Advances in therapy: eribulin improves survival for metastatic breast cancer

Patrick G. Morris

Despite advances in cancer biology, chemotherapy remains the backbone of treatment approaches for many patients with metastatic breast cancer (MBC). Halichondrins, derived from marine sponges, have significant potential as potent antimicrotubule agents. Eribulin, with proven preclinical activity, is a synthetic halichondrin analog with novel actions on tubulin including suppression of microtubule polymerization. Phase I and II studies in MBC identified neutropenia as the dose-limiting toxicity and a maximum tolerated dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. An encouraging response rate of 11.5% in refractory MBC led to the launch of the phase III Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin trial, in which heavily pretreated patients with MBC were randomized 2 : 1 to intravenous eribulin or monotherapy of the investigator's choice. Recently, it was reported that this important study of 762 patients met its primary endpoint of overall survival: eribulin was associated with an improvement in median overall survival from 10.65 months to 13.12 months (hazard ratio 0.8; 95% confidence interval 0.66–0.99) and a response rate of 12.2%. In general, the side effect profile of eribulin seems to be acceptable, as although neutropenia occurred in 45% of the patients, febrile neutropenia was rare and the incidence of neuropathy was low. These findings show that eribulin is potentially a new active agent for MBC, although results of ongoing studies are awaited to confirm the reported benefit. Future studies will investigate the potential role of eribulin in other settings, including for early breast cancer, to ascertain how to optimally incorporate this new agent into current treatment paradigms. *Anti-Cancer Drugs* **21:885–889 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Every year more than one million new cases of breast cancer are diagnosed worldwide [1]. In many developed countries, including the United States, breast cancer is the most commonly diagnosed malignancy and a leading cause of cancer death [2]. Although the diagnosis of metastases without a history of early stage disease is rare, and the overall incidence of early breast cancer has been declining in recent years, metastatic breast cancer (MBC) remains an important public health concern, as approximately one-third of women with early stage breast cancer will eventually develop MBC within 5 years of their initial diagnosis. Despite advances in treatment, MBC remains incurable and accounted for over 40 000 deaths in the United States in 2009 [2]. Recently, advances in molecular medicine and a greater understanding of tumor biology have begun to translate into therapeutic innovations for subgroups of patients with MBC.

Breast cancer is a chemosensitive disease, for which numerous active cytotoxic agents are currently available. Many patients are treated with chemotherapy after definitive local therapy for early stage breast cancer, and this approach is associated with improved survival independent of the choice of regimen [3]. For patients who develop MBC, many investigators favor the use of serial endocrine manipulation for patients with tumors that express the estrogen receptor and progesterone receptor, as this is an effective approach with a corresponding low risk of serious side effects [4]. However, for patients with hormone-refractory disease, hormone receptor-negative disease, or for women with rapidly progressive visceral metastases, systemic chemotherapy has a major role in treatment [4]. Furthermore, chemotherapy generally forms the backbone of treatment in combination with novel targeted therapies. For patients with tumors that overexpress the human epidermal growth factor receptor 2 (HER2), the monoclonal antibody, trastuzumab, is usually combined with cytotoxic chemotherapy [5]. More recently, the addition of an inhibitor of poly-ADP-ribose polymerase to DNA damaging cytotoxic chemotherapy has improved survival for patients with 'triple-negative' (estrogen receptor, progesterone receptor, HER2 negative) breast cancer [6,7]. In selecting an appropriate chemotherapy regimen, the individualized approach to treatment requires consideration of both patient and tumor characteristics.

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These include consideration of a patient's functional status, symptoms, the patient's own treatment preferences, earlier therapies, and residual toxicities. In general, anthracyclines and taxanes are the most active cytotoxic agents. However, as many patients receive these treatments as adjuvant therapy, broader use in the metastatic setting is more limited. For example, anthracycline use is limited by the cumulative risk of cardiomyopathy and broader taxane use is restricted by cumulative neurotoxicity and tumor progression on earlier taxane-based therapy. Therefore, chemotherapy remains an important part of the treatment paradigm for breast cancer regardless of the stage, and the development of novel cytotoxic agents is desirable.

Eribulin

The search for active agents for the treatment of MBC has included a meticulous assessment of naturally occurring compounds from the oceans. One such agent is halichondrin B, a large polyether macrolide, which is derived from the marine sponge *Halichondria okadai* found off the coast of Japan [8–11]. Halichondrins are potent antimicrotubule cytotoxic agents with activity against a variety of tumor cells *in vitro* [11–13]. However, a major limitation to the use of many naturally occurring substances as anticancer agents is the availability of adequate quantities of the naturally occurring compound. Hence, the synthesis of eribulin mesylate, formerly E7389, a synthetic halichondrin analog, was a major step in the investigation of these substances as possible anticancer agents [14,15].

Preclinical studies showed that the cytotoxic effect of eribulin was maintained in paclitaxel-resistant cell lines, including those with mutations in β-tubulin [16–18]. Furthermore, eribulin inhibited the growth of human tumor xenografts, including breast cancer [18]. This notable activity may be related to a somewhat novel mechanism of action. Similar to other microtubule agents, eribulin seems to bind to a single site on tubulin, close to the vinca-binding site, and exerts a cytotoxic effect by blocking cell cycle progression at the G2–M phase, leading to apoptosis and ultimately resulting in tumor growth suppression [13,17–20]. However, unlike other microtubule agents such as taxanes, vinca alkaloids, and epothilones, eribulin seems to have no effect on tubule shortening and causes sequestration of tubulin into nonfunctional aggregates [13,19,20]. Taken together, these attributes make eribulin an exciting compound for investigation in clinical studies.

Clinical studies of eribulin: phase I trials

In a phase I study, 21 patients with solid tumors received eribulin as a 1-h infusion once every 21 days and the maximum tolerated dose was found to be 2 mg/m^2 [21]. The dose-limiting toxicity was febrile neutropenia, which occurred in three patients treated at 4 mg/m^2. Common toxicities included alopecia, fatigue, anorexia, and nausea. However, for other agents in MBC, such as paclitaxel, an alternative weekly dose schedule is often preferred, as this approach improves the tolerability and efficacy [22]. Therefore, eribulin was examined weekly in two phase I studies on days 1, 8, and 15 of a 28-day cycle [23,24]. Again, the main dose-limiting toxicities were neutropenia (25% patients) and febrile neutropenia, although there was some hypoglycemia, hypophosphatemia, and fatigue (53% patients) [23]. These studies identified a maximum tolerated dose of 1.4 mg/m^2. Interestingly, unlike other antimicrotubule agents, these early studies suggested that neuropathy was not a prominent side effect of eribulin. For example, in the study by Goel *et al.* [23], eight out of the 32 (25%) patients had grade 1/2 neuropathy and there was no grade 3/4 neuropathy. Furthermore, only five (16%) patients had alopecia. This latter approach using the weekly dose schedule of eribulin has been adopted in subsequent clinical trials.

Clinical studies of eribulin: phase II trials

Initially a phase II trial (study 201) of 1.4 mg/m^2 of eribulin on days 1, 8, and 15 of a 28-day cycle was launched [25]. However, there were substantial problems with neutropenia at day 15 in the first 70 patients treated, leading to dose interruption or omission. Therefore, the schedule was changed to days 1 and 8 of a 21-day cycle for the subsequent 33 patients. In total, these 103 patients, who were all treated with weekly eribulin, had received both anthracyclines and taxanes and a median of four chemotherapy regimens earlier [25]. In the per-protocol population ($n = 87$), the objective response rate was 11.5% [95% confidence interval (CI), 5.7–20.1]. In addition, the clinical benefit rate (response plus stable disease ≥ 6 months) was 17.2% (95% CI, 10.0–26.8) and the median progression-free survival (PFS) was 2.6 months (range: 1–453 days). Interestingly, for the subgroup of 10 patients who experienced disease response to eribulin, a substantial benefit in overall survival (OS) was seen (median 18.4 months; range: 372–785 days). Despite the change in treatment schedule, the most common grade 3/4 drug-related toxicity remained neutropenia (64% patients). Grade 3 neuropathy occurred in only 5% and there was no grade 4 neuropathy, which is notable as patients with preexisting grade 2 neuropathy were eligible. In a second phase II trial (study 211), 299 patients who had previously been treated with anthracyclines, taxanes, and capecitabine received weekly with 1.4 mg/m^2 eribulin on days 1 and 8 of a 21-day cycle [26]. A similar response rate of 9.3% (95% CI, 6.1–13.4%) has been seen. Again, the clinical benefit rate was similar (17.1%) and the toxicities were as reported earlier.

Clinical studies of eribulin: phase III trials

These encouraging results in heavily pretreated patients led to randomized phase III trials of eribulin for MBC. As noted, anthracyclines and taxanes are the most active chemotherapy agents in breast cancer. For patients who

experience disease progression despite these agents, numerous other active cytotoxic agents have been investigated including gemcitabine, vinorelbine, capecitabine, and ixabepilone. However, for patients with heavily pretreated MBC, no standard of care exists and no individual agent has shown an OS benefit in clinical trials in this setting. Against this background, the Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin (EMBRACE) (305) study was conducted to compare single-agent eribulin with standard chemotherapy for patients with heavily pretreated disease [27]. The results of a planned analysis after 411 deaths were recently presented at the 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago. This was a large international phase III study comparing eribulin with the 'treatment of physician's choice' (TPC). Eligible patients had received two to five chemotherapy regimens earlier, at least two of which must have been for MBC. In addition, the patients were required to have received both anthracyclines and taxanes, to have progressed within 6 months of past chemotherapy, have baseline neuropathy less than or equal to grade 2, and Eastern Cooperative Oncology Group performance status less than or equal to 2. Patients were randomized 2 : 1 to intravenous eribulin of 1.4 mg/m^2 given over 2–5 min on days 1 and 8 of a 21-day cycle or TPC, consisting of any monotherapy (cytotoxic chemotherapy/hormonal therapy/biologic therapy) or supportive care only.

Baseline characteristics in the EMBRACE study were well matched between the treatment arms as shown in Table 1. In total, 762 patients were treated (508 with eribulin and 254 with TPC) who were of a median age of 55.2 years (range: 27–85 years). Patients had received a median of four earlier chemotherapy regimens (range: 1–7). No patients randomized to the TPC arm received best supportive care or biological therapy alone. Furthermore, 96% of the patients in this arm received chemotherapy, consisting of vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxane (15%), and anthracyclines (10%) in decreasing frequency. The study met its primary endpoint; treatment with eribulin was associated with an improvement in the median OS from 10.65 months to 13.12 months; hazard ratio 0.81 (95% CI, 0.66–0.99), $P = 0.041$. In addition, the 1-year survival of patients treated with eribulin was 53.9% as compared with 43.7% for patients who received TPC. In terms of secondary endpoints, on independent review of the intention to treat population, eribulin showed a trend to improvement in median PFS from 2.2 months to 3.7 months (hazard ratio 0.87, 95% CI, 0.71–1.05), although this result was not statistically significant ($P = 0.14$). However, eribulin was associated with an increased response rate (12.2%) over TPC (4.7%) $P = 0.002$, and the clinical benefit rate (response + stable disease ≥ 6 months) was 22.6% as compared with 16.8%. Furthermore, the toxicity profile seemed manageable and consistent with the earlier studies of eribulin. For example, 25% of patients treated with eribulin had a serious adverse event as compared with 25.9% of patients treated with TPC. Although eribulin treatment was commonly associated with neutropenia (45.2% of patients $\geq$ grade 3), as reported earlier, this did not translate into a high rate of febrile neutropenia (Table 2). Furthermore, as predicted from earlier clinical studies, the incidence of neuropathy was low (8.2% of patients $\geq$ grade 3). This does not seem excessive considering that the patients were heavily pretreated and were eligible with less than or equal to grade 2 neuropathy at baseline. Therefore, in summary, this study shows that for patients with heavily pretreated MBC, eribulin is associated with improved OS over standard chemotherapy and a manageable toxicity profile.

Table 1 Patient characteristics in the EMBRACE study [27]

	Eribulin (N=508)	TPC (N=254)	Total (N=762)
Median age (range)	55 (28–85)	56 (27–81)	55 (27–85)
ECOG performance status (%)			
0	43	41	42
1	48	50	49
2	8	9	8
Earlier capecitabine treatment (%)			
Yes	73	74	73
No	27	26	27
Estrogen receptor positive (%)	66	67	67
Progesterone receptor positive (%)	50	48	50
HER2 positive (%)	16	16	16

ECOG, Eastern Cooperative Oncology Group; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin; HER2, human epidermal growth factor receptor 2; TPC, treatment of physician's choice. Adapted from [27].

Table 2 Main toxicities of eribulin in the EMBRACE study occurring in greater than or equal to 2% patients

	Grade 3	Grade 4
Hematological toxicity (%)		
Neutropenia	21.1	24.1
Leukopenia	11.7	2.2
Anemia	1.8	0.2
Febrile neutropenia	3.0	1.2
Nonhematological toxicity (%)		
Fatigue	8.2	0.6
Peripheral neuropathy	7.8	0.4
Dyspnea	3.6	0

EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus Eribulin. Adapted from [27].

Discussion of the EMBRACE study

The EMBRACE study clearly shows that eribulin is active in the treatment of MBC. Importantly, this seems to be the first phase III study to meet its primary endpoint of improved OS in patients with heavily pretreated MBC. This survival benefit for eribulin over standard therapy in this setting is remarkable and contrasts with the failure of agents such as bevacizumab to improve OS when added to chemotherapy in clinical

trials earlier in the treatment paradigm [28–30]. Furthermore, the design of the EMBRACE study reflects 'real-world' practice, wherein physicians chose a therapy based on a combination of patient and tumor-related characteristics. Therefore, this study has obvious implications for clinical practice and potentially establishes eribulin as a new therapeutic option for MBC. Furthermore, it seems that eribulin has a manageable side-effect profile, associated with a low incidence of neuropathy, and unlike some antimicrotubule agents, it can apparently be delivered as a short infusion without the need for premedications. For example, although neutropenia occurred in 45% of patients receiving eribulin in this study, it resulted in febrile neutropenia in only 4.2% patients.

Although the findings from this study are striking, there are some important caveats to consider. First, this was an open-labeled study rather than a placebo-controlled trial. Therefore, investigator bias may have impacted on subsequent therapy (or lack thereof) beyond progression. Although OS is generally considered to be a clean endpoint, it is possible that the patients in the TPC arm may have discontinued therapy at an earlier time-point resulting in inferior survival for that group. Of note, the OS benefit of eribulin occurred without a corresponding clinically significant benefit in PFS. Second, many patients (possibly up to half) received a class of treatment, to which their disease may have already been resistant. For example, although all patients had received anthracyclines and taxanes earlier, in the TPC arm, 38 (15%) patients received taxanes and 24 (10%) were treated with anthracyclines. If patients who were treated with an agent, to which they had been exposed earlier, are excluded from the analysis, would the survival advantage for eribulin be maintained? Third, to date there are no data on the quality of life correlates in this study, and the potential increased costs associated with the use of eribulin are unknown. Finally, these are results from one clinical trial and further validation is required.

Future and ongoing studies

Confirmation of the potential benefits of eribulin for heavily pretreated patients with MBC will hopefully be provided by another ongoing phase III trial. In this trial, (study 301), 1100 patients will be randomized to receive eribulin or oral capecitabine of 2500 mg/m^2/day in two divided doses on days 1–14 of a 21-day cycle [31]. This study has two coprimary endpoints: PFS and OS, and can be stopped early for superiority in OS but not in PFS. In addition, this study contains important quality of life and pharmacokinetic/pharmacodynamic correlates. This important study will use the same eribulin dosing schedule as the EMBRACE study and will also study patients with disease progression despite receiving anthracyclines and taxanes [32]. However, unlike the 305 study reported by Twelves *et al.* [31], patients are not permitted to have received capecitabine or more than two regimens for MBC. Therefore, this study will hopefully offer confirmatory evidence of the benefit of eribulin in anthracycline and taxane-resistant disease. Furthermore, as some patients in this study will be less heavily pretreated, the results will offer an insight into the activity earlier in the disease paradigm. In another randomized phase II study, a comparison of associated neuropathy from eribulin and ixabepilone is being assessed [33].

Eribulin is clearly an exciting new active agent for refractory breast cancer, and further studies are warranted to examine its possible role in other settings and to ascertain how to optimally incorporate this active agent into the current treatment paradigms. For example, the role of this agent in combination with anti-HER2 therapy, such as trastuzumab, should be explored for patients with HER2-positive MBC. It is unknown how the single-agent response rate of eribulin (12.2%) would compare with taxanes (or indeed anthracyclines) for patients earlier in the treatment paradigm. At present, it is unknown which subgroups of patients with MBC (such as HER2 positive or triple-negative breast cancer) are more likely to benefit from eribulin as opposed to an established therapy. Therefore, an important part of the design of future studies will be the identification of biomarkers of response. Eribulin has a wide therapeutic window, is minimally renally excreted and is mainly cleared by hepatic metabolism [34,35]. Therefore, there are potential concerns about eribulin use in patients with hepatic impairment and those receiving concomitant medications that interfere with the cytochrome 3A4 enzyme, the major enzyme responsible for hepatic metabolism of eribulin [35]. This was the subject of a recent pharmacokinetic study presented at the 2010 ASCO Annual Meeting, which showed that although eribulin exposure was increased in patients with mild and moderate hepatic impairment, this did not seem to translate into a high rate of serious hematological toxicities [35].

There are other ongoing studies of eribulin in multiple solid tumors including prostate, bladder, ovarian, and non-small cell lung cancer. Furthermore, recent data presented at the 2010 ASCO Annual Meeting showed some activity in urothelial cancer, prostate cancer, and sarcomas [36–38]. Finally, clinical trials investigating eribulin in the adjuvant setting for breast cancer are warranted and some studies are already being planned. For example, a phase II study examining eribulin after dose-dense anthracycline-based chemotherapy is being designed at the Memorial Sloan-Kettering Cancer Center. In the future it is hoped that these and other studies will translate the important survival advantage seen in the refractory setting in the EMBRACE study into corresponding benefit for patients with early-stage breast cancer.

In summary, eribulin has proven activity in refractory MBC and seems to be an important addition to the breast cancer armamentarium. Future studies will hopefully

establish the optimum use of eribulin and improve our individualization of the current treatment strategies for breast cancer.

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