Eribulin Mesylate: Unique Advancement in Metastatic Breast Cancer

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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Breast cancer is the most common malignant disease among women in the United States, with 209,060 new cases estimated in 2010. Although 40,230 deaths were predicted to occur in 2010 overall, thanks to early detection and advancing treatments, there has been a decline in breast cancer mortality (American Cancer Society, 2010). Initial treatment options for breast cancer include surgical, radiation, endocrine, biologic, and cytotoxic therapies used alone or in combination. Therapy is personalized based on tumor histology, axillary node status, hormone receptor status, HER2/*neu* status, menopausal status, age, comorbid conditions, and gene expression analysis (NCCN, 2011; Anders & Carey, 2008).

Treatment of early-stage and locally advanced breast cancer has resulted in improved disease outcomes. Whereas they were once employed in the metastatic breast cancer (MBC) setting, category 1 evidence now supports the use of both anthracyclines and taxanes in the neoadjuvant and adjuvant settings (NCCN, 2011). Unfortunately, despite aggressive initial therapy, 20% of women with early-stage breast cancer will be diagnosed with distant metastases within 5 years (Cigler & Vahdat, 2010).

Although the standard of care in MBC is poorly defined, one choice for relapsed disease is retreatment with anthracyclines or taxanes. Unfortunately, those pretreated with such agents will often demonstrate resistance with subsequent treatment rechallenges; with a median survival of 2 to 4 years, prognosis in MBC remains poor (Brufsky, 2010). At present, cure is not possible in the metastatic setting but 40% of patients achieve disease control for 6 months or longer with third-line chemotherapy (Gradishar, 2010). Therefore, the development of novel agents with unique mechanisms of action, such as eribulin mesylate (Halaven), can offer viable options to some pretreated patients with MBC.

Development

Eribulin is a structurally simplified synthetic analog of the marine natural macrolide halichondrin B, a product first isolated from the Japanese sponge *Halichondria okadai* (Gradishar, 2010; Jimeno, 2009). Initial results were promising in terms of antitumor potential but early experiments were limited by a small supply of natural product. Development continued once the National Cancer Institute funded the collection of 1 metric ton of the sponge that produced 310 mg of halichondrin B. Following this action, a laboratory was able to completely synthesize halichondrin B in 90 chemical steps (Jimeno, 2009).

Based on the initial synthesis, Eisai Research Institute created a number of halichondrin B derivates that

were bioactive and retained the potent cell growth inhibitory activity of the natural product. Eribulin, consisting of a biologically active C1-C38 moiety of halichondrin B, is one such analog (Cigler & Vahdat, 2010). In preclinical studies, eribulin demonstrated antitumor activity in breast, colon, prostate, and melanoma cancer cell lines in vitro. In vivo, antitumor activity was demonstrated in human tumor xenografts, including melanoma, ovarian, colon, and breast cancers. Importantly, eribulin restricted in vivo tumor growth in human ovarian cancer cell lines felt to be taxane-resistant (Cigler & Vahdat, 2010; Tan et al., 2009).

Mechanism of Action

Most tubulin-binding agents—including the taxanes, vinca alkaloids, and epothilones—inhibit both the shortening and growth phases of microtubule dynamic instability. Eribulin is a nontaxane microtubule dynamics inhibitor with a unique mechanism of action. It inhibits the growth phase of microtubules without affecting microtubule-shortening parameters and sequesters tubulin into nonproductive aggregates (Eisai, Inc., 2010; Smith et al., 2009). Anticancer activity occurs by preventing the formation of functional spindles by jamming microtubule polymerization with no effect on depolymerization, thus inducing G2M cell cycle blockade, mitotic arrest, and eventual apoptosis (Gradishar, 2010; Smith et al., 2010; Tan et al., 2009).

Clinical Studies

With exciting findings from the preclinical studies of eribulin, four phase I trials were designed to explore the ideal route of administration, appropriate dosing regimen, and pharmacokinetics in patients with advanced solid tumors (Goel et al., 2009; Gradishar, 2010; Tan et al., 2009). These trials demonstrated manageable toxicity and measured a long terminal half-life of up to 48 hours after administration, with low renal clearance. When given in combination with carboplatin, no pharmacokinetic interactions were reported, marking eribulin as an important compound for future use in combination therapy trials (Gradishar, 2010).

Building on phase I results, three phase II trials investigated the efficacy and tolerability of eribulin in heavily pretreated patients with locally advanced or MBC. All three trials revealed a manageable tolerability profile, with the most commonly reported adverse event being neutropenia at 64%, 54%, and 95.1%. There was a low incidence of grade 3/4 peripheral neuropathy at 5%, 6.9%, and 3.7% across the three trials (Gradishar, 2010; Iwata et al., 2010; Vahdat et al., 2009). These trials proved that eribulin, with its unique mechanism of action, was a therapeutically active agent worthy of additional investigation in the MBC setting.

With efficacy and tolerability established, EMBRACE (E305), a phase III trial, was initiated to compare overall survival (OS) for eribulin to a novel comparator arm consisting of a treatment of the physician's choice (Twelves et al., 2010). This was an open-label, randomized, multicenter trial of 762 patients with MBC who had received ≥ 2 prior therapies and experienced disease progression within 6 months of their last chemotherapy. Patients had to have received prior anthracycline- and taxane-based chemotherapy for adjuvant or metastatic disease. Patients were randomized (2:1) to receive eribulin (n = 508) or a single agent selected prior to randomization (n = 254). Randomization was stratified by geographic region, HER2/*neu* status, and prior capecitabine exposure (Eisai, Inc., 2010; Twelves et al., 2010).

Eribulin was administered at 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. Control arm therapy was reflective of standard physician practices in that 97% of patients received chemotherapy consisting of single-agent vinorelbine, gemcitabine, capecitabine (Xeloda), a taxane, an anthracycline, or other. Endocrine therapy was given to 3% of patients. Baseline characteristics and demographics were comparable between treatment arms, with a median age of 55 years and 92% of participants Caucasian. Population characteristics were as follows: 67% estrogen receptor positive, 49% progesterone receptor positive, 16% HER2/*neu* positive, 19% triple negative status, 82% visceral disease, and 61% bone disease (Eisai, Inc., 2010; Cigler & Vahdat, 2010; Gradishar, 2010).

Eribulin demonstrated a statistically significant (p = .041) OS benefit, with a median OS of 13.12 vs. 10.65 months in the control arm. An updated analysis was conducted when 77% of events had been observed, which was consistent with the primary analysis. Eribulin patients had an objective response rate of 11% as measured by RECIST criteria and a median response duration of 4.2 months (Eisai, Inc., 2010). Again, patients were heavily pretreated, and had previously received between two and five therapies (Twelves et al., 2010).

Adverse Effects

Among patients receiving eribulin, the most common adverse events (reported in > 25%) were neutropenia, anemia, asthenia, fatigue, alopecia, peripheral neuropathy, nausea, and constipation. Patients with baseline absolute neutrophil counts < 1,500/µL were not included in the study. Of patients in the EMBRACE trial, 28% experienced grade 3 neutropenia and 29% experienced grade 4 neutropenia. Febrile neutropenia occurred in 5% of patients with two deaths recorded. The most common adverse event resulting in drug discontinuation was peripheral neuropathy (5%). QT prolongation was seen on day 8, independent of eribulin concentration (Eisai, Inc., 2010).

Table 1. Dose Modification in Hepatic and Renal Impairment

Descriptor	Dosage adjustment
Mild hepatic impairment (Child-Pugh A)[a]	1.1 mg/m^2
Moderate hepatic impairment (Child-Pugh B)[a]	0.7 mg/m^2
Severe hepatic impairment	Not studied
Mild renal impairment (CrCl = 50–80 mL/min)	None
Moderate renal impairment (CrCl = 30–50 mL/min)	1.1 mg/m^2
Severe renal impairment (CrCl < 30 mL/min)	Not studied

Note. CrCl = creatinine clearance. Recommendations of the manufacturer. For full details see Halaven prescribing information (Eisai, Inc., 2010).
[a]See Table 2

Dosing and Administration

Eribulin is recommended at 1.4 mg/m^2 IV on days 1 and 8 of a 21-day cycle, administered over a 2- to 5-minute period. As outlined in Table 1, dose reduction is recommended in those with hepatic (based on Child-Pugh scoring as shown in Table 2) and renal impairment; use in pregnancy has not been studied. Eribulin comes in a single-use vial, 1 mg/2 mL, and can be stored, undiluted, in a syringe for up to 4 hours at room temperature or for 24 hours under refrigeration (40°F/4°C). It can be administered undiluted or diluted in 100 mL of 0.9% sodium chloride injection, USP, and is not listed as a vesicant. Eribulin should not be diluted or given with any solution containing dextrose (Eisai, Inc., 2010).

Table 2. Child-Pugh Scoring System

Variable	1 point	2 points	3 points
Albumin	> 3.5 g/dL	2.8–3.5 g/dL	< 2.8 g/dL
Ascites	None	Controlled	Refractory
Encephalopathy	None	Controlled	Advanced
Bilirubin	< 2 mg/dL	2–3 mg/dL	> 3 mg/dL
Prothrombin time	1–3 sec	4–6 sec	> 6 sec

Class assignment/Score interpretation: Class A, 5–6 points; Class B, 7–9 points; Class C, 1–15 points

Note. Adapted from Durand & Valla (2008)

Implications for Advanced Practice

With the approval of eribulin, advanced practitioners (APs) have a new therapeutic option, with a novel mechanism of action, to offer patients in the metastatic setting. Primary roles for APs with regard to eribulin include patient monitoring and counseling, nursing staff education, appropriate dosage adjustments, and management of adverse effects. A history and physical exam should be performed on each patient prior to the start of eribulin therapy. If a patient has a known cardiac history, the AP should recommend electrocardiogram monitoring and should not administer eribulin to patients with congenital long-QT syndrome (Eisai, Inc., 2010).

Advanced practitioners should monitor a complete blood count (CBC) prior to each dose of therapy and, given that the average time to nadir was 13 days, may choose to monitor the CBC more frequently. Although prophylactic growth factor was not administered in the EMBRACE trial, APs may want to consider the addition of a growth factor up front, particularly in patients with an increased risk of neutropenic complications. See Table 3 for the recommended dosage adjustments in the presence of neutropenia.

Patients with liver enzymes measured > 3 times the upper limit of normal (ULN) and those

Table 3. Recommended Dose Reductions for Toxicity

Toxicity scale	Recommended dose
ANC < 500/µL for > 7 days	1.1 mg/m^2
ANC < 1,000/µL with fever or infection	1.1 mg/m^2
Platelets < 25,000/µL	1.1 mg/m^2
Platelets < 50,000/µL requiring transfusion	1.1 mg/m^2
Grade 3 or 4 peripheral neuropathy[a]	1.1 mg/m^2
Do not reescalate eribulin dose after it has been reduced Occurrence of any event requiring dose reduction while at 1.1 mg/m^2 → 0.7 mg/m^2 Occurrence of any event requiring dose reduction while at 0.7 mg/m^2 → discontinue	

Note. ANC = absolute neutrophil count. Toxicities graded using National Cancer Institute adverse events criteria. Adapted from Halaven package insert (Eisai, Inc., 2010).
[a]Resume at reduced dose once neuropathy has recovered to ≤ grade 2.

with bilirubin levels > 1.5 times the ULN experienced a higher incidence of grade 4 neutropenia (Eisai, Inc., 2010). Therefore, APs should review baseline liver functions prior to each dose of therapy, and dose-adjustment as indicated (Table 1). Advanced practitioners should assess for the presence of peripheral neuropathy at baseline and prior to each dose of eribulin and, as recommended (see Table 3), dose-delay or dose-adjust in the case of grade 3 or 4 peripheral neuropathy.

Summary

Among MBC patients, morbidity and mortality are of significant clinical concern. To date, cure is not possible in the relapsed setting. Novel treatments that preserve quality of life are needed to improve outcomes in the metastatic setting. As a nontaxane microtubule dynamics inhibitor with a unique mechanism of action, eribulin has demonstrated an improvement in OS vs. control in pretreated patients with MBC. On November 15, 2010, the FDA granted approval of eribulin for use in patients with MBC who have received at least two prior therapies for treatment of their disease (prior therapy must have included an anthracycline and a taxane in the adjuvant or metastatic setting). With its manageable toxicity profile, this drug provides APs with an important addition to their MBC chemotherapy armamentarium.

DISCLOSURES

The author has no conflicts of interest to disclose.

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