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Research Paper

Eribulin as first-line treatment in older patients with advanced breast cancer: A multicenter phase II trial [SAKK 25/14]

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ABSTRACT

Introduction: Standard-dose eribulin mesylate (1.4 mg/m^2 d1 + 8) achieves clinical benefit rates of 26%–52% in patients with metastatic breast cancer (mBC). <10% of patients in the registration trial were ≥ 70 years old; dose reductions were common in these older patients.

Materials and Methods: This single-arm phase II trial explored the efficacy of reduced starting dosing of first-line eribulin at 1 mg/m^2 d1 + 8 q3 weeks in patients with mBC aged ≥70 years. The primary endpoint was a disease control rate (DCR) ≥55%. The secondary endpoints were objective response (OR), progression-free survival (PFS), overall survival (OS), and patient-reported neurotoxicity.

Results: Overall, 77 patients were accrued; their median age was 76 years and Eastern Cooperative Oncology Group performance status was 0–1 in 90%. The DCR was 40% (90% confidence interval [CI]: 31–50); therefore, the primary endpoint was not reached. The overall response rate was 22% (95%CI: 13–33), median PFS 5.4 months (95%CI: 4.5–7.7), and median OS 16.1 months (95%CI: 13.5–26.9). Dose modifications were necessary in 35% of patients. In nine patients, more than fifteen cycles were given; 48 patients (62%) experienced at least one grade 3 toxicity. Median patient-reported neurotoxicity scores remained stable for at least fifteen cycles. The main reason for treatment discontinuation was disease progression (57%).

Discussion: We report the first prospective data on first-line eribulin in older patients. The reduced starting dose of 1.1 mg/m^2 was safe, with prolonged treatment and DC achieved in a considerable proportion of patients (but less than the 55% assumed), without cumulative neurotoxicity. The reduced dose was apparently within the range of

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the minimal effective dose, as shown by the efficacy lack in patients requiring further dose reductions. Thus, our results do not support the approach of a reduced starting dose for older patients.

1. Introduction

Breast cancer is the most common malignancy in women and the leading cause of cancer mortality worldwide. In Europe, about 500,000 women are diagnosed with breast cancer each year, with a mortality rate of 26% [1].

One of the strongest risk factors for developing breast cancer is age, with a prevalence approaching 7% in women >70 years; >40% of breast cancer patients are >65 years [2]. Patients >65 years often experience a similar treatment effect as younger patients, while also exhibiting higher toxicity rates, dose modifications, treatment discontinuations, and decreased quality of life [3].

Palliative treatment aims to maintain or improve quality of life by reducing disease symptoms while inflicting minimal toxicities [4], particularly in the older population. There are scarce data on any chemotherapy regimens in older patients. Study results coming largely from a huge proportion of younger patients are frequently extrapolated to the entire patient population when it comes to decision-making in individual patients. Guidelines recommend a "full dose" in fit older patients based on relatively little data from specifically designed trials [5].

There is no generally accepted optimal first-line chemotherapy regimen for patients with metastatic breast cancer (mBC). However, the use of taxanes and anthracyclines, particularly as monotherapy or, occasionally, in different two-drug combinations, is widely accepted. The updated fifth European School of Oncology-European Society for Medical Oncology international consensus guidelines for advanced breast cancer (ABC-5) have recommended single-agent chemotherapy agents with favorable safety profiles for older patients [4].

Both taxanes and anthracyclines exert significant adverse effects (AEs), especially in older patients. Anthracyclines may impair cardiac function, whereas taxanes likely cause severe hypersensitivity reactions (requiring antiallergic premedication), as well as cumulative peripheral neuropathy. Eribulin, a synthetic analogue of a cytotoxic compound derived from the sea sponge *Halichondria okadai*, acts as a non-taxane inhibitor of microtubule dynamics; its most common AEs include neutropenia, leucopenia, and peripheral neuropathy [6]. It is registered as a palliative chemotherapy in patients with advanced breast cancer after anthracyclines and taxanes and does not require premedication to prevent hypersensitivity. In the eribulin registration trial Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389 (EMBRACE) [6], only 44 out of 508 patients (<10%) were > 70 years of age. There was a significant overall survival (OS) benefit with eribulin compared to a monotherapy of the physician's choice in this heavily pretreated population with a median of four previous chemotherapy regimens. An age-based assessment suggested that survival outcomes with eribulin are independent of age [7]. AEs associated with eribulin therapy were reported not to be greater in older versus younger patients [7]. However, safety data revealed high numbers of dose modifications (interruptions, delays, omissions, or reductions) early in the treatment course (e.g., mostly by the second cycle), especially in the older population [7]. Eribulin is the only chemotherapy that has shown a significant OS benefit in patients who have received at least two prior chemotherapy lines. Compared to treatment with taxanes, eribulin seems to induce less neurotoxicity [8] based on early phase II studies. However, in a phase ll trial with eribulin as the first-line therapy in a population with a mean age of 56 years, a starting dose of 1.4 mg/m^2 required dose adjustments in 64.3% of patients (mainly due to hematologic toxicity) [9]. Granulocyte-colony stimulating factor (G-CSF) was administered in 39% of these patients. A total of 35% of the patients had a dose reduction, and of those, 40% needed a further dose-reduction to <1.1 mg/m^2. Half of the dose reductions occurred by cycle 3.

In another phase II trial for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who received eribulin/trastuzumab as the first-line treatment [10], both the overall response rate (ORR) and clinical benefit rate (CBR) were higher in patients who required dose reductions because of toxicity.

These observations led us to prospectively investigate a regimen starting with a reduced dose of 1.1 mg/m^2 as a first-line therapy in an older population ≥ 70 years, including patient-reported neurotoxicity and geriatric assessments, with the hypothesis that this would lead to less treatment discontinuation and thus to longer DC.

2. Patients and Methods

2.1. Trial Design and Patients

This study was a single-arm, two-stage phase II trial investigating a reduced starting dose of eribulin in older patients as first-line chemotherapy for mBC. Included were women ≥70 years old, with locally advanced or metastatic HER2-negative and hormone-receptor-positive or -negative adenocarcinoma of the breast who had not received chemotherapy for their advanced disease (adjuvant chemotherapy and previous endocrine therapies were allowed).

Further key inclusion criteria were adequate hematological values, normal or only mildly impaired hepatic function (bilirubin ≤1.5 x ULN, AST ≤3 x ULN), normal or only mildly impaired renal function (creatinine clearance >40 ml/'), and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. The disease had to be evaluable or measurable according to response evaluation criteria in solid tumors (RECIST) v1.1. The key exclusion criteria were known central nervous system (CNS) metastases, palliative irradiation of >30% of marrow-bearing bone, and pre-existing neuropathy ≥G2 (according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 4.0) at registration. Patients with severe or uncontrolled cardiovascular disease (congestive heart failure New York Heart Association [NYHA] III or IV), unstable angina pectoris, history of myocardial infarction within the last three months, significant arrhythmias, and congenital long QT syndrome were also excluded.

2.2. Procedures and Assessments

Eribulin mesylate was given at 1.1 mg/m^2 on Day 1 and Day 8 every three weeks via a two- to five-minute intravenous injection. The treatment duration was planned until progression or intolerable toxicity. Premedication was not required, and use of antiemetics was at the investigators' discretion. Supportive treatment with G-CSF was allowed but not recommended. Doses had to be omitted for an absolute neutrophil count ≤1 G/l, platelet count ≤75 G/l, or any non-hematological toxicity of grade 2 or higher (except alopecia and renal function). Dose reductions were prescribed as follows: the dose was reduced to 0.9 mg/m^2 after the second occurrence of an absolute neutrophil count of 0.5–1 G/l, thrombocytopenia of 50–75 G/l, or any grade 3/4 non-hematological toxicity. If these AEs reappeared with a dose of 0.9 mg/m^2, the dose was further reduced to 0.7 mg/m^2. If there was another grade 3/4 toxicity despite this second dose reduction, treatment was stopped indefinitely. Treatment was also stopped if it had to be delayed for more than six weeks for any reason.

Radiological tumor assessments were performed every twelve weeks until disease progression or start of the next antitumor therapy. Objective response (OR) was evaluated according to the RECIST v1.1 criteria.

Patient-reported neurotoxicity was assessed at baseline, on Day 1 of

each cycle, within 30 days after the last dose, and at the first follow-up visit or the next anticancer treatment using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx [11]) subscale, which included eleven symptoms. Higher scores (range 0–44) indicated less neurotoxicity. At baseline, the patients participated in a cancer-specific geriatric assessment (C-SGA) measuring five domains (comorbidity, functional status, psychosocial, nutrition, and cognition). The C-SGA score was the sum of the number of "deficit" scores in each domain and was dichotomized as either "vulnerable" (≥3) or "not vulnerable" (≤2) (supplementary Table S1).

All AEs and laboratory abnormalities were graded according to CTCAE (Version 4.03).

The trial (NCT02404506) was conducted in line with the Declaration of Helsinki. The protocol was approved by the local ethics committee.

2.3. Trial Endpoints

The primary endpoint was disease control (DC), defined as complete response (CR) or partial response (PR) at any time point during treatment or stable disease (SD) for at least 24 weeks. Secondary endpoints were the time to treatment failure (TTF), progression-free survival (PFS), OS, and OR. TTF was defined as the time from registration until treatment discontinuation due to any reason or the occurrence of a second tumor; PFS was defined as the time from registration until progression according to RECIST v1.1 or death, whichever occurred earlier. OS was defined as the time from registration until death; OR was defined as having CR or PR according to RECIST v1.1 at any time point during treatment. Patients who received at least one dose of eribulin and fulfilled the major eligibility criteria were evaluable for the efficacy endpoints. The safety endpoints were evaluated in all patients who had received at least one dose of eribulin and based on the AE assessment, laboratory tests, physical examination, and vital signs. Patients still on treatment were censored at the last eribulin administration.

2.4. Statistical Analyses

Simon's optimal single-arm two-stage design was used assuming that the DC rate (DCR) under the null hypothesis was 35%. To detect a DCR ≥50% (alternative hypothesis) at a 5% significance level with 80% power, 77 evaluable patients, including 27 for the first stage, were needed. One interim analysis for futility was performed after the inclusion of 27 patients.

For the primary endpoint, the DCR with a corresponding 90% Clopper–Pearson confidence interval (CI) was calculated. All time-to-event endpoints were calculated using the Kaplan–Meier method with its corresponding 95% CI. Categorical endpoints were descriptively summarized using proportion and the 95% Clopper-Pearson CI.

The following subgroups were prospectively looked at: administration of bone-targeted agents (yes vs. no), presence of bone metastases as the only site of disease (yes vs. no), hormone receptor status (positive vs. negative), age (<80 vs. ≥80 years at registration), and vulnerability according to geriatric assessment (≤2 vs. ≥3 deficits). A further subgroup analysis of patients with early dose reduction (during the first two cycles) was not predefined, but we decided to specifically look at this because most of the dose reductions took place during the first two cycles in the EMBRACE trial [6].

The changes in the patient-reported neurotoxicity over the whole observation period were calculated and descriptively summarized at each time point using median and range. The individual and summary C-SGA scores were compared between the OR groupings (DC vs. not achieving DC under trial therapy) by a two-sample *t*-test for continuous variables and chi-square/Fisher's exact test (where appropriate) for categorical variables.

The statistical significance was set at a p-value <0.05, and SAS 9.4 (SAS Institute Inc., Cary, NC) and R v3.5.3 (Foundation for Statistical Computing, Vienna, Austria) were used for the analyses.

3. Results

3.1. Patients

From August 2015 to February 2019, 77 patients were accrued in eighteen Swiss centers. During the planned interim analysis for futility after 27 patients, accrual was suspended for six months. The baseline characteristics are summarized in Table 1.

The median age was 76 years (range 70–89). The PS was 0–1 in 90%, 64% of patients had comorbidities, 45% had liver metastases, and 3% had bone-only disease. In total, 25 patients (37%) had received prior adjuvant chemotherapy. Details on the types of previous chemotherapy regimen in the adjuvant setting were not reported.

3.2. Efficacy

The median follow-up was 25.6 months. At the time of the analysis, one patient was still on treatment. DC was reached in 31 patients, corresponding to a DCR of 40% (90% CI 31–50). The lower boundary of the 90% CI crossed the predefined threshold of 35%; thus, the null hypothesis could not be rejected.

Two patients had CR (2.6%) and fifteen had PR (19.5%), corresponding to an ORR of 22% (95% CI 13–33). A further fourteen patients (18.2%) had SD ≥24 weeks.

The median OS was 16.1 months (boundary% CI 13.5–26.9) (Supplementary Fig. S1), and the median PFS was 5.4 months (95% CI 4.5–7.7) (Fig. 1). The efficacy endpoints are summarized in Table 2.

3.3. Delivery of Treatment

The median number of cycles was six (1–24); dose reductions were necessary in 27 patients (35%), mostly due to neutropenia. The median dose per cycle was 2.1 mg/m^2 (1.1–2.3). In nine patients (12%), more than fifteen cycles were given. The main reasons for treatment discontinuation were disease progression (57%), patient refusal (14%), and unacceptable toxicity (11%). In those 31 patients who reached the primary endpoint DC, progressive disease was the reason for treatment discontinuation in only twelve of the patients (39%). In the remaining patients, unacceptable toxicity ($N = 6$), patient refusal ($N = 5$), withdrawal by the physician ($N = 3$) and other causes ($N = 5$) were the main reasons.

Table 1
Baseline characteristics.

Variable	Total ($N = 77$)
Age at registration	
Median (Min–Max)	76 (70–89)
WHO performance status	
0	33 (43%)
1	36 (47%)
2	8 (10%)
Weight [kg]	
Median (Min–Max)	66.0 (47.9–114.0)
Height [cm]	
Median (Min–Max)	160 (145–173)
Body surface area (Mosteller) [m^2]	
Median (Min–Max)	1.7 (1.4–2.3)
Previous anticancer therapies	67 (87%)
Other clinically relevant diseases	49 (64%)
Liver metastases	35 (45%)
Measurable disease	72 (94%)
Hormone receptor-positive	64 (83%)
Bone metastases as only site of disease	2 (3%)

WHO, Word Health Organization.

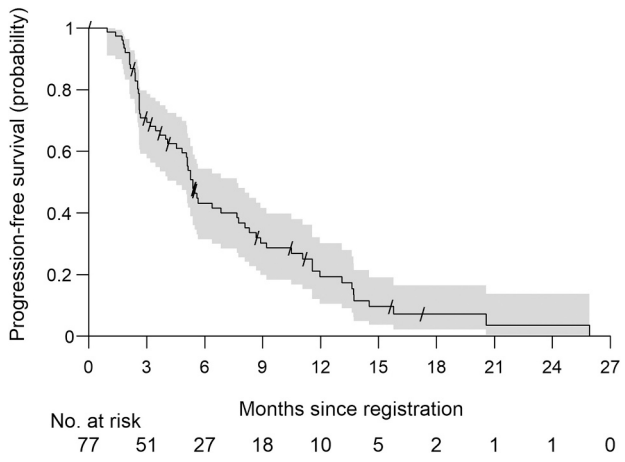

Fig. 1. Kaplan-Meier plot for progression-free survival.

Table 2
Efficacy endpoints.

Category	Variable	Total ($N = 77$)
Primary endpoint	CBR (90% CI)	0.40 (0.31–0.50)
Secondary endpoint	ORR (95% CI)	0.22 (0.13–0.33)
Secondary endpoint	Median PFS in months (95% CI)	5.4 (4.5–7.7)
	PFS events	63 (82%)
	Death	7
	Progression	56
Secondary endpoint	Median OS in months (95% CI)	16.1 (13.5–26.9)
	OS death reason	48 (62%)
	Progressive disease	40
	Unknown	7
	Other	1

CBR, clinical benefit rate; ORR, overall response rate; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

3.4. Subgroup Analyses

3.4.1. Subgroups of Patients According to Hormone Receptor Status

The DC was higher in patients with hormone-receptor-positive disease than with hormone-receptor-negative (triple-negative) disease (44% vs. 23%, respectively). In the group of patients with fifteen or more cycles of eribulin, the disease was always estrogen receptor (ER)-positive.

3.4.2. Subgroups of Patients According to Comorbidities

Comorbidities did not preclude long-term treatment: 89% of patients with long treatment (≥15 cycles) had other clinically relevant diseases.

3.5. Exploratory Subgroup Analysis

3.5.1. Subgroup of Patients with Early Dose Reduction (during the First Two Cycles)

Early dose reduction during the first two cycles occurred in thirteen patients (17%), i.e., in eight patients due to toxicity, in one patient due to error, and in four patients due to the patients' decisions. No patient who needed a dose reduction during the first two cycles had a long-term treatment (i.e., fifteen or more cycles). In all patients with early dose reduction, treatment had to be stopped due to disease progression.

3.5.2. Toxicity

In total, 48 patients (62%) experienced at least one occurrence of grade 3 toxicity, including one patient who died (not clearly attributed to the study drug). Grade 3 neutropenia was observed in 10% of all patients and grade 4 in 12%. Two patients (3%) had febrile neutropenia. Moreover, G-CSF was administered in only three patients, and 34 serious AEs occurred in 27 patients (35%).

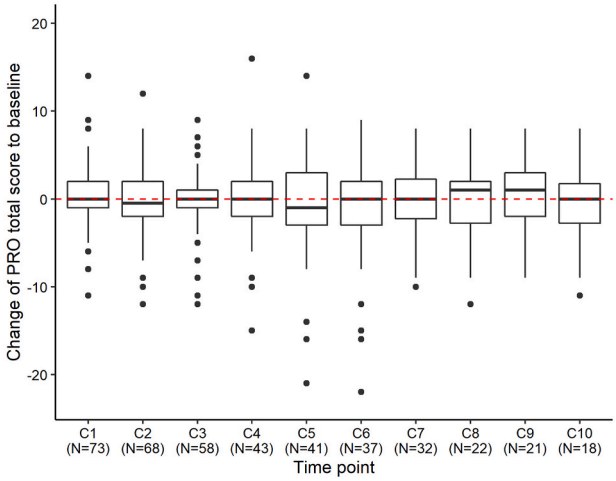

Fig. 2. Changes in patient-reported neurotoxicity over the first 10 cycles. PRO, patient-reported outcome.

Sensory neuropathy occurred in 23% of patients (12% grade 1, 5% grade 2, and 6% grade 3). The three patients with grade 1 peripheral neuropathy at baseline did not deteriorate during treatment. None of the patients with grades 2 or 3 neurotoxicity under treatment had a sensory neuropathy at baseline (in five patients, grade 3 neurotoxicity occurred between two and eight months of treatment). Only three patients needed a dose reduction due to neurotoxicity. Dose reductions in another 24 patients were required due to non-neurotoxicity reasons (other toxicities, patient's decision, physician's decision, etc.). Treatment discontinuation due to toxicity occurred in eight of all patients (10%).

3.5.3. Patient-Reported Neurotoxicity and Geriatric Assessment

The submission rates of the FACT/GOG-Ntx were above 80% for most of the assessment time points (supplementary Table S2). Overall, patients reported stable neurotoxicity scores for at least 10 cycles (Fig. 2). The pretreatment C-SGA showed that about one-third of the patients ($N = 23$; 30%) were considered vulnerable. More than half of the patients had severe comorbidities (62%); 39% were at risk of functional decline, 22% of depression, 5% of social isolation, 42% of malnutrition, and 18% of cognitive impairment (Supplementary Table S3). No significant differences in any of the geriatric domains and summary C-SGA scores were found between the patients who achieved DC compared to those who did not (Table 3).

4. Discussion

In this study, a reduced starting dose of eribulin in older patients showed efficacy in the expected range, although the DCR at 40% was below the assumed 55%, thus failing to meet the primary endpoint. In 57% of patients, progressive disease was the reason for treatment discontinuation.

Interestingly, there were a considerable number of patients ($N = 9$) who were treated with ≥15 cycles and had continuous good tolerance, showing that long-term treatment with eribulin is well tolerated in a subgroup of older patients. Comorbidities did not affect the efficacy or tolerance of eribulin. Patients considered vulnerable based on the geriatric assessment did not differ in terms of the DC when compared to non-vulnerable patients.

Reduced bone marrow function, a common cause of intolerance to chemotherapy in older patients, was not a reason for treatment failure with this reduced starting dose of 1.1 mg/m^2. Neurotoxicity, usually a dose-limiting AE of eribulin, was observed in 23% of patients and was mostly mild, as reflected by the stable scores in the patient-reported

Table 3
Cancer-specific geriatric assessment (C-SGA) dimensions and summary score by disease control.

Variable	Disease control (N = 31)	No disease control (N = 46)	p-value*
Charlson Comorbidity Index (CCI, age-adjusted) (Median, Min-Max)	4 (3, 7)	4 (3, 8)	0.88
Severe comorbidity (≥4)	21 (68%)	27 (59%)	0.42
Average comorbidity (1–3)	10 (32%)	19 (41%)	
Vulnerable elderly survey (VES-13) (Median, Min-Max)	1 (0, 8)	2 (0, 8)	0.31
High risk for functional decline (≥3)	10 (32%)	20 (43%)	0.32
Low risk for functional decline (<3)	21 (68%)	26 (57%)	
Geriatric Depression Scale (GDS-5) (Median, Min-Max)	1 (0, 4)	1 (0, 4)	0.24
Depression possible (≥2)	9 (29%)	8 (17%)	0.23
Depression unlikely (0–1)	22 (71%)	38 (83%)	
Modified Medical Outcomes Study Social Support Survey (mMOS-SSS) (Median, Min-Max)	5 (3, 5)	5 (1, 5)	0.85
At risk for social isolation (≤2.5)	–	4 (9%)	0.09
No risk for social isolation (>2.5)	31 (100%)	42 (91%)	
Mini Nutritional Assessment (MNA) (Median, Min-Max)	12 (3, 14)	12 (7, 14)	0.54
At risk for malnutrition (≤11)	13 (42%)	19 (41%)	0.96
Normal nutritional status (>11)	18 (58%)	27 (59%)	
Cognitive Function Test (MiniCog) (Median, Min-Max)	4 (0, 5)	4 (1, 5)	0.40
Possible impairment	7 (23%)	7 (15%)	0.37
Suggests no impairment	23 (77%)	39 (85%)	
Missing	1	–	
C-SGA summary measure			
Vulnerable (≥3 deficits)	10 (32%)	13 (28%)	0.71
Not vulnerable (0–2 deficits)	21 (68%)	33 (72%)	

* Wilcoxon rank-sum or Chi-square for continuous or categorical, respectively.

neurotoxicity. Despite a prospective recording of neurotoxicity in our trial, this number was lower than that in the EMBRACE trial, in which patients reported 35% neurotoxicity of any grade and 8% of grade 3.

Despite the reduced initial dose, an early further dose reduction (during cycles 1 and 2) was still necessary in 17% of patients, and for an additional 18 patients (23%) during the remaining treatment period. This occurred more often in patients with liver metastases, indicating possibly more severe (hemato-) toxicity due to impaired hepatic metabolism (since mild hepatic dysfunction was not an exclusion criterion, bilirubin ≤1.5 x ULN and AST ≤3 x ULN were required). However, due to the low numbers, no definitive conclusions could be drawn from this observation.

An early dose reduction of this already reduced starting dose was associated with early tumor progression, suggesting that this dose is in the range of minimal effectiveness.

An exploratory analysis from two other single-arm phase II studies and one open-label, randomized phase III study included only 79 patients who were aged ≥70 years, out of about 800 total patients [7]. In this highly selected population of older patients, treatment with eribulin was generally well tolerated. In the first-line treatment, the median number of cycles delivered was seven [7]. In the registration trial involving later lines, nearly two-thirds of the patients received five or more cycles of eribulin [6]. The patients could often be treated for prolonged periods with eribulin without cumulative intolerable toxicity.

In EMBRACE [6], AEs leading to dose reduction, delay, or discontinuation increased slightly with age (<50 years, 45.8%; >70 years, 51.9%; difference not statistically significant). Similarly, the use of hematopoietic growth factors was found to be independent of age. Age-specific data on dose modifications or AEs leading to treatment discontinuation were not shown.

In a phase III trial comparing eribulin with capecitabine in mBC, about 20% of patients received eribulin as the first-line chemotherapy for advanced disease [12]. Only 14% of this population was >65 years old; in a subgroup analysis by age, no differential effect in the OS was observed. Safety data according to age subgroups were not reported. The most common AEs in this trial were neutropenia, leucopenia, and peripheral neuropathy.

Based on earlier phase II studies, eribulin seems to induce less neuropathy than taxanes [8]. This supports our findings that neurotoxicity was rarely prohibitive in this trial; longer treatment was possible without cumulative deterioration of patient-reported neurotoxicity.

Since this trial's beginning, several publications on treating mBC patients with eribulin have confirmed dose-limiting AEs [13–18]. Seeking better eribulin tolerability, several alternative treatment schedules have been evaluated since starting the current trial. A biweekly treatment schedule resulted in no improvement in hematotoxicity and was equally effective as the conventional schedule [14]. Roughly half of the patients were treated with G-CSF, as compared to 4% in our trial. A further multicenter, single-arm trial investigated eribulin as a first-line therapy for patients with aggressive taxane-pretreated, HER2-negative mBC (MERIBEL study) [18]. The time to progression (TTP), OS, and ORR were better for patients with toxicity-related dose delays and grades 3/4 neutropenia.

4.1. *Strengths and Weaknesses of the Trial*

The strengths of this trial included the prospective evaluation of older patients, with strict rules for dosing and dose modifications, and the assessment of patient-reported neurotoxicity. One of the weaknesses was the single-arm phase II design, with a broad CI because of the small sample size. Another weakness was the lack of pharmacokinetic measurements, which would have helped interpreting the observed efficacy and toxicity.

5. Conclusion

We report the first prospective data on treatment with first-line eribulin mesylate in older patients at a reduced starting dose of 1.1 mg/m^2. This dose was safe, but the efficacy was somewhat lower than assumed, with the lower boundary of the 90% CI for DCR crossing the predefined threshold. Prolonged treatment and DC were possible in a considerable proportion of the population without cumulative neurotoxicity. However, this reduced dose is apparently in the range of the minimal effective dose, as shown by the complete lack of efficacy in the patients who required further dose reductions. Thus, our results do not support the approach of a reduced starting dose for older patients.

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Disclosure

The authors have declared no conflicts of interest. They all have approved the final article.

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