Article

Efficacy and Safety of Eribulin in Taxane-Refractory Patients in the "Real World"

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Abstract: Taxanes have been shown to be the most effective treatment for recurrent or metastatic breast cancer. However, for patients pretreated with taxanes, more active and possibly less toxic drugs are needed. In this retrospective study, we investigated on the effectiveness and safety of eribulin mesylate in 91 taxane-refractory subjects, extracted from the ESEMPIO database, which included 497 metastatic breast cancer patients treated with eribulin allover the Italy. This analysis included only those patients who have shown disease progression while receiving taxane therapy (primary refractory), or those who achieved a response followed by progression while still on therapy (taxane failure). Overall, 41/91 patients (45.2%) showed a clinical benefit; 1 complete response (2.2%) and 16 partial responses (17.6%) were observed. The median progression free survival was 3.1 months (95% CI: 2.8–3.5) and the median overall survival was 11.6 months (95% CI: 8.7–16.7). With regard to toxicity, 53 patients (58%) experienced asthenia/fatigue, 23 (25%) showed peripheral neurotoxicity, 18 (20%) alopecia, 12 (13%) mild constipation and 27 (30%) neutropenia. The toxicity related to the treatment led to eribulin dose reduction in 19 (21%) and discontinuation in 9 (10%) patients, respectively. In conclusion, this study suggests that eribulin is effective and well tolerated also in taxane-refractory patient.

Keywords: metastatic breast cancer; taxanes; eribulin; observational study

1. Introduction:

In metastatic breast cancer patients, despite the availability of several active agents, which can obtain many and durable responses, long-term survival has only minimally improved [1,2]. In fact, patients affected with advanced breast cancer, frequently receive multiple sequential lines of treatment [3]. Thus, there is a need to develop more active and possibly less toxic, additional drugs, in order to increase treatment options. [4]. In particular, taxanes are the most frequently used agents for recurrent or metastatic breast cancer [5]. However, they are associated with alopecia, peripheral neuropathy, neutropenia and other serious adverse events. Moreover, the emergence of resistance to taxanes represents a major clinical challenge [6].

Eribulin mesylate is a synthetic analogue of *Halichondrin B*, a natural product isolated from a marine sponge. Eribulin inhibits microtubule polymerization, thus inducing an irreversible mitotic block at the G2-M phase and eventually causing apoptosis [7]. In the open-label phase III EMBRACE study, conducted in heavily pretreated breast cancer patients, eribulin caused an advantage in overall survival (OS) compared with treatment of physician's choice [8]. Moreover, eribulin was associated with an acceptable toxicity profile with asthenia and neutropenia being the most common adverse events [8]. Further to the results of the EMBRACE trial, eribulin was approved for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens, including anthracyclines and taxanes in either adjuvant or metastatic setting.

However, the efficacy of eribulin in patients with well-defined taxane resistance has seldom been investigated to date. In a recent phase II trial on 52 patients, treated with a median of four previous chemotherapy cycles, including taxanes, eribulin determined a clinical benefit rate of 39.2% and was not associated with any relevant safety concern [9].

Well-conducted field-practice experiences have mounting importance in the oncology setting [10]. In fact, observational studies can complement the results of clinical trials, which are often conducted in selected populations under stringent treatment and follow-up conditions.

2. **Patients and methods**

Study setting and design

ESEMPIO was a large multicenter observational study on 497 Italian patients with advanced breast cancer receiving eribulin [11]. Clinical management was conducted according to the standard practice of each Centre in order to evaluate the efficacy and safety of eribulin. The study considered evaluable all patients who received at least one administration of drug. From January 2012 to December 2013, 497 patients from 39 Italian centers were included. All data were updated to March 31st 2015.

The study was conducted according to the Helsinki declaration and with the approval of all local Ethical Committees. All patients signed an informed consent before inclusion.

For the present analysis of the ESEMPIO database, only patients with well-defined taxane resistance and complete data available in the database were considered. Taxane-resistance was defined as

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follows: (i) disease progression while receiving paclitaxel/docetaxel therapy (primary taxane resistance) (ii) response followed by progression while still on therapy (taxane failure), (iii) breast cancer recurring within 6 months after the last administration when undergoing neo- or adjuvant chemotherapy with taxanes [12].

Data analysis

The following endpoints were considered: (i) best response according to the RECIST criteria [13] during eribulin treatment; (ii) progression-free survival (PFS), defined as time from the initiation of eribulin treatment to disease progression, death for any cause or loss to follow-up; and (ii) overall survival (OS), defined as time from the initiation of eribulin treatment to death for any cause or loss to follow-up. Safety considerations were also performed. Baseline characteristics, best response and toxicities were summarized using descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables). Median follow-up time PFS and OS were estimated using the Kaplan-Meier method.

Results

In total, 91 patients who have shown primary resistance to taxanes (disease progression while receiving taxane therapy), or those who achieved a response to taxanes followed by progression while still on therapy (taxane failure) were extracted form the ESEMPIO population. Table 1 shows the baseline characteristics of these patients. Median age was 62 years (range, 33-85). Nine patients (11%) were triple-negative; HER2 status was negative in 66 patients (81%). In most cases, patients (n=70; 78%) had received more than 3 prior chemotherapy lines before eribulin.

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Table 1. Patients' characteristics (n=91).

			N patients (%)
Age (years)		Median	61.8
		Range	32.9-84.8
ECOG	0		32 (36.4)
	1		46 (52.3)
	2		13 (14.3)
ER/PgR status (%)	ER and/or PgR+		70 (76.9)
	ER and/or PgR-		28 (30.7)
Triple negative			9 (10.6)
Her2 status	Negative		66 (81.5)
	Positive		15 (18.5)
	Unknown		10 (11.0)
N° organs involved	1		51 (56.0)
	2		27 (29.7)
	3		13 (14.3)
Most common metastatic sites	Bone		50 (54.9)
	Brain		3 (3.3)
	Soft tissue		31 (34.1)
	Visceral		60 (65.9)
Taxane in (neo)adjuvant setting	Yes		22 (29.7)
	No		52 (70.3)
Taxane in metastatic setting	Yes		89 (97.8)
	No		2 (2.2)
N° of previous chemotherapy lines			
	2		8 (8.8)
	3		13 (14.4)
	4		18 (20.0)
	5		20 (22.2)
	6		11 (12.2)
	7-12		21 (23.3)

(Neo)-adjuvant taxane treatment was administered to 22 patients (30%); almost all subjects (n=89, 98%) received taxanes in the metastatic setting, whereas two patients relapsed during taxane adjuvant treatment. Median time between resistance to taxane and the first dose of eribulin was 2.9

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weeks (range, 1.6-11.9). All patients initiated treatment with eribulin within three months from the onset of resistance to taxane therapy.

Eribulin treatment

Eribulin was administered at dosage of 1.4 mg/m2 on day 1 and 8 every 3 weeks (one cycle). Patients received a median of 4 cycles of eribulin (range: 1-20), and the median duration of eribulin treatment was 2.9 months (range: 0.2-24.4). The median cumulative dose of eribulin was equal to 12.8 mg/m^2 (range: 1,2-25.6).

Eribulin dose was reduced in 26 patients (32%): in 19/26 (73%) because of toxicity related to the treatment, and in 7 patients due to other causes (in 3 patients due to persisting toxicities from previous treatments and in 4 due to poor clinical conditions). Eribulin therapy was stopped for disease progression in the wide majority of cases (n=82, 90%); in the remaining 9 subjects, eribulin was stopped for toxicity (G4 neutropenia, n=4; G3 elevated AST/ALT, n=2; asthenia, neurological toxicity and elevated creatinine, n=1 each).

Effectiveness evaluation

Median follow-up was 17.7 months (range, 1.8-31.5). Best clinical response to eribulin treatment is summarized in Table 2. Overall, 41 patients (45.2%) experienced a clinical benefit; 1 complete response (CR; 2.2%) and 16 partial responses (PR; 17.6%) were observed.

Table 2. Response to treatment.

	Eribulin (n=91)
CR, %	**1 (2.2%)**
PR, %	**16 (17.6%)**
SD, %	**24 (26.4%)**
PD, %	**50 (54.8%)**
Clinical benefit rate	**41 (45.2%)**

Median PFS was 3.1 months (95% CI: 2.8-3.5) (Figure 1). Median OS was 11.6 months (8.7-16.7) (Figure 2). Overall, 34/83 patients (41%) were alive at the time of analysis.

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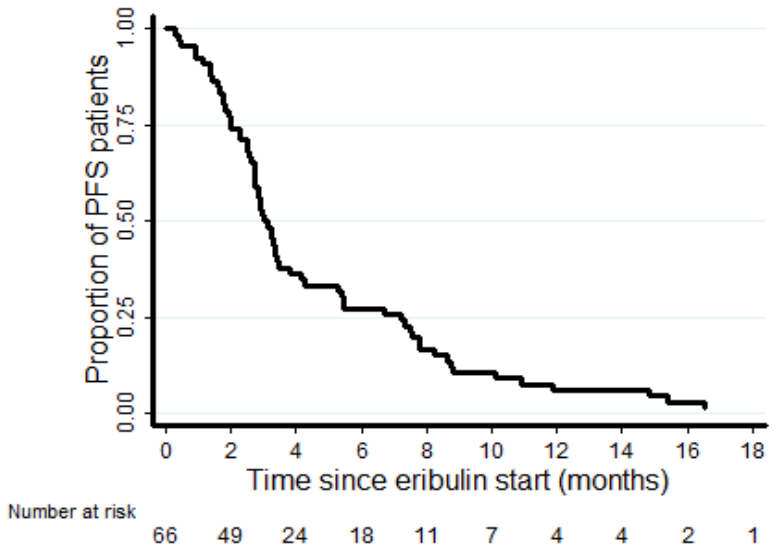

Figure 1. Progression Free Survival.

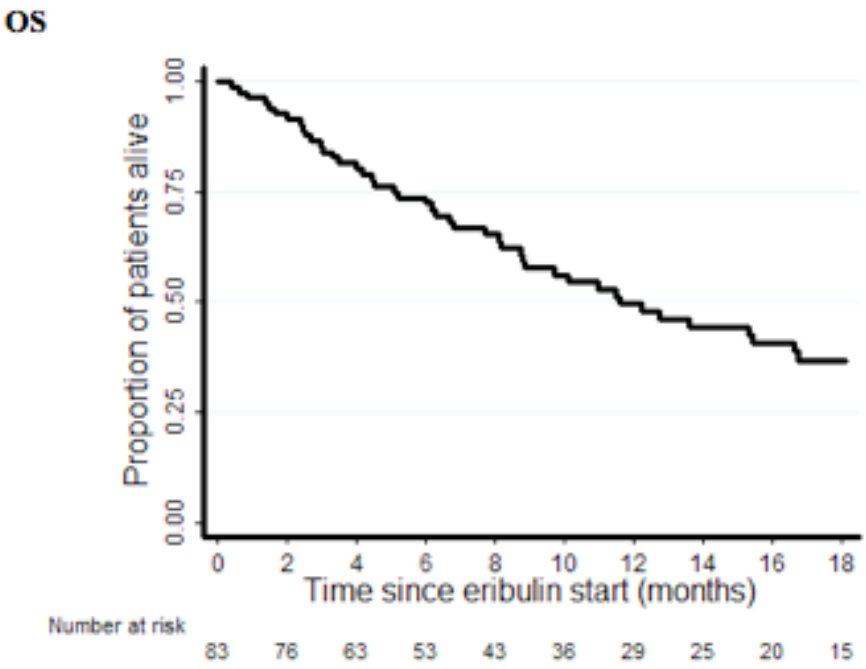

Figure 2. Kaplan-Meier analysis of overall survival.

Safety evaluation

With regard to toxicity (Table 3), 53 patients (58%) experienced asthenia/fatigue, which was mild to moderate in 54 % of the cases, being of grade 3 in only 4 % of patients. This symptom was dose-related, appearing usually after a median of 3-4 cycles. Peripheral neurotoxicity of any grade was observed in 23 (25%) of the patients, being mild to moderate (grade 1-2) in 21/23 (91%); neurotoxicity

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of grade 3 and 4 was observed in 1 patient each (only one patient discontinued treatment due to neurotoxicity). This symptom was dose related and cumulative, however, it rapidly improved or disappeared after a dose-reduction, or treatment discontinuation. Alopecia was encountered in 33% of the patients. Microsites was never observed and gastrointestinal toxicity, as mild constipation, was recorded in 12 patients (13%). Neutropenia was of grade 1-2 in 16 patients (18%), of grade 3 in 7 (8%) and grade 4 in 4(4%), respectively; no febrile neutropenia was recorded. Mild anemia or thrombocytopenia was observed only occasionally.

Table 3. Incidence of adverse events.

AEs	All grades	Grade 3	Grade 4
Neutropenia	27 (30%)	7 (8%)	4 (4%)
Neutr.febrile	0	0	0
Alopecia	18 (20%)	0	0
Nausea	13 (14%)	0	0
Peripheral neuropathy	23 (25%)	1 (1%)	1 (1%)
Constipation	12 (13%)	0	0
Astenia	53 (58%)	4 (4%)	0
Anemia	15 (16%)	2 (2%)	0
Thrombocytopenia	4 (4%)	0	0
Got/Gpt	3(3%)	2 (2%)	0
Creatinine	2 (2%)	1(1%)	0

Eribulin dose was reduced in 26 patients (32%): in 19/26 (73%) because of toxicity related to the treatment, and in 7 patients due to other causes (in 3 patients due to persisting toxicities from previous treatments and in 4 due to poor clinical conditions). Therapy was discontinued for disease progression in the wide majority of cases (n=82, 90%); in the remaining 9 subjects, eribulin was stopped for toxicity (G4 neutropenia, n=4; G3-4 elevated AST/ALT, n=2; asthenia, neurological toxicity and elevated creatinine, n=1 each). No significant differences in toxicity were observed according to age, and even in patients older than 70 years treatment was well tolerated.

Discussion

Medical treatment of breast cancer has remarkably evolved in recent years, due to the availability of new, more effective drugs as anthracyclines and taxanes, which greatly improved cure rate in early stages, and prolonged duration of remission in metastatic patients, although they had only limited impact on overall survival [4,5,14,15]. Indeed, anthracyclines and taxane-based regimens are commonly used in (neo)-adjuvant and first line metastatic setting [16], making difficult the choice

of therapy for relapsing patients. Thus, new active therapeutic options need to be identified so far.

Commonly used agents include gemcitabine, capecitabine, vinorelbine, ixabepilone, and eribulin. In anthracyclines and taxanes pre-treated patients, gemcitabine achieved an overall response rate ranging from 12% to 30%, but with significant hematological toxicity [17]. Vinorelbine has been widely employed in pretreated breast cancer, either in its intra-venous or oral formulation, yielding response rates ranging from 10% to 35% [18,19]. Additional agents include nab-paclitaxel, which in two phase II trials yielded a response rate of 15% and 48% respectively in taxane pre-treated patients [20,21]. Ixabepilone, was quite active in heavily pre-treated patients, with a 18.5% response rate, however, because of its relevant neurotoxicity, observed in 63% of the patients, was not approved by EMA [22-24]. With regard to capecitabine, it is an active and well-tolerated oral anti-metabolite. A recent review of 28 single-agent capecitabine trials reported a median overall response rate of 28%, with a median overall survival of 11 month [25]. Moreover, a pooled analysis of data from capecitabine mono-therapy clinical trials showed, in second-line, a response rate of 19%, a progression free survival of 3.7 months, and a median overall survival of 13 months, with safety comparable to previous studies [26]. Overall, none of the above mentioned single agents, truly showed any benefit in overall survival over other treatments in heavily pre-treated patients.

Eribulin has shown activity in metastatic heavily pre-treated breast cancer and represents an outstanding therapeutic option in these patients after failure of anthracyclines and taxanes [8,27].

Phase I studies have established that the optimal dose for eribulin mesylate was 1.4 mg/m2 on days 1 and 8 every 3 weeks [28]. Phase II and III studies have investigated the efficacy of eribulin in heavily pre-treated metastatic breast cancer patients. Two phase III trials have compared eribulin to either physician's choice [8] or capecitabine [29]. In the first, of these multicenter, open label randomized trials, called EMBRACE [8], 762 women who had received at least 2 previous lines of chemotherapy, were randomized in a 2:1 fashion to receive either eribulin or a treatment of their physician's choice (TPC). Almost all patients entering into this trial had previously received anthracyclines and taxanes and most of them had also received capecitabine before study entry. Although the study did not demonstrate any improvement in progression free survival (PFS), it showed a statistically significant benefit in OS for patients receiving eribulin treatment (OS = 13.1 mos vs 10.6 mos, hazard ratio 0.81, 95% CI 0.66-0.99; p= 0.041). The most common adverse events in both groups were asthenia or fatigue

(54% in eribulin treated patients vs 40% of TPC) and neutropenia (52% in eribulin treated patients vs 30 % in TPC arm at all grades). Peripheral neuropathy was the most common adverse event in the eribulin arm, leading to drug discontinuation in 5% of patients. In the second phase III trial, 1102 patients, who had previously received anthracyclines and taxanes, were randomized in a 1:1 ratio to eribulin or capecitabine [29]. This trial did not show superiority of eribulin over capecitabine either for PFS or OS. Median PFS was 3.7 mos in the first and 4.1 mos in the second phase III study. Twelves et al [30] pooled the results of these two randomized studies confirming a statistically significant OS benefit in favor of eribulin with a median OS of 15.2 mos as compared to 12.8 mos in the control arm. It is worth of note that in this pooled study, a sub-group analysis showed that, compared to the control group, patients with triple negative subtypes obtained a slightly greater benefit in OS as compared to other patients subgroups, who achieved an OS benefit as well [30].

With regard to the definition of taxane resistance, most of the trials (if not all) in heavily pretreated breast cancer include taxane-pretreated patients, but very few trials have focused on "truly" taxane refractory patients. In fact, the correct definition of "taxane refractory patient" was given by Blum et al [12] who treated with capecitabine, in a phase II study, patients who "have shown either primary resistance to paclitaxel (disease progression while receiving paclitaxel therapy) or response followed by progression while still on therapy (paclitaxel failure)". Contrarily to this definition, most trials have defined as "taxane refractory" those patients with tumor progression within 1 year after treatment with taxanes, which is quite different from the definition given by Blum et al.

In our retrospective study we have selected only those patients who were strictly adherent to the Blum's definition of taxane resistance. The 19.8% response rate observed and the 42.5 % overall disease control is of particular relevance in this population of "truly" taxane refractory patients. Our results compare well to those reported by Gamucci et al [31], in another observational study: 21.1% response in 133 taxane pretreated patients.

Nevertheless, one limitation of observational studies is their retrospective nature. In fact, the observational studies may overestimate the effectiveness of a drug because of: 1) potential bias in outcome assessment; 2) patient selection bias; 3) poor reporting; 4) presence of mixed population; 5) lack of external validation and follow-up. On the other hand, this kind of studies gives a picture of the drug activity in a "real world" scenario. With regard to eribulin, our results show that clinical

outcome observed in clinical practice is very similar to that reported in phase II-III studies, confirming eribulin as "reference drug" in taxane pretreated patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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