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Use of Eribulin mesylate as second-line therapy in elderly patients with HER/2 negative metastatic breast cancer (MBC): efficacy, tolerability and Quality of Life

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Abstract. – OBJECTIVE: Eribulin mesylate (Halaven®) is a non-taxane inhibitor of microtubule indicated as monotherapy in patients with metastatic breast cancer (MBC), which progresses after anthracycline and taxanes therapy. In this retrospective observational study, we want to evaluate the efficacy of Eribulin in elderly women with MBC pretreated with anthracyclines and taxanes.

PATIENTS AND METHODS: 40 elderly patients > 70 years of age were enrolled, and the median age was 76 years (range 70-82). Overall survival (OS), Progression Free Survival (PFS), Objective Response Rate (ORR) were primary endpoints, tolerability, carcinoembryonic antigen levels 15.3 (Ca 15.3), before and after treatment, and Quality of Life (QoL) were secondary endpoints.

RESULTS: Eribulin treatment was well tolerated, produced a good level of disease control, a manageable toxicity profile and a significant impact on QoL. Median OS was 12.8 months and median PFS was 3.2 months. A significant correlation was observed between reduction of Ca 15.3 and PFS with a value of 0.59 ($p = 0.002$).

CONCLUSIONS: Despite a limited number of patients and a modest manageable toxicity, Eribulin is a chemotherapy treatment that has showed to be an effective and well-tolerated therapeutic option in elderly patients with MBC. Further analysis should focus on the elderly patients in our setting of study.

Key Words:
Halaven, Metastatic breast cancer, Elderly patients, Survival, Ca 15.3, Quality of life.

Introduction

Breast cancer is the most diagnosed neoplasm and the main cause of death in female population, both in industrialized and developing countries. 30% of breast cancer patients are diagnosed over 70 years old and recent data suggest a continuous increase in older women[1]. The probability of developing breast cancer is 2.3% up to 49 years, 5.4% between 50 and 69 years old, and 4.5% between 70 and 84 years old[2]. Therapeutic objective in elderly patients with metastatic breast cancer (MBC) is palliative and mainly consists of controlling symptoms, prolonging survival and improving Quality of Life (QoL)[3,4]. Anthracyclines and taxanes are the most commonly used drugs in MBC and after their failure, there aren't gold standard of cure. In elderly patients, single agent therapy is generally preferred to poly-chemotherapy, because this is associated at multiple side effects[5,6]. Eribulin (Eisai GmbH, Frankfurt, Germany) is an irreversible microtubule growth inhibitor, no taxane, with a new mechanism that blocks mitosis in G2-M phase, inducing apoptosis[7-9]. In EMBRACE trial, Eribulin treatment conferred a significant survival advantage compared with treatment of physician's choice (TPC) with a manageable toxicity profile. The Embrace study demonstrated a significant prolongation of overall survival with good tolerability in MBC. The median overall survival in patients treated with Eribulin was 13.2 months *vs.* 10.6 months

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in control arm (p = 0.04), with other treatment of physician's choice with 19% reduction in mortality risk (HR 0.81, 95% CI 0.66-0.99). Furthermore, the drug has been shown to offer significant benefits also in terms of progression free survival (3.7 months *vs.* 2.2) and the overall response rate (12.2% *vs.* 4.7%). Age is not a potential factor in increasing toxicity or reducing Eribulin efficacy. Eribulin improved overall survival with manageable toxicity in elderly patients with MBC. Therefore, age alone should not preclude consideration of Eribulin for patients > 70 years of age[10,11,5]. Despite the high incidence of this disease in older women, the number of clinical studies conducted specifically for this population unfortunately remains limited. The current therapeutic approach for elderly patients with MBC is very similar to that of younger patients. Eribulin has been shown to be effective in prolonging the survival of elderly patients with MBC HER2 negative, with manageable toxicity. A post-hoc analysis, the ESEMPiO study, in older patients with MBC, could benefit of Eribulin treatment in a similar way than their younger counterparts. The efficacy of Eribulin treatment in older patients was similar to that reported for overall ESEMPiO population with an OS to 11.6 months and PFS to 4.1 months[12-14].

Study Design

This retrospective observational study was conducted to evaluate therapeutic benefits and tolerability profiles of Eribulin in elderly patients with MBC after the failure of anthracyclines and taxanes. Overall Survival (OS), Progression Free Survival (PFS), Objective Response Rate (ORR), were primary endpoints, tolerability, reduction of Carcinoembryonic Antigen 15.3 (Ca 15.3) levels, before and after treatment, and Quality of Life (QoL) were secondary endpoints. The research was conducted in accordance with the principles of Helsinki Declaration and good clinical practice guidelines and all patients enrolled provided written informed consent.

Patients and Methods

Patients' Selection

This study was approved by the Ethics Committee Palermo 1. In this study, we enrolled a total of 40 patients with over age of 70 years, and diagnosed with MBC between Jun 2018 and Jun 2019. All patients enrolled in the study provided written informed consent and were selected according to the following inclusion criteria: 1) histological or cytological confirmed breast cancer with measurable or evaluable disease; 2) unresectable stage IV cancer pretreated with conventional anthracycline and taxanes therapies; 3) age over 70 years old; 4) performance score status between 0 and 1 according to the Eastern Cooperative Oncology Group (ECOG); 5) life expectancy of > 3 months; 6) regular heart function with left ventricular ejection fraction at rest (LVEF) > 50% and sinus rhythm on the Electrocardiogram (ECG); 7) clinical or radiological evidence of metastatic measurable disease by spiral computer tomography (CT) scan or magnetic resonance imaging (MRI) scan, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with a number of lesions ≥ 1; 8) with the following laboratory results: neutrophils 2.0×10^9/L; platelets 100×10^9/L; hemoglobin 10 g/dL; creatinine, 1 mg/dL, the upper limit of the standard (ULN); creatinine clearance > 60 mL/min if creatinine was above the indicated limit; bilirubin, 1×ULN; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 5×ULN; and alkaline phosphatase, 5×ULN (except in presence of bone metastases). Patients with asymptomatic central nervous system metastases were approved, and treatment with surgery or radiation therapy of brain lesions should have been completed no more than 3 months before study entry. As in previous studies[15-17], exclusions criteria were as follows: 1) patients hypersensitive to Eribulin and its excipients or to other components of formulation; 2) patients with a diagnosis of other malignancies, with exception of skin basal cell carcinoma, adequately treated; 3) patients with symptomatic brain metastases; 4) patients presenting severe co-morbidities not adequately controlled by other ongoing therapies (e.g. liver disease, diabetes, infections, heart disease, etc.). Other concomitant anticancer therapies were not admitted, and radiotherapy to extracranial sites or hormonal therapy should have been terminated at least 1 month before starting Eribulin treatment.

Method of Administration

All patients received Eribulin 1.23 mg/m^2 intravenously over 2-5 minutes, on days 1 and 8 of each 21-day cycle[13]. Dose reduction (0.62 mg/m^2) has been performed to manage treatment related toxicity; discontinuation occurred with unmanageable toxicity. Patients were premedicated at least thirty minutes before infusion, with steroid (dexamethasone sodium phosphate), antiemetic, antihistamine and with H_2 antagonists. Further-

more, during the entire treatment period, adequate hydration was advised to patient in order to prevent complications such as renal failure. Treatment was given until disease progression or the development of unacceptable toxicity or patient rejection. Basic laboratory assessments were made 14 days before enrollment and during the treatment. Grade 3 or 4 toxic effects were managed with dose modifications or delaying days of drug infusion and according to clinical practice procedures. Therapy was postponed for up to 2 weeks if neutrophil count was < 1.5×10^9/L prior or if platelet count was < 100×10^9/L, if hemoglobin level was < 8.5 g/dl, or if bilirubin and/or aminotransferase levels were > 1.5×ULN. In the case of neutropenia (G3-G4) G-CSF under the skin was also administered in advance. In the case of anemia (G4) blood transfusions were performed or, in less severe cases (G2-G3) erythropoietin vials under skin, and finally for major thrombocytopenia (G2-G3) steroid therapy or (G4) intravenous platelet infusion. Concomitant treatments that did not interfere with the evaluation of Eribulin, such as bisphosphonates or denosumab, were administered. Electrocardiogram (ECG) with QT interval measurement was repeated on day 8, every three cycles; hematological and chemical investigations were performed on first day and repeated on day 8 and day before next cycle. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal.

Evaluation on Response and Toxicity

Evaluation of response rate in terms measurable pathology reduction, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)[18], was conducted at beginning of treatment, and every 3 months until disease progression. The spiral CT scan, with and without contrast medium, was performed before the start of treatment, every three months until disease progression, or a presumed clinical progression. Total body bone scintigraphy was always performed before treatment and a physician discretion or patient characteristics, every six or twelve months. PET total body was performed at the oncologist discretion or any suspected disease progression. In the case of brain metastases, a magnetic resonance imaging (MRI) was performed every 6-12 weeks. Ca15.3 was determined before the treatment thereafter every three months. Furthermore, was evaluated the response percentage in terms of Ca 13.5, enzyme reduction by comparing the mean scores of serum Ca 15.3 levels, before and at treatment end. The Ca15.3 progression was considered as: an increase of Ca15.3 ≥ 25% compared to the baseline values, in those patients who did not obtain a significant reduction (≥ 50%) of the serum Ca15.3 levels during treatment; an increase of ≥ 50% of the lowest level observed in patients who achieved a significant reduction (≥ 50%) of serum Ca15.3 levels during treatment. Treatment continued until the clinical benefit was observed or until treatment was no longer tolerated. Treatment-related toxicity (DRT) and side effects were assessed at the end of each cycle and reported in line with the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Quality of Life Value

QoL was routinely assessed to all patients, at start of treatment and at first follow-up, through the administration of a questionnaire by psycho-oncologist. The questionnaire EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer)[14] is composed of both multi-item scales and single-item measures. There are five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and six single items (dyspnea, loss of appetite, insomnia, constipation, diarrhea and perceived financial impact of the disease). A higher scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 24.0 for Mac (IBM Corp., Armonk, NY, USA). Standard descriptive statistics were useful for providing a clinical data representation and distribution of all variables. The normality of distribution was checked using the univariate skewness and kurtosis indices with an acceptance threshold equal to 1. All the variables were conformed to the normality indexes. The rate of disease control was defined as the percentage of patients with an objective response and/or stable disease > 6 months. OS was evaluated from start of treatment until death for any cause, PFS was calculated from start of treatment until progres-

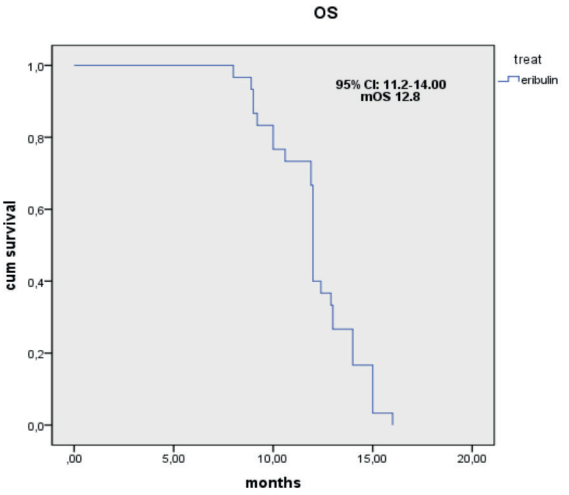

Figure 1. Median Overall Survival (OS) with Kaplan-Meier plot (n. 40).

sion disease. OS and PFS curve were estimated using the Kaplan-Meier method. Last follow-up in June 2020. Bravais-Pearson (r) linear correlation index was used to quantify the relation between PFS and Ca 15.3 with 95% confidence interval (CI). The statistical significance was defined as a *p*-value of less than 0.05.

Results

Characteristic of Patients

The study included 40 patients with MBC, the average age was 76 years (range 70-82), the demographic and clinic-pathological characteristics are shown in Table I. All patients were metastatic and were HER2 negative, twenty-eight patients had positive estrogen (ER) and progesterone (PR) receptors; twelve patients had negative estrogen (ER) and progesterone (PR) receptors; twelve patients had triple negative tumors. All Italian patients were white and postmenopausal. Patients with Performance Status (Eastern Cooperative Oncology Group) ECOG 0 were 16 and ECOG 1 were 24. Patients with an ECOG 2 or more were excluded. The localization of metastasis was: 18 patients had bone metastases; 12 have liver metastases; 16 have lung metastases; 26 have lymph node metastases, and 6 patients other. All patients had received anthracycline and taxanes regimens before starting Eribulin, 46% in an adjuvant setting and 54% in metastatic. All patients enrolled with positive hormone receptors received hormone therapy. Two patients performed thermal ablation on liver metastases and no patients died from treatment-related adverse events. Moreover, no patients were hospitalized and the adverse advent was managed generally on an outpatient basis.

OS and PFS Analysis

Among 40 patients enrolled in this study, the Kaplan-Meier method showed a median OS analysis value of 12.8 months (95% CI: 11.2-14.00) (Figure 1) and a median PFS value of 3.2 months (95% CI: 2.8-5.4) (Figure 2).

Objective Response Rate Analysis

Our analysis shows that treatment was well-tolerated in all patients with a good level of disease control (PR + SD > 50%). The median response time was 3.8 months (95% CI: 1.7 - 7.2), after an average follow-up duration of 12.1 months (range 3-18) with a significant impact on clinical benefits and an improvement of QoL. No patients had a complete response (CR); 18% had a partial response (PR), 40% had disease stabilization (SD) 38% of patients had disease progression (PD). Eribulin mesylate treatment was well-tolerated and led to a good level of disease control (PR + SD > 50%).

Ca15.3 Reduction

A Bravais-Pearson index demonstrated a good correlation between PFS and Ca 15.3 reduction with a r (95% CI: 0.28 - 0.86) value of 0.59, $p = 0.002$ (Table II). In particular, the reduction of Ca15.3 was > 50%, and we further demonstrated that this reduction was linked to an increase in

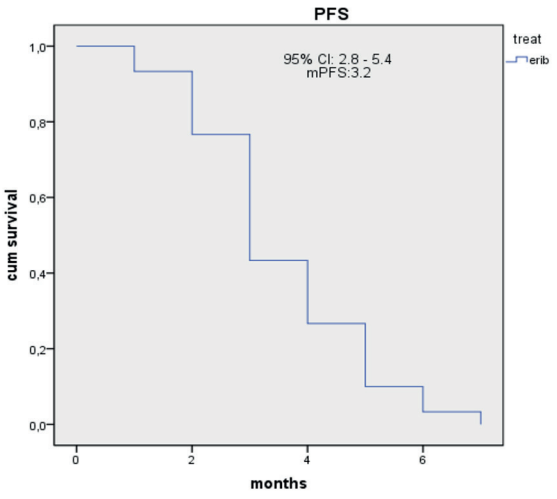

Figure 2. Median Progression Free Survival (PFS) with Kaplan-Meier plot (n. 40).

Table I. Baseline demographic and clinical characteristics (n = 40).

Characteristic	All patients
Mean age [range]	76 [70-82]
ECOG performance status	
0	16 (40%)
1	24 (60%)
Histology	
ER and PR (+)	28
ER and PR (-)	12
Triple Negative	12
Median Ca 15.3 level [range], ng/mL < 35 cut off	160 [90-307]
Metastatic site	
Liver	12
Lung	16
Bone	18
Lymph nodes	26
Other	6

Note: ECOG = Eastern Cooperative Oncology Group; ER= estrogen receptors; PR = progesterone receptors.

PFS. The reduction of Ca15.3 has been demonstrated in patients with a greater response to treatment.

Quality of Life Value

At baseline (start treatment), the scores of questionnaires EORTC QLQ-C30 described a general QoL slightly low (score for global health status was 64.53 ± 21.98). At follow up the score was higher (79.93 ± 25.76). In the symptom scales, patients reported sleeping problems (15.85 ± 31.10), fatigue (23.76 ± 19.75), and pain (12.63 ± 22.98). The improvement of the quality of life was identified, at follow-up with a reduction of pain symptoms and an improvement of general health status in 47% of patients. The patients reported pain due to skeletal metastases and they were treated with non-opioid analgesics and, in some cases, with radiation therapy.

Table II. Pearson's correlation among Ca15.3 and Progression Free Survival (PFS) (n = 40).

	Ca15.3	PFS	*p*
Ca15.3	1	-0.59**	0.002
PFS	-0.59**	1	0.002

Note: Ca15.3 = Carbohydrate Antigen 15-3; PFS = Progression Free Survival; $^{**}p < 0.01$.

Table III. PAdverse events graded according CTCAE, Version 4.0 (n = 40).

Adverse Events	All Grades	Grade 3-4
Anemia	8 (20%)	3 (7.5%)
Neutropenia	23 (57.5%)	11 (27.5%)
Thrombocytopenia	3 (7.5%)	1 (2.5%)
Febbrile neutropenia	2 (5%)	2 (5%)
Non-hematological		
Nausea	8 (20%)	
Vomiting	4 (10%)	
Constipation	5 (12.5%)	2 (5%)
Fatigue	9 (22.5%)	5 (12.5%)
Alopecia	12 (30%)	1 (2.5%)
Stomatitis/mucositis	6 (15%)	2 (5%)
Peripheral neuropathy	4 (10%)	2 (5%)
Bone pain	8 (20%)	2 (5%)

Note: CTCAE = Common Terminology Criteria for Adverse Events.

Tolerability

Treatment-related toxicity was well tolerated, and adverse events were assessed after each course of therapy and reported in line with CTCAE version 4.0. No patient died from treatment-related adverse events. Hematological toxicity was one of the main complications managed with dose adjustment or reduction. Eleven patients (27.5%) developed G3-G4 neutropenia which required use of G-CSF as prophylaxis. Two patients (5%) developed febrile neutropenia which required the use of antibiotics and G-CSF. One patient developed grade G3 thrombocytopenia which required the use of corticosteroids; three patients (7.5%) developed G3 anemia which required the administration of erythropoietin under skin. All G4 toxicity effects were managed by dose modifications. The dose was reduced in five patients and it was postponed in three patients. Due to deteriorating clinical conditions, advanced age and comorbidities, one patient stopped treatment after three infusions. One patient received 80% Eribulin from the first cycle due to clinical conditions. Only one patient showed asymptomatic prolongation of the QT interval but overall Eribulin showed no side effects on the cardiovascular system. Other toxicities were peripheral neuropathy G2-G3 in five patients; asthenia/fatigue G2-G3 in seven patients; alopecia (G3-G4) in one patient; mucositis and constipation G2-G3 in three patients;

increased transaminases (G2-G3) and bilirubin (G2-G3) in four patients. But no patients stopped treatment for serious side effects and no patients died from Eribulin treatment. The events associated with the treatment of toxicity and side effects are described in Table III.

Discussion

In recent years, 22% of new breast cancer diagnoses and 14% of breast cancer deaths concern women over the age of 70 years. In elderly patients, the chosen treatment is generally mono chemotherapy to be preferred to poly-chemotherapy, with which multiple side effects are associated. Treatment in elderly patients should not only aim to increase survival, but above all to control symptoms and preserve QoL[20-22]. Eribulin in this study showed a good tolerability profile and acceptable toxicities, similar to those reported in EMBRACE studies with young patients. An analysis of the subgroup of Embrace study and of the ESEMPiO study did not indicate age as a potential factor of increased toxicity or decreased efficacy of Eribulin. The safety profile was similar between age groups, but adverse events leading to dose reductions, delays or discontinuation increased slightly with age[23,24,13]. Dose reductions were permitted to manage treatment related adverse events according to drug guidelines[25,26]. Consistent with literature, this study, also with a small sample, confirm that Eribulin monotherapy in elderly patients > 70 years and highly pretreated has led to an improvement in OS and PFS[27], with a manageable toxicity profile among the elderly[28,29] which did not differ from that described in younger patients. The data from this study showed an improvement in median OS of 12.8 months and median PFS was 3.2 months and with a good level of disease control >50% without particularly significant adverse effects and with a good profile safety, suggesting that it could a potential treatment option for heavily elderly patients. Considering adverse events associated with therapy appeared no greater in elderly patients, compared with younger patients, age alone should not preclude the possibility of Eribulin treatment for older patients with MBC. However, it is important consider the performance status of patient before starting Eribulin treatment, the drug should be used with caution in patients in ECOG2 or higher with patients who are most comorbidity. The management to toxicity and tolerability of most frequent adverse events which neutropenia, fatigue, and peripheral neuropathy contributed to maintaining a good QoL. The disease control and the tolerability profile contributed also to guaranteeing the QoL from the first doses of treatment. In the setting of metastatic disease, the QoL is an objective most importance, thus contributing to compliance therapy and extending time to progression. Eribulin treatment can lead to an effective disease control and, in some cases, an important debulking in the presence of metastases, moreover, could considered as a suitable therapeutic option for elderly patients. Bearing in mind this is a retrospective analysis and the limited number of patients, our results can yield valid hypotheses for future studies. In several clinical studies, Eribulin monotherapy in patients > 70 years of age has shown a good efficacy and a modesty tolerability, results similar shows in study with younger patients. Neutropenia, anemia, alopecia, fatigue and peripheral neuropathy have not been found more frequently in older patients than in younger patients, while other adverse events had a similar incidence[30,31]. Of clinical variables examined, those that had a significant impact favoring improved OS were having, an ER-positive and HER negative tumor. In addition, improved baseline performance status is predictive of an improvement in the overall survival. The limitations of this analysis include the limited patients' number and the non-random sampling of patients. The results provided some observations for daily clinical practice among older MBC patients who Eribulin is therefore a valid and effective treatment, well-tolerated and safe in elderly patients. Our results are consistent with those observed of ESEMPiO study, in phase III clinical trials (Studies 301 and 305), and in the subgroup of Embrace thus showing that Eribulin is a safe and feasible treatment also for elderly women with MBC[13,28,29].

Conclusions

We observed that use Eribulin in MBC elderly patients > 70 years old, with HER2 negative, prolonged survival, confirming its efficacy in disease control with a response on metastatic lesions[32]. Adverse events associated with therapy appeared no greater in elderly patients, compared with younger patients, and age alone should not preclude the possibility of Eribulin treatment for older patients with MBC. Predictive factors performance status and number of metastatic sites

were predictive factors of PFS, and discriminant function analysis (DFA) could be a promising tool to discriminate responses to Eribulin among MBC in elderly patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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