

Eribulin Mesylate: A New Therapeutic Option for Metastatic Breast Cancer

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ABSTRACT

More than a million women are diagnosed with breast cancer annually worldwide. Death from breast cancer is usually a result of chemotherapy-resistant metastatic disease. Eribulin mesylate is a recent addition to the therapeutic armamentarium for treating locally advanced or metastatic breast cancer (MBC) in patients who have received at least two prior chemotherapy regimens for late-stage disease. This synthetic analog, derived from a marine sponge macrolide halichondrin B, inhibits microtubule stability by blocking microtubule growth without affecting microtubule shortening. The US Food and Drug Administration has approved eribulin mesylate as a third-line treatment for MBC refractory to anthracyclines and taxanes based on a Phase III clinical trial showing significantly increased overall survival compared to treatment of investigator's. Asthenia, fatigue, neutropenia, alopecia, nausea, anorexia, and neuropathy are the most frequent adverse effects associated with this drug. The aim of this review was to highlight the importance of this drug in the management of breast cancer. Medline, Excerpta Medica database, cochrane database, medscape, Elsevier Scopus, and clinicaltrials.gov were searched using terms "eribulin," "E7389," "halichondrin," "metastatic breast cancer." Journal articles published from 2007 to 2012 discussing pharmacology and/or clinical trials were screened. The development of this microtubule inhibitor helps to address the need for additional effective regimens for patients progressing after standard treatment with anthracycline- and taxane-containing regimens.

KEY WORDS: Eribulin, halichondrin B, metastatic breast cancer

INTRODUCTION

Breast cancer is the most common cancer in females worldwide accounting for 23% of all newly occurring cancers.^[1] Breast cancer is the most common cause of cancer-related death among women in the USA.^[2] In India, breast cancer ranks as the second most common cancer except in metropolitan cities where its incidence is higher than cervical cancer.^[3] In addition, breast cancer accounts for the second most common (1.7%) cause of cancer-related deaths.^[3]

Breast cancers have been grouped into four distinct molecular subtypes based on gene expression profiling: Luminal A, Luminal B, basal-like and human epidermal growth factor-2 (HER2) tyrosine kinase positive.^[4] HER2-positive subtype is a particularly aggressive clinical phenotype shown by approximately 20-30% patients and characterized by amplification or overexpression of the HER2 gene; patients

of this subset generally benefit from anti-HER2-targeted therapy.^[5] Triple negative breast cancer (TNBC) is another aggressive phenotype with a poor prognosis, classified as basal and defined as disease negative for HER2 as well as for estrogen and progesterone. About one-third cases have a central nervous system (CNS) metastasis.^[6,7] There remains an urgent unmet need for improved targeted agents for this patient population.^[8]

Multiple factors delay the diagnosis in Indian women, such as limited availability and access to cancer health services, lower health literacy, and a social stigma attached to breast cancer. The increasing burden of disease is associated with lifestyle factors such as late age at marriage, age at first birth, reduced breast feeding, westernization of diet, and physical activity patterns.^[1]

Though only 5% of patients have overt metastatic disease at diagnosis, but at least 30% of those initially diagnosed with early breast cancer will later relapse.^[9] Despite significant advances, metastatic breast cancer (MBC) is still considered an incurable disease, with a median survival of 2-3 years; it varies according to histological and molecular

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10.4103/2278-960X.112571

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subtype and age of patient. The most common sites of distant metastasis are lungs, liver, lymph nodes, and bone. Low-risk group includes patients who develop metastatic disease after a long disease-free interval, those whose tumors are positive for a hormone receptor (estrogen or progesterone), those with bone-only disease, and those without extensive visceral organ involvement. High-risk patients include those with rapidly progressive disease or visceral involvement and those with disease shown to be refractory to hormonal manipulation. Factors that predict early recurrences (within 2-3 years of diagnosis) include advanced stage of the primary tumor, younger age, poorly differentiated histology, negative hormonal receptors, ErbB2 receptors and urokinase plasminogen activator overexpression, and the type of treatment modality used at the time of initial diagnosis; HER2, TN, and luminal B subtypes relapse earlier.

Stage IV breast cancer comprising of locally advanced breast cancer (LABC) or MBC is a major therapeutic challenge. Factors that help decide the choice of therapy include longer versus shorter disease-free interval, age, menopausal status, site(s) of recurrence (soft-tissue and bone vs. visceral), the bulk of recurrent disease, symptomatic disease or not, prior adjuvant therapy, organ functions, performance status, co-morbidities, as well as tumor characteristics such as hormone responsiveness status and ErbB2/HER 2-neu receptor expression.^[10]

The current standard strategy to predict hormone sensitivity is the detection of estrogen receptor (ER) and/or progesterone receptor, which are present in Luminal A and Luminal B breast cancer. Endocrine therapy is recommended as primary systemic therapy for patients with MBC and positive hormone receptors. Endocrine manipulations used in treatment of post-menopausal MBC as well as in pre-menopausal women with non-visceral, bone disease as well as low-bulk visceral MBC are selective estrogenic receptor modulators, aromatase inhibitors, and progestational agents. The first-line hormonal therapy consists of an aromatase inhibitor or tamoxifen. Second-line agents include fulvestrant, a selective estrogenic receptor down regulator and luteinizing hormone releasing hormone agonists.

The choice of therapy for patients with MBC typically depends on the risks and benefits of each treatment option, the disease burden and subtype, prior therapeutic exposure, availability, and the patient and physician preference.^[5,11] Initiation of systemic chemotherapy is appropriate for women with metastatic disease that is either hormone receptor-negative, refractory to endocrine therapy, or rapidly progressive, with important visceral involvement regardless of hormonal status. Current

chemotherapeutic options for treatment of MBC include taxanes, anthracyclines, vinca alkaloids, gemcitabine, capecitabine, ixabepilone, and newer formulations of old drugs such as cationic liposomal anthracyclines and nanoparticle-albumin-bound paclitaxel. Taxanes have serious dose-limiting toxicities such as myelosuppression, peripheral sensory neuropathy, allergic reactions, and eventual development of drug resistance.^[12] A recent trial comparing docetaxel with vinorelbine in anthracycline pre-treated disease showed lower response rates with vinorelbine as compared to docetaxel, though hematological adverse effects were ten-fold greater with docetaxel.^[13] Most of these chemotherapeutic agents have not demonstrated an impact on survival in patients.^[14] A recent trial showed that ixabepilone plus capecitabine significantly improves progression-free survival (PFS) compared with capecitabine alone in anthracycline-, taxane-pre-treated, or resistant patients.^[11] Use of chemotherapy can give up to 50-70% response rates when used in combination, but it can also produce more toxicity. Sequential administration of taxanes and anthracyclines is preferred except in aggressive, bulky visceral involvement, especially in young patients. Though debate continues over combination chemotherapy versus sequential mono-therapy, a recent survey of 152 practicing nationwide oncologists revealed preference for use of platinum agents and oral agents (such as capecitabine), despite the lack of evidence from large randomized trials.^[15] The exact total duration of therapy depends on the response and toxicity profile of the drugs used.

Recent advances in the therapeutic armamentarium against MBC include anti-ErbB2 therapy, exemplified by trastuzumab, pertuzumab, and neratinib. Trastuzumab has shown prolonged overall survival (OS) as first-line therapy for MBC. Though cardiac toxicity prevents its concurrent use with anthracyclines, it can be safely given with vinorelbine or taxanes. Lapatinib is a reversible dual tyrosine kinase inhibitor that is active in trastuzumab-resistant ErbB2-positive cells. T-DM1 is an antibody–drug conjugate. The antibody is trastuzumab; DM-1 (emtansine) is an anti-tubule agent. Other drugs in pipeline include HER-affitoxin, anti-DNA repair therapy, anti-angiogenic therapy, and poly (adenosine diphosphate ribose) polymerase-1 (PARP-1) inhibitors. Advances in treatment of MBC are being rapidly moved to the neoadjuvant and adjuvant settings where eradicating micrometastasis is producing better survival and more cures.^[10]

Microtubule inhibitors are among the most frequently used agents for breast cancer chemotherapy, with proven efficacy in both localized and metastatic disease.^[16] Current microtubule-targeted treatment is often limited by development of primary or acquired drug resistance and common side-effects of chronic peripheral sensory and

motor neuropathy that have driven the quest for agents that could be used in taxane-resistant disease or replace taxanes in the early stages of treatment.^[17] Recognized mechanisms of resistance include altered expression of the adenosine triphosphate-binding cassette superfamily of transporters, alteration in DNA repair pathways, mutations in cellular targets, resistance to initiation of the apoptotic pathway, and the development of constitutively activated signaling pathways. The combined use of agents that intersect in receptor crosstalk, such as between the ER and the mammalian target of rapamycin have demonstrated synergy in anti-tumor effects. The recent report of exemestane used in combination with everolimus has shown great promise in this regard.^[18]

Eribulin mesylate is a synthetic analog of halichondrin B, a large polyether macrolide and is a natural product isolated from the marine sponge *Halichondria okadai*. Scarcity of the natural product once hampered efforts to develop halichondrin B as an anti-cancer drug, but a synthetic and structurally simplified derivative with retained high potency and the biologically active macrocyclic lactone C1-C38 moiety of the parent compound was developed.^[19]

METHODS OF LITERATURE SEARCH

Medline, Excerpta Medica database (EMBASE), cochrane database, medscape, Scopus database, and clinicaltrials.gov were searched for published studies using the terms "eribulin," "E7389," "halichondrin B," and "metastatic breast cancer." Journal articles published in English language from 2007 to 2012 discussing pharmacology and/or clinical trials of eribulin were screened.

PHARMACOKINETICS

Eribulin is prepared as an aqueous solution with no requirement of a solvent. It shows linear pharmacokinetics, with rapid distribution, slow elimination, and low renal excretion of unchanged drug. Eribulin has a mean half-life of 40 h, rapid and extensive volume of distribution, and slow-to-moderate clearance. Though metabolized by cytochrome P450 (CYP3A4), it does not affect the metabolism of other therapeutic agents. The recommended dose of eribulin is 1.23 mg/m² (equivalent to 1.4 mg/m² eribulin mesylate) to be administered intravenously over 2-5 min on days 1 and 8 of a 3-week cycle.^[20] Eribulin, which is prepared in an aqueous solution, has a short infusion time, can be administered with or without dilution, does not require steroid or anti-histamine pre-medications, and protection from light is not necessary. These are the distinct advantages of eribulin as compared to currently approved microtubule-targeting agents.^[21] The recommended

dose of eribulin in normal, mild hepatic (Child Pugh A), moderate hepatic (Child Pugh B), and moderate renal impairment (creatinine clearance 30-50 mL/min) is 1.4, 1.1, 0.7, and 1.1 mg/m², respectively, as a 2-5 min intravenous bolus on days 1 and 8 of 21-day cycle.^[21]

MECHANISM OF ACTION

Microtubules are a core component of the mitotic spindle that separates chromosomes during eukaryotic cell division.^[22] Microtubule-targeted agents such as taxanes (paclitaxel and docetaxel), vinca alkaloids (vinorelbine and vinblastine), and epothilones (ixabepilone) act by inhibiting microtubule dynamics, thereby promoting cell cycle arrest and apoptosis.^[22,23] Eribulin possesses a unique chemical structure compared with approved tubulin-targeted agents [Figure 1]. The novel mechanism of action of eribulin, distinct from other known classes of tubulin-targeted agents involves suppression of microtubule polymerization without affecting microtubule depolymerization. In contrast to taxanes and vinca alkaloids which suppress both the growth and shortening phase of microtubule dynamic instability, eribulin binds to interdimer interface or β -tubulin subunit alone and inhibits only the microtubular growth phase of microtubular dynamics instability in interphase cells (polymerization) with no effect on shortening (depolymerization).^[24,25] Eribulin also promotes centromere spindle relaxation without affecting the rate of stretching.^[9] Tubulin is sequestered into non-functional aggregates, leading to an irreversible arrest at G₂-M phase followed by apoptosis after prolonged mitotic blockade.^[26-28] Several biochemical correlates of apoptosis are seen in eribulin-treated human lymphoma and prostate cancer cells, including phosphorylation of Bcl-2, cytochrome c release from mitochondria, activation of caspase-3 and -9, and cleavage of PARP.^[19]

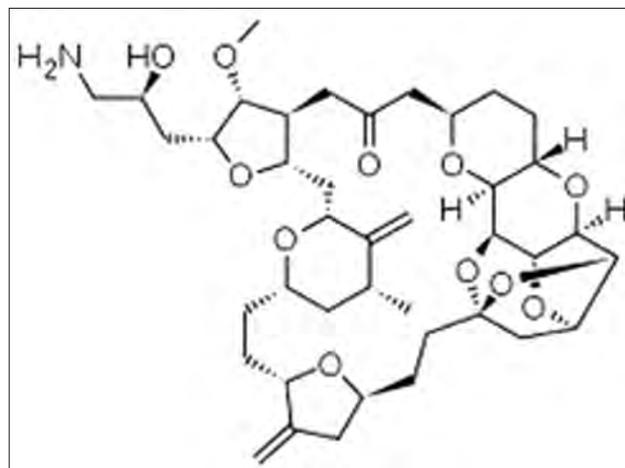


Figure 1: Eribulin mesylate

CLINICAL STUDIES WITH ERIBULIN MESYLATE

Eribulin has demonstrated broad spectrum pre-clinical anti-tumor activity against a wide variety of human cancer types.^[29] Encouraging Phase I and Phase II studies paved the way for the Phase III trial EMBRACE (Eisai MBC study Assessing Physicians choice vs. E7389).^[30] 762 women with LABC or MBC were randomly allotted in a 2:1 ratio to eribulin 1.4 mg/m² over 2-5 min on days 1 and 8 of a 21-day cycle ($n=508$) or treatment of physicians choice (TPC) ($n=254$), defined as any single-agent chemotherapy or hormonal, or biological treatment approved for the treatment of cancer and to be administered according to local practice, radiotherapy, or symptomatic treatment alone.^[31] The TPC arm was selected because at that time, there was no single internationally acceptable or approved chemotherapy regimen for women with heavily pre-treated MBC. This design had the added advantage of reflecting “real life” choices for these women. Treatment continued until disease progression, unacceptable toxic effects, patient or physician request to discontinue, or serious protocol non-compliance. The study results showed a significant increase in OS for eribulin (13.1 months, 95% confidence interval (CI): 11.8-14.3) compared with TPC (10.6 months, 95% CI: 9.3-12.5; hazard ratio (HR): 0.81, 95% CI: 0.66-0.99; $P=0.041$) in the intention-to-treat population. The median PFS in eribulin-treated and TPC groups was 3.7 months (95% CI: 3.3-3.9) and 2.2 months (2.1-3.4), respectively (HR: 0.87, 95% CI: 0.71-1.05; $P=0.137$).^[32] The study highlighted that improvement in OS is an achievable endpoint in the advanced breast cancer setting.^[33]

In a recent Phase III trial that compared eribulin with capecitabine involving 1102 patients, eribulin showed anti-cancer activity early in the course of MBC. Although not statistically significant, eribulin in comparison with capecitabine demonstrated an OS benefit (15.9 vs. 14.5 months (HR: 0.879; 95% CI: 0.770-1.003; $P=0.056$)). Further evaluations of patient subsets showed greater median OS in HER2-negative breast cancer (15.9 vs. 13.5 months (HR: 0.838; 95% CI: 0.715-0.983; $P=0.030$)) and TNBC patients (14.4 vs. 9.4 months).^[34,35]

Preliminary results from a Phase II study of eribulin with trastuzumab as first-line therapy for HER2 + LABC/MBC showed an objective response rate (ORR) of 59.3% and median PFS of 9.2 months (range: 1.35-14.19 months). The combination showed considerable activity with acceptable toxicity to warrant further exploration.^[36]

In a single-arm, multi-center open-label Phase II trial, Japanese patients pre-treated with an anthracycline and a taxane received 1.4 mg/m² eribulin mesylate; ORR observed

was 21.3% (95% CI: 12.9-31.8), PFS was 3.7 months (95% CI: 2.0-4.4), and OS was 11.1 months (95% CI: 7.9-15.8).^[37]

A Phase II study is evaluating the toxicity profiles of combination of eribulin and cyclophosphamide versus docetaxel/cyclophosphamide as neoadjuvant therapy for locally advanced HER2-negative breast cancer. Another Phase II trial will study how well the co-administration of eribulin mesylate and carboplatin together before surgery works in treating patients with stage I-III TNBC. Ongoing trials are investigating the role of eribulin (mono-therapy and combination) as first-line therapy for MBC and also along with targeted agents such as lapatinib and ramucirumab. A study evaluating important quality of life and pharmacokinetic correlates is currently recruiting participants. Eribulin is also being evaluated in advanced or recurrent cervical cancer.^[38]

Though eribulin has been evaluated in Phase II studies in other advanced solid carcinomas, such as non-small-cell lung carcinoma, pancreatic carcinoma, and head and neck tumors, it did not result in clinically significant median PFS in these tumors.^[39-42] However, in a recent Phase II study, eribulin mesylate demonstrated activity and a relatively favorable toxicity profile in patients with metastatic castration-resistant prostate cancer.^[43]

ADVERSE EFFECTS

Eribulin has demonstrated a manageable tolerability profile. In the EMBRACE study, direct comparison of individual toxicity between eribulin and TPC is complicated by the heterogenous nature of the TPC treatments and their differing side-effect profiles. The most common adverse effects observed in both the treatment arms were asthenia (or fatigue) and neutropenia, most of which were Grade 1 or 2.^[44,45] Grade 3 or 4 events that were more frequent in the eribulin group than in the TPC group were leukopenia, neutropenia, and peripheral neuropathy. There was more myelosuppression with eribulin, incidence of Grade 3 or 4 neutropenia being 45% versus 21%; majority of these were asymptomatic. Nevertheless, the incidences of Grade 3 and 4 febrile neutropenia and peripheral neuropathy were low.

Peripheral neuropathy was the most common adverse event leading to discontinuation of eribulin in 5% of patients, but in those patients with Grade 3 or 4 peripheral neuropathy who discontinued treatment, neuropathy improved to Grade 2 or lower in later cycles after delays and dose reductions.^[46] An experimental study by Wozniak *et al.* indicated that eribulin mesylate induces less neuropathy in mice than paclitaxel or ixabepilone at equivalent maximum tolerated dose-based doses.^[47]

Clinically also, eribulin has shown a lower incidence of severe neuropathy as compared to ixabepilone and paclitaxel. In a Phase II study, incidences of peripheral neuropathy and treatment-emergent neuropathy eribulin versus ixabepilone were 31.3% versus 44.0% ($P=0.16$) and 33.3% versus 48.0% ($P=0.13$). Eribulin showed a longer time to onset of treatment-emergent neuropathy and fewer discontinuations due to neuropathy and other toxicities.^[48]

CURRENT PLACE IN THERAPY

The Food and Drug Administration (FDA) has approved three agents for treatment of patients with MBC refractory to anthracyclines and taxanes: Capecitabine, ixabepilone, and eribulin mesylate.^[49] As MBC is no longer curable, primary goals of therapy in this setting and particularly in later lines of therapy include improving/maintaining quality of life, reducing tumor-related symptoms, and prolonging survival. However, there is no fixed algorithm of therapeutic choices.^[50]

Eribulin is a promising new alternative for women with pre-treated (including an anthracycline and a taxane) MBC. It is the third single-agent chemotherapy that has improved OS (after anthracycline and taxane) in advanced breast cancer.^[51] The US FDA has approved eribulin mesylate as a third-line for MBC refractory to anthracyclines and taxanes. Its unique mechanism of action enhances its ability to overcome chemo-resistance. Eribulin has shown clinical activity in patients with a wide range of tumors who had exhausted established treatment options.^[9,52] Many tubulin-targeted agents have the disadvantage of long infusion times. The infusion time for eribulin is significantly shorter than other intravenously administered microtubule-targeted agents (less than 5 min vs. 180 min).^[53] Unlike current agents that need to administer pre-medications, and special storage, mixing, or administration requirements, eribulin does not need any such preparations.^[54] In a cost-analysis study based on clinical data from the EMBRACE trial, eribulin added 0.208 life-years saved and 0.119 quality-adjusted life years (QALY) with an incremental cost over TPC of \$24,035; and therefore, a cost of \$115,369/LY and an incremental cost-effectiveness ratio of \$201,790/QALY. Eribulin was shown to be cost-effective when compared to doxorubicin, nab-paclitaxel, ixabepilone, and capecitabine but showed marginal cost-effectiveness for less expensive drugs such as vinorelbine and gemcitabine.^[55,56]

A manageable side-effect profile, a low incidence of peripheral neuropathy, tolerance at full doses in renal dysfunction, and lack of drug–drug interactions or hypersensitivity make eribulin a welcome addition to the therapeutic armamentarium against advanced breast

cancer. Novel amine-containing analogs of eribulin mesylate are being designed and have shown efficacy in multidrug resistant (MDR) tumors.^[57] Since eribulin is the only drug that has shown a survival advantage, it is likely to be partnered with other chemotherapy agents, anti-HER2 agents, and other drugs targeting important biologic pathways. Ultimately, identification of predictors of response will be critical for rational patient selection and for limiting non-specific toxicities in those who are unlikely to benefit. The identification of biomarkers to predict therapeutic response to eribulin will greatly enhance its use in the breast cancer treatment armamentarium.^[19] Nevertheless, eribulin establishes a potential new standard treatment for women with heavily pre-treated MBC, for whom there was no chemotherapy treatment with proven survival benefit till now.

CONCLUSION

Breast cancer is the most common cancer in women through the 21st century. Management of advanced breast cancer depends on the site and extent of metastases, co-morbid conditions, and clinical tumor characteristics. Resistance to chemotherapeutic agents remains a consistent obstacle in treatment success. Eribulin is a non-taxane microtubule dynamics inhibitor, approved by the FDA for use in patients who have previously received at least two prior chemotherapeutic regimens for MBC. The low probability of drug–drug interactions, easy administration as bolus, low hypersensitivity chances, and good tolerability in renal dysfunction patients make eribulin a promising drug. This novel spindle toxin presents clinicians with a beneficial addition to the therapeutic arsenal.

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How to cite this article: Aditya S. Eribulin mesylate: A new therapeutic option for metastatic breast cancer. *J Basic Clin Reprod Sci* 2013;2:6-12.
Source of Support: Nil, **Conflict of Interest:** None declared

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