

Prospective Analysis of Patients with Metastatic Breast Cancer receiving Eribulin Mesylate as Second or More Lines of Chemotherapy: An Indian Experience

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ABSTRACT

BACKGROUND: Eribulin mesylate is a non-taxane microtubule inhibitor which can be used after anthracycline and taxane treatment in patients with metastatic breast cancer (MBC). The purpose of this study was to investigate the efficacy and safety of eribulin monotherapy in heavily pretreated patients with MBC.

METHODS: In this study, a total of 45 eligible patients with MBC who received eribulin in HCG Cancer Speciality Center from November 2014 to March 2016 were prospectively analyzed. Breslow (generalized Wilcoxon) survival analysis was carried out for progression-free survival and for overall survival. Patients were excluded if they had not taken treatment for 3 cycles and defaulted/expired during the treatment.

RESULTS: In this study, median age of patients was 52 years. A total of 27 (60%) patients had estrogen receptor and progesterone receptor (PR) positive primary tumors, whereas HER2 was overexpressed or amplified in 7 (15.6%); a triple negative subtype was recorded in 13 patients (28.9%). Regarding toxicity, 30 patients (66.67%) tolerated treatment well and 3 patients (6.67%) got anemia, 6 patients (13.3%) experienced neutropenia, and 7 (15.62%) patients had neurological toxicity. About 14 (31.1%) patients showed PR, 12 (26.7%) patients had stable disease (SD), whereas 19 (42.25%) patients showed progression disease (PD). Response evaluation at 6 cycles was possible in 18 patients and revealed that 4 (22.5%) patients showed PR, 10 (55.5%) patients had SD, whereas 4 (22.2%) patients had PD. Progression-free survival of the overall study population was 3.95 months.

CONCLUSIONS: Eribulin mesylate is efficacious and tolerable chemotherapy as second- and third-line treatment options for MBC.

KEYWORDS: Breast cancer, eribulin mesylate, progression-free survival, overall survival, cancer chemotherapy

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Introduction

Breast cancer is the most common cancer in women, affecting almost 1 in 8 women worldwide, and the second most common cause of cancer deaths in women and one of the leading cancers in India.^{1,2} Metastatic breast cancer (MBC) remains an incurable disease despite considerable progress and new treatment options.^{3,4} Anthracyclines and taxanes are both standard treatment in the adjuvant setting; therefore, most of the patients with MBC are generally already exposed to such agents. Treatment guidelines for managing MBC do not preferentially recommend any particular chemotherapeutic agent, neither as combination nor monotherapy in the second line and later settings. Although capecitabine, gemcitabine, and vinca alkaloids are popular choices in these patients, there is still a great unmet need of improving the response rates and quality of life, along with possibly providing overall survival (OS) benefits.^{5,6}

Eribulin mesylate is a non-taxane microtubule inhibitor which is a structurally synthetic halichondrin B analogue. Eribulin shows its cytotoxic effect by inhibiting microtubule growth and sequestering tubulin, finally causing G2-M cell cycle arrest and cell death through apoptosis.³ In addition to its anti-mitotic effects, eribulin may cause tumor vasculature remodeling and the reversal of epithelial-mesenchymal transition, which may decrease the invasiveness and metastasis of tumor cells.⁷

Data from at least 4 phase 1 clinical trials of eribulin showed that neutropenia, fatigue, alopecia, and nausea were the most frequently reported adverse effects. Neutropenia was a dose-limiting toxicity among few subjects across all 4 trials. The maximum tolerated dose during these trials ranged between 1 and 2 mg/m². Eribulin treatment did show partial response in a few patients during these phase I trials.^{8,9} A dose of 1.4 mg/m²/



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Table 1. Sample characteristics and distribution.

DEMOGRAPHIC DETAILS		MEAN ± SD, NO. (%)
Age		52.11 ± 11.29 y
Receptor status	TNBC	13/45 (28.9)
	ERPR +ve	27/45 (60)
	Her2 +ve	7/45 (15.6)
Stage	I	1/45 (2.2)
	II	15/45 (33.33)
	III	14/45 (31.13)
	IV	15/45 (33.33)
Menopause status	Pre	27/45 (60)
	Post	18/45 (40)
Treatment plan	Anthracycline	39/45 (86.7)
	Taxane	42/45 (93.3)
	Capecitabine	24/45 (53.3)
Eribulin line	As second line	10/45 (22.2)
	As third line	15/45 (33.33)
	As fourth line	9/45 (20)
	As fifth or >line	11/45 (24.44)
Toxicity	None	30/45 (66.67)
	Anemia	3/45 (6.67)
	Neutropenia	6/45 (13.3)
	Thrombocytopenia	1/45 (2.2)
	Neuropathy	7/45 (15.6)
	Myelosuppression	4/45 (8.8)

wk as an intravenous bolus was taken ahead for further clinical development among patients with MBC. Results from 3 phase 2 trials among 437 patients with MBC pretreated with anthracyclines. The toxicities observed were similar across all the 3 phase 2 trials with neutropenia being the most commonly reported adverse event.⁹

In EMBRACE study, a pivotal phase 3 trial, eribulin was given at a dose of 1.4 mg/m² as 2- to 5-minute infusion on days 1 and 8 of a 21-day schedule. The OS of heavily pretreated patients with MBC was significantly higher among patients receiving eribulin (13.1 months) as compared with those receiving treatment of physician's choice (10.6 months, $P < .04$).¹⁰ Based on these studies, eribulin was in United States and Europe for treatment of patients with MBC who have received at least 2 prior chemotherapy regimens for late-stage disease, including both anthracyclines and taxanes.^{11,12}

There is, however, paucity of data on eribulin efficacy in India. Given the burden of breast cancer in India,^{1,2} this clearly

shows an unmet need in terms of generating Indian data to see how well this new therapy acts. In the present prospective observational study, we evaluated the safety and efficacy of eribulin in Indian patients with breast cancer, who failed on first-line chemotherapy.

Materials and Methods

The study was submitted for review of institutional ethics committee at HCG Cancer Speciality Center, Bangalore, India. Considering that the subjects in the trial were not being given any additional intervention apart from standard of care, the study was exempted from review by ethics committee.

All study subjects provided written informed consent before any study-related processes were conducted.

The study included patients who were 20 to 74 years of age having histologically or cytologically confirmed MBC. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) had to be ≤ 2 . Patients had to have received and failed on one or more lines of chemotherapy and adequate function of all major organs (including bone marrow, liver, kidney, and lungs).

Eribulin was administered at a dose of 1.4 mg/m² in 2 to 5 minutes by the intravenous route on days 1 and 8 every 3 weeks, until disease progression, severe toxicity, or patient refusal. This was part of subjects' ongoing standard of care and not given additionally as a study medication. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4) (CTCAE guideline). The efficacy of treatment was evaluated by conventional Response Evaluation Criteria in Solid Tumors (RECIST) criteria (RECIST guideline; Eisenhauer et al, 2009) after 3 cycles or whenever clinically indicated.

Patients who had not taken treatment for 3 cycles or defaulted or expired during the course of treatment were excluded from the study.

Primary objective of this study was to assess the response rate of eribulin. Evaluation of toxicity and survival rates was secondary objectives.

Statistical Methods

All data were tabulated, after removing personal identifiers, into database software, and statistical analyses were done using (IBM SPSS version 19.0). Frequency distributions and percentages were evaluated and survival rates were assessed. Breslow (generalized Wilcoxon) survival analysis was performed for progression-free survival (PFS) and for OS.

Results

From November 2014 to March 2016, out of 60 patients screened, 45 patients with MBC were included in the study. The mean age of study patients was 52.11 ± 11.29 years (Table 1); median ECOG PS was 1. Estrogen receptor (ER) and progesterone receptor (PR) were positive in 25 (55%)

Table 2. Frequency distribution of response after third and sixth cycles.

RESPONSE	3 CYCLES	6 CYCLES
	NO. (%)	NO. (%)
PR	14/45 (31.1)	4/18 (22.2)
SD	12/45 (26.7)	10/18 (55.56)
PD	19/45 (42.2)	4/18 (22.2)

Abbreviations: PD, progression disease; PR, progesterone receptor; SD, stable disease.

Table 3. Survival time of study samples.

HORMONAL TYPES	MEAN	STD. ERROR	95% CONFIDENCE INTERVAL	
			LOWER BOUND	UPPER BOUND
TNBC	3.500	0.477	2.565	4.435
Hormone +ve	4.034	0.356	3.337	4.732
Overall	3.897	0.291	3.327	4.468

primary tumors and human epidermal growth factor 2 (HER2) was overexpressed in 7 (15.6%) of the primary tumors, whereas 13 (28.79%) patients showed a triple-negative subtype. Most of the enrolled patients had visceral disease (80.5%), and more than 80% of the patients had multiple metastatic sites, with a median of 2 sites. Within the study patients, 39 (86.7%) had previously received anthracyclines and 42 (93.3%) received taxanes, whereas 24 patients (53.4%) had received capecitabine previously.

In the present prospective observational analysis, patients receiving a median of 3 cycles of eribulin therapy were included. In total, 15 (33.33%) of them received eribulin as the third-line treatment.

No toxicity was observed in 30 (66.67%) patients, whereas 3 (6.67%) patients had anemia, 6 (13.3%) patients experienced neutropenia irrespective of grades, and 7 (15.6%) patients experienced grade 1 and grade 2 neurological toxicity. None of the patients who reported toxicity discontinued treatment.

Partial response was seen after 3 cycles of eribulin among 14 (31.1%) patients, whereas 12 (26.7%) patients had stable disease. Remaining 19 (42.2%) patients showed progressive disease.

Response evaluation at 6 cycles was possible on 18 patients and revealed that 4 patients showed a partial response, 10 patients had a stable disease, whereas 4 patients had progressive disease.

Overall response (OR), defined as patients showing a partial response or a stable disease, was seen in 26 (57.8%) patients at the end of 3 cycles. Clinical benefit, defined as a partial response

or stable disease lasting for 6 months or more, was observed in 14 (77.76%) patients (Table 2).

The response rates were better in patients treated on the third line followed by the fifth line, fourth line, and second line of eribulin. Progression-free survival of the overall study population was 3.89 months (95% confidence interval: 3.32-4.47).

Discussion

This prospective observational study involved 45 patients with MBC treated with eribulin after previous standard treatment with anthracyclines and taxanes. Eribulin had been given to the patients as the second, third, or later lines of chemotherapy.

It is well established that heavily pretreated breast cancer may benefit from later lines of therapy; our analysis shows that OR in the second, third, and later lines of therapy was 40%, 68%, and 52%, respectively. We observed better response in heavily pretreated patients as the third and more than fourth line of chemotherapy which is similar to the results seen in EMBRACE trial. Gamucci et al reported a significant difference in the third line when compared with more advanced lines of chemotherapy.

We recorded 26.5% OR with 6 cycles in 18 patients.

When compared with EMBRACE trial, patients who were pretreated with other chemotherapeutic agents, our analysis also demonstrates that the use of eribulin shows favorable results in terms of response and efficacy.

Regarding the safety of the drug, most of the patients, ie, 66.67%, tolerated eribulin well. The adverse events seen were consistent with known adverse event profile of eribulin such as neutropenia and anemia. The relative high rate of neuropathy in our series may be mainly due to the fact that 7 (15.6%) patients were exposed to more than 3 lines of chemotherapy. As per our data, thrombocytopenia as adverse event was reported less frequently (2.2%), and increased level of transaminases is quite common using eribulin. This has been described in other reports.¹³⁻¹⁶

We did not observe any significant difference in median PFS when compared among the hormonal subgroups, namely, ER/PR positive (4.364 months), triple positive (ER/PR/HER2—4.0 months), and HER2 positive (3.2 months). In case of triple negative, median PFS was 3.455 months (Table 3).

The OR rate in hormonal-positive and triple-negative groups of our study was 52% and 71%, respectively.

A median PFS in the overall study population was 3.95 months; all these results are comparable with the data within the EMBRACE trial (Figure 1).^{10,12}

Main findings of our study suggest that eribulin has achieved similar results as reported in the EMBRACE study in terms of activity and toxicity with this small cohort of patients which can further be tested in large number of patients. Although the EMBRACE trial did not include any Indian patients, this small study gives an idea of understanding the efficacy and safety of eribulin mesylate in Indian patients.

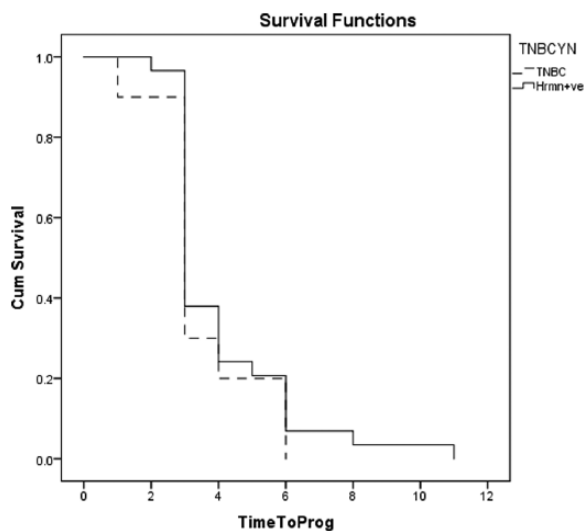


Figure 1. Graph to represent survival over time in months.

Conclusions

Eribulin mesylate is efficacious and tolerable chemotherapy as second- and third-line treatment options for MBC.

Author Contributions

BJS: Primary, Manuscript writing, corresponding author; BPL: Manuscript writing and valuable suggestion; GD: Supervised progress of work; DH: Providing the literature related to manuscript work; NM: Helped in evaluating and editing the manuscript, critical analysis of data; DT: Helped in data collection and data Management; SS: Helped in data collection; AR: Statistical part of manuscript; RR: Statistical part of manuscript; SP: Supervision of work; RN: Supervise in final execution of work.

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