lines	
3 line	8 (22.2)
4 line	9 (25.0)
5 line	4 (11.1)
6 line	6 (16.7)
7 line	7 (19.4)
8 line	2 (5.5)
Metastatic treatments	
Taxane	29 (80.6)
Gemcitabine	20 (55.6)
Capecitabine	28 (77.8)
Vineralbine	26 (72.2)
CMF	2 (5.5)

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ER: estrogen receptor, PR: progesterone receptor, Her-2: human epidermal growth factor 2 receptor IHC: immunohistochemistry, FISH: floresan in situ hibridisation, ECOG PS: Eastern Cooperative Oncology Group performance status

survival (OS) were recorded. Radiological and clinical evaluations were made for efficacy analysis. Imaging assessment was performed at 2-3 monthly intervals. Tumor response evaluation was made according to RECIST criteria version 1.1. Adverse events were registered retrospectively according to the standard terminology criteria for adverse events, version 4.0.

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-trastuzumab 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 multivariate 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. The objective response rate (ORR) was defined as the sum of partial response (PR) and complete response (CR). The clinical benefit rate (CBR) was defined as the sum of PR, CR, and SD. In all assessments, a p value <0.05 was considered as statistically significant. SPSS 18.0 software package was used for statistical analyses of the data.

Table 2. Efficacy outcomes

	All: 36 (100%) n (%)	*HR(-) (n=14) n (%)*	*HR(+) (n=22) n (%)*
ORR	9 (25.0)	3 (21.4)	6 (27.3)
CR	0 (0)	0 (0)	0 (0)
PR	9 (25.0)	3 (21.4)	6 (27.3)
SD	17 (47.2)	7 (50.0)	10 (45.4)
PD	10 (27.8)	4 (28.6)	6 (27.3)

CR: complete response, PR: partial response, ORR: objective reponse rates defined as CR+PR, SD: stabile disease, PD: progressive disease, HR: hormone receptor

Results

Thirty-six patients who received eribulin-trastuzumab treatment were registered. The median age of the patients at the time of diagnosis was 43.3 years (range 20-60). 75% of the patients were premenopausal, 80.5% had invasive ductal carcinoma histology, 52.8% were estrogen receptor-positive, 47.2% progesterone receptor-positive, and 38.9% hormone receptor-negative. The majority of patients had previously received adjuvant (n=20, 55.6%) or neoadjuvant (n=5, 13.9%) chemotherapy before they were diagnosed with metastases. In most of the patients, Eastern Cooperative Oncology Group performance status (ECOG PS) was 0-1 (n=30, 83.3%). 36% of the patients were metastatic at the time of diagnosis and they had taken a median number of five lines (range 3-8) of chemotherapy. The fourth, fifth, sixth, and seventh lines of eribulin treatments were 25.0, 11.1, 16.7, and 19.4%, respectively. Bone metastasis was present in 25 patients (69.4%), lung metastasis in 22 (61.1%), brain metastasis in 16 (44.4%), and liver metastasis in 20 (55.6%). Patient demographic and baseline clinical characteristics are given in Table 1.

At the end of the follow-up period, patients had received a median number of 5.5 cycles (range 2-16) of eribulin-trastuzumab. Nine patients (25.0%) responded to treatment with PR, and 17 (47.2%) had SD. There was no difference in treatment response rates between hormone receptor-positive and negative patients (Table 2). Median PFS was 4 months (95% CI: 3.8-6.1), and median OS was 10 months (95% CI: 7.5-12.4). No PFS or OS difference was demonstrated between patients who received 1-4 chemotherapy lines and those who had more than 4 chemotherapy lines. Median OS was 9 months (3.6-14.3) for 1-4 line and 11 months (6.9-13.3) for more

Table 3. OS analysis in selected subgroups of patients

	n	*Events*	*Median OS (months)*	*p value*
All patients	36	30	10 (7.5-12.4)	
HR(+)	22	16	10 (6.3-13.6)	0.90
CT line				
1-4	17	15	9 (3.6-14.3)	
>4	19	15	11 (6.9-13.3)	
Liver	20	18	9 (5.8-12.1)	0.18
Brain	16	15	9 (3.1-14.8)	0.20
Lung	22	18	9 (4.6-13.4)	0.57
Visceral				0.23
1	26	22	10 (7.6-12.3)	
0	8	6	15 (1.2-40.7)	0.44

HR: hormone receptor, CT: chemotherapy, OS: overall survival

Table 4. PFS analysis in selected subgroups of patients

	n	*Events*	*Median PFS (months)*	*p value*
All patients	36	23	4 (3.8-6.1)	
HR(+)	22	14	5 (3.4-6.6)	0.16
CT line				
1-4	17	12	4 (2.5-5.4)	
>4	19	11	5 (2.5-7.4)	
Liver	20	11	3 (0.8-5.1)	0.10
Brain	16	11	5 (3.8-6.2)	0.91
Lung	22	12	4 (1.8-5.4)	0.92
Visceral				0.84
1	26	15	5 (2.5-7.4)	
0	8	6	4 (1.0-8.9)	0.30

HR: hormone receptor, CT: chemotherapy, PFS: progression free survival

Table 5. Eribulin treatment-related adverse events

Adverse events	*Grade 1-2* *n (%)*	*Grade 3-4* *n (%)*	*Total* *n (%)*
Anemia	12 (33.3)	2 (5.6)	14 (38.9)
Neutropenia	12 (33.3)	2 (5.6)	14 (38.9)
Thrombocytopenia	1 (2.8)	1 (2.8)	2 (5.6)
G-CSF usage	NA	NA	5 (13.9)
Transaminase elevation	10 (27.8)	1 (2.8)	11 (30.6)
Neuropathy	1 (2.8)	4 (11.1)	5 (13.9)
Dose reduction	NA	NA	4 (11.1)
Hospitalization	NA	NA	4 (11.1)
Treatment discontinuation	NA	NA	1 (2.8)

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

than 4 lines of chemotherapy (p=0.18). Metastatic localization and the presence of visceral metastasis were seen not to have a significant effect on PFS and OS (Tables 3,4).

Treatment tolerance was generally acceptable. No hypersensitivity reaction or toxic death were observed. The most common adverse events were grade 1-2 anemia (n=12, 33.3%), neutropenia (n=12, 33.3%), and grade 3-4 neuropathy (n=4, 11.1%). Four patients were admitted to the hospital during eribulin-trastuzumab treatment. One patient was hospitalized for febrile neutropenia, two patients with respiratory failure due to lung metastases, and one patient due to liver failure. Four patients (11.1%) required a dose reduction due to toxicity. G-CSF application was needed in 5 patients (13.8%) due to neutropenia or febrile neutropenia. Treatment was discontinued due to grade 4 neutropenia in only one patient during eribulin-trastuzumab treatment.

Discussion

In this single-center retrospective study, it was shown that the combination of eribulin and trastuzumab is a tolerable and effective treatment alternative in HER2-positive MBC patients, progressing following several sequential chemotherapy treatments. In this study, the efficacy of the combination of eribulin and trastuzumab was determined as PR 25%, CR 0%, ORR 25%, median PFS 4 months, and median OS 10 months. Patients tolerated the treatment well, and no allergic reactions or toxic deaths were observed in the patients in this study.

Eribulin mesylate is a synthetic halichondrin B analog and is a microtubule inhibitor that is not available in taxane structure. In many phases II and III studies, the efficacy of eribulin has been proven in advanced-stage MBC patients progressing after anthracycline and taxane treatment [11,19]. Compared with other intravenous cytotoxic agents and

the short intravenous administration time that does not require premedication, the low toxicity profile makes eribulin a preferred alternative for both clinicians and patients. After understanding the efficacy of eribulin in advanced metastatic breast cancer, many studies were conducted investigating its efficacy in MBC subtypes [20,21].

The EMBRACE study was the first study in which the significant survival advantage of eribulin in MBC was shown [22]. In this study, patients with MBC progression after anthracyclines and taxanes were randomized into two groups. One group received eribulin 1.4 mg/m^2 chemotherapy on the 1st and 8th days, and the other group was given physician-preferred chemotherapy protocol. Both groups were compared in terms of objective response rate, overall survival, and time to progression. Median OS was 13.1 months in patients treated with eribulin and 10.6 months in the other group (HR 0.81, 95% CI 0.66-0.99; p=0.041). Despite the improvement in OS, the median PFS was 3.7 months in the eribulin group and 2.2 months in the other group, without statistical significance between the two groups (p=0.137). The objective response rate (ORR) was significantly higher in patients treated with eribulin than the treatment chosen by the physician (12% vs. 5%; p=0.002).

In the second phase III study [23] examining the efficacy of eribulin, eribulin mesylate and capecitabine were compared in patients with MBC who were previously treated with anthracyclines and taxanes. Patients included in this study often received one or more (maximum 3) chemotherapy regimens for advanced disease. In this phase III study, although there was a trend of improvement in OS in patients treated with eribulin (15.9 vs. 14.5 months, p=0.056), there was no statistical significance. PFS was similar in both groups (4.1 months vs. 4.2 months p=0.736).

To provide further information on the efficacy of eribulin in HER2-negative or HER2-positive patients, the European Medicines Agency (EMEA) requested a pooled analysis of both phase III studies. In this pooled analysis, a total of 1062 patients were randomized to the eribulin group and 802 patients to the control group [19]. The mean survival was 15.2 months in the eribulin group and 12.8 months in the control group (HR 0.85, 95% CI 0.77, 0.95; p=0.003). In HER2-negative patients, the median OS was 15.2 months in the eribulin group and 12.3 months in the control group (HR 0.82; p=0.002). A difference of 2.9 months was found in OS, which was statistically significant. However, this effect was not statistically significant in HER2-negative but hormone-receptor-positive patients (p=0.060). Median survival in HER2-positive patients was higher in the eribulin group but was not statistically significant (13.5 vs. 12.2 months; HR 0.82; p=0.135). However, the number of patients was smaller in this subgroup than in the HER2-negative group (HER2-positive, eribulin n=169, control n=123; HER2-negative, eribulin n=748, control n=572). In patients with triple-negative disease, the median survival was longer than 4.7 months in patients treated with eribulin. In this pooled analysis, statistical insignificance in the HER2- positive patient was associated with a small number of patients.

Although eribulin did not provide a statistically significant survival benefit in HER2-positive breast cancer patients in the above-pooled analysis, phase II studies were performed in this group with the combination of eribulin and trastuzumab plus pertuzumab or only trastuzumab, and promising results were obtained [9-13]. In addition, many retrospective studies have shown that it has acceptable efficacy in HER2-positive MBC groups who received at least two-line treatment and progressed [25,26].

According to current treatment guidelines, the standard first-line treatment of HER2-positive MBC is the combination of trastuzumab-pertuzumab and a taxane [27]. In the second line, the standard treatment is trastuzumab-emtansine, and in the next lines, the treatment is trastuzumab combined with single-agent chemotherapy or lapatinib-capecitabine combination [28,29]. A multicenter Japanese phase II study was conducted based on the hypothesis that eribulin was superior to docetaxel in terms of safety and tolerability and allowed longer triple therapy [24]. In this study, the efficacy and safety of the eribulin-trastuzumab-pertuzumab (ETP) regimen (eribulin 1.4 mg/m^2 days 1 and 8 / every 21 days, trastuzumab and pertuzumab every 21 days on day 1) was investigated as first-line therapy in HER2-positive MBC patients. Twenty-five patients with a mean age of 57 years were included in the study. In that study, ETP treatment exhibited efficacy variables equivalent to those in the CLEOPATRA baseline study [27]: Objective response rates and mean PFS values were respectively 80.0% (n=20) in ORR ETP, 80.2% (n=275) in CLEOPATRA study, mean PFS ETP 23.1 months, 18.5 months in CLEOPATRA. While the mean number of chemotherapy cycles was 10 in the ETP study, it was 8 in the CLEOPATRA study. The researchers attributed the good clinical results to the study design as a first-line treatment for this patient population, the administration of eribulin, a drug with proven efficacy in clinical studies, to patients who did not use the drug before and the higher eribulin exposure than docetaxel. In this

study, the incidence of reduction in neutrophil count (all grades) (32.0%) was significantly lower than in the CLEOPATRA study (52.8%). The median relative dose intensity (RDI) for eribulin was 96.4%, indicating that most patients received the planned dose of 1.4 mg/m^2 on days 1 and 8 of the 21-day cycle. ETP treatment resulted in a decrease in grade 3/4 neutrophil count (28.0%) without causing febrile neutropenia. In general, 30% of patients treated with microtubule targeted chemotherapy agents, including taxanes and epothilones, had severe (3rd to 4th grade) peripheral neuropathy. In this study, the incidence of grade 3 sensory peripheral neuropathy, grade 4 sensory and motor peripheral neuropathy, and febrile neutropenia were as low as 4% (1/25 patients), 0% (0/25 patients), 0 (0/25 patients), respectively. In a Japanese study, the incidence of neuropathy was particularly notable, given the potential contribution of the median 10 cycles of eribulin to cumulative neuropathic toxicities compared to the median 8 cycles of docetaxel in the CLEOPATRA study. Triple therapy consisting of eribulin, trastuzumab, and pertuzumab provided a high ORR, long-term PFS, and an acceptable safety profile. Therefore, ETP therapy was considered to be a potentially important first-line treatment alternative for HER2-positive patients. The EMERALD trial, a phase III taxane controlled clinical trial of eribulin, trastuzumab, and pertuzumab in Japan, is ongoing [30].

In another single-arm, open-labeled, phase II study [31], 30 HER2-positive MBC patients who had previously received taxanes and trastuzumab were treated with eribulin in combination with pertuzumab and trastuzumab. The median number of chemotherapy regimens received by metastatic patients before ETP treatment was 3.5 (range 1-9), and the median age of patients was 58 years (range 31-76). The pharmacokinetic parameters of eribulin in this combination were similar to previous reports of eribulin monotherapy. In this study, the ORR was 34.8% (95% CI:16.4-57.3, n=23) and the median PFS was 42.6 weeks (95% CI:20.3-51.9, n=30). The clinical benefit rate was 60.9% (95% CI:16.4-57.3). No symptomatic cardiac dysfunction was observed in any patient. The most common grade 3-4 side effect was neutropenia in 20 patients (66.7%). The dose of eribulin had to be reduced in 27 patients due to adverse events, particularly grade 3 neutropenia.

There are many studies in the literature examining the efficacy of eribulin and trastuzumab in patients with HER2-positive MBC in the first or next lines. In a multicenter, phase II, single-arm Japanese study evaluating the first-line efficacy of eribulin and trastuzumab in HER2-positive MBC patients, 28 patients (median age 62.5 years) received a median of 12 cycles (range 2-53) of eribulin and trastuzumab. The response rate (RR) was 53.6% (complete response 4; partial response 11), median PFS was 344 days. The clinical benefit rate was 64.0%. Grade 3 and 4 side effects were observed in 12 patients (42.9%). In this study, neutropenia in 8 (28.6%) patients, peripheral neuropathy in 2 (7.1%) patients, interstitial pneumonia in 1 (3.6%) patient, ALT elevation in 1 (3.6%), jaw osteonecrosis in 1 (3.6%) patient, and fatigue in 1 (3.6%) patient were detected. No symptomatic congestive heart failure was observed [32].

In another multicenter phase II, single-arm Japanese study [18], 52 patients with recurrent or metastatic HER2-positive MBC who received eribulin with trastuzumab in first-line therapy were evaluated. ORR was 71.2%, duration of response and PFS were 11.1 and 11.6 months, respectively. Patients received a median of 10 cycles of eribulin and 11 cycles of trastuzumab. The most common grade 3/4 adverse events were neutropenia in 20 (38.5%) patients, grade 3 peripheral neuropathy in 14 (26.9%) patients, fatigue in 4 (7.7%), and febrile neutropenia in 4 (7.7%). In another retrospective analysis from Italy [25], the efficacy of eribulin and trastuzumab in 24 HER-2 positive MBC patients who progressed after multi-step treatment the ORR was 41.7% and the clinical benefit ratio (CBR) 79.2%. In the study, one patient had CR, 9 patients had PR, 9 patients had SD, and 5 had progressive disease. In this study, the median number of chemotherapy patients received before the eribulin + trastuzumab treatment was 3. Median PFS was 5.4 months (range 1-10.5), and the median OS was 8 months (range 1.3-14.8).

In a study conducted by Ates et al [26] in Turkish patient population, median PFS was 5 months (95% CI: 4.1-5.8), and median OS was 8 months (95% CI: 6.0-9.9) in patients with MBC who progressed after many eribulin and trastuzumab treatments. Fifteen patients (22.7%) responded to treatment with PR, and 36 (54%) patients had SD. In this study, there were 11 HER2-positive MBC patients. At the time of the study, PR was 27.3% in 3/11 patients in this group whose OS was not reached yet. The PFS in this group was 5 months (range 3.4-6.6). In this study, in which the efficacy and safety of eribulin and trastuzumab were re-evaluated by adding 25 new HER2-positive MBC patients to 11 patients during the follow-up period, the PR rate was 25%, ORR 25%, CBR 72.2%, median PFS 4 months, and median OS 10 months. The median number of chemotherapy patients received before eribulin and trastuzumab was 5 (range 3-8) ,higher than in the Italian study. In our study, the lower re-

sponse rate was attributed to the patients receiving eribulin and trastuzumab at later stages. However, compared with the Italian study, the survival rate in our patient series was found to be higher, 10 months versus 8 months.

The side effects of eribulin are generally well tolerated and manageable. Fatigue, myelosuppression, and peripheral neuropathy are characteristics that are the most common side effects of microtubule destabilizing agents that do not usually require hospitalization [11,19,33,34]. The side effects of eribulin observed in our study were similar to those of other studies' side effects. The most common grade 3-4 side effects were neuropathy 11.1%, and myelosuppression 5.6%. GCSF was applied to 13.9% of the patients, and dose reduction was performed in 11.1% of the patients. Treatment was discontinued in only one patient because of grade 4 neutropenia. No allergic reaction was observed in any of the patients during and after the infusion. This study has some limitations that should be emphasized. The main limitation was that it provided data from a group of patients out of clinical trials, the study group was inhomogeneous, and patients represented the general population profile. Secondly, we did not evaluate the quality of life parameters while recording our patients' side effects. Finally, the retrospective nature of our study and the small number of patients were important limitations of this study.

Conclusion

Eribulin is an effective and safe treatment alternative when used with HER2-blocking monoclonal antibodies in HER2-positive MBC patients. While the response rate in the primary stage is 80%, it shows 20% efficiency even when used in very advanced stages. In countries where necessary treatment modalities such as pertuzumab and TDM1 are not available, it can be used safely in combination with trastuzumab both in the first-line treatment and subsequent lines of HER 2-positive MBC patients. This efficacy and safety have been demonstrated in the Turkish patient population. This efficacy and safety should be demonstrated in randomized controlled trials with a higher number of patients in the future.

Conflict of interests

The authors declare no conflict of interests.

References

1. American Cancer Society (2011). Breast cancer facts & figures 2011-2012.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Breast. Available at: http://seer.cancer.gov/statfacts/html/breast.html. Accessed January 14, 2014.
3. Jordan MA, Kamath K. How do microtubule-targeted drugs work? An overview. Curr Cancer Drug Targets 2007;7:730-42.
4. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. Adv Exp Med Biol 2007;608:1-22.
5. Andreopoulou E, Sparano JA. Chemotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer: An overview. Curr Breast Cancer Rep 2013;5:42-50.
6. Colozza M, de Azambuja E, Personeni N, Lebrun F, Piccart MJ, Cardoso F. Achievements in systemic therapies in the pregenomic era in metastatic breast cancer. Oncologist 2007;12:253-70.
7. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology Breast Cancer Version 3. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf
8. Lund MJ, Butler EN, Hair BY et al. Age/race differences in HER2 testing and in incidence rates for breast cancer triple subtypes: a population-based study and first report. Cancer 2010;116:2549-59.
9. Aicher TD, Buszek KR, Fang FG et al. Total synthesis of halichondrin B and norhalichondrin B. J Am Chem Soc 1992;114:3162-4.
10. Jordan MA, Kamath K, Manna T et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005;4:1086-95.
11. Vahdat LT, Pruitt B, Fabian CJ et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2009;27:2954-61.
12. Eisai Inc. (2012) Halaven (eribulin mesylate) injection [prescribing information]. Eisai Inc., Woodcliff Lake
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Breast Cancer. Fort Washington, PA: National Comprehensive Cancer Network; 2014.
14. Redana S, Donadio M, Nole F et al. Trastuzumab with either docetaxel or vinorelbine as first-line treatment for patients with HER2-positive advanced breast

cancer: a retrospective comparison. BMC Cancer 2010;10:28.

15. Wardley AM, Pivot X, Morales-Vasquez F et al. Randomized phase II trial of firstline trastuzumab plus docetaxel and capecitabine compared with trastuzumab plus docetaxel in HER2-positive metastatic breast cancer. J Clin Oncol 2010;28:976-83.
16. Tonyali O, Benekli M, Berk V et al. Efficacy and toxicity of trastuzumab and paclitaxel plus capecitabine in the first-line treatment of HER2-positive metastatic breast cancer. J Cancer Res Clin Oncol 2013;139:981-6.
17. Moulder S, Li H, Wang M et al. A phase II trial of trastuzumab plus weekly ixabepilone and carboplatin in patients with HER2-positive metastatic breast cancer: an Eastern Cooperative Oncology Group Trial. Breast Cancer Res Treat 2010;119:663-71.
18. Wilks S, Puhalla S, O'Shaughnessy J et al. Phase 2, multicenter, single-arm study of eribulin mesylate with trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. Clin Breast Cancer 2014;14:405-12.
19. Twelves C, Cortes J, Vahdat L et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat 2014;148:553-61.
20. McIntyre K, O'Shaughnessy J, Schwartzberg L et al. Phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic human epidermal growth factor receptor 2-negative breast cancer. Breast Cancer Res Treat 2014;146:321-8.
21. Pizzuti L, Krasniqi E, Barchiesi G et al. Eribulin in Triple Negative Metastatic Breast Cancer: Critic Interpretation of Current Evidence and Projection for Future Scenarios. J Cancer 2019;10:5903-14.
22. Cortes J, O'Shaughnessy J, Loesch D 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;377:914-23.
23. Kaufman PA, Awada A, Twelves C et al. A phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. J Clin Oncol 2015;33:594-601.
24. Inoue K, Ninomiya J, Saito T et al. Eribulin, trastuzumab, and pertuzumab as first-line therapy for patients with HER2-positive metastatic breast cancer: a phase II, multicenter, collaborative, open-label, single-arm clinical trial. Invest New Drugs 2019;37:538-47.
25. Lutrino ES,Orlando L, Febbraro A et al. Eribulin plus trastuzumab in pretreated HER2-positive advanced breast cancer patients: safety and efficacy. An Italian experience. Tumori 2020;106:301-5.
26. Ates O, Babacan T, Kertmen N et al. Efficacy and safety of eribulin monotherapy in patients with heavily pretreated metastatic breast cancer. JBUON 2016;21:375-81.
27. Baselga J, Cortés J, Kim SB et al. CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
28. Verma S, Miles D, Luca G et al. EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
29. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-92.
30. Yamashita T, Masuda N, Saji S et al. Trastuzumab, pertuzumab, and eribulin mesylate versus trastuzumab, pertuzumab, and a taxane as a first-line or second-line treatment for HER2-positive, locally advanced or metastatic breast cancer: study protocol for a randomized controlled, non-inferiority, phase III trial in Japan (JBCRG-M06/EMERALD). Trials 2020;21:391.
31. Araki K, Fukada I, Yanagi H et al. First report of eribulin in combination with pertuzumab and trastuzumab for advanced HER2-positive breast cancer. Breast 2017,35:78-84.
32. Sakaguchi K, Nakatsukasa K, Koyama H et al. Phase II Clinical Trial of First-line Eribulin Plus Trastuzumab for Advanced or Recurrent HER2-positive Breast Cancer. Anticancer Res 2018;38:4073-81.
33. Ates O, Sunar V, Aslan A, Karatas F, Sahin S, Altundag K. The short-term safety of adjuvant paclitaxel plus trastuzumab - A single centre experience. JBUON 2017;22:320-4.
34. Oruc Z, Kaplan MA, Geredeli C et al. Is eribulin treatment prognostic factor in patients with metastatic breast cancer treated with this drug? Retrospective analysis of a multicentre study. JBUON 2020;25:641-7.