CLINICAL INVESTIGATION

Clinical evidence for the role of eribulin mesylate in the treatment of breast cancer

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The development of drugs improving overall survival (OS) in late-stage metastatic breast cancer (MBC) remains a challenge. Eribulin mesylate, a new chemotherapy agent, has shown significant results in this setting. This agent is a synthetic analog of a macrolide isolated from a marine sponge. It inhibits microtubule polymerization, inducing mitotic arrest and apoptosis, and aggregates soluble tubulin in a nonproductive form. In Phase II studies, this drug gave a partial response and stable disease. The EMBRACE study showed that eribulin mesylate improved OS in heavily pretreated (particularly with anthracycline and taxane) MBC with good tolerance. Currently, eribulin mesylate is the first major single-agent that has improved OS in heavily pretreated MBC. These results suggest that this drug could become a new standard in the treatment of advanced breast cancer and should be developed in earlier stages.

Keywords: EMBRACE study • eribulin mesylate • halichondrin B • metastatic breast cancer • microtubule dynamics

Breast cancer is the most frequently diagnosed cancer and the second highest cause of cancer mortality in females worldwide. In 2008, it accounted for 23% (1.38 million) of total new cancer cases and 14% (458,400) of total cancer-related deaths [1]. Approximately 10% of women with breast cancer have a metastatic disease initially and 20% will be metastatic within 10 years of their initial diagnosis [2]. Anthracycline and taxane are the main chemotherapeutic drugs in metastatic breast cancer (MBC), producing an overall survival (OS) benefit. Moreover, their efficacy has been shown in adjuvant settings in combination with surgery, radiotherapy and hormonal therapy. Other drugs (capecitabine, gemcitabine and vinorelbine) have been developed for MBC. The survival benefit of these last drugs is shown only in combination with taxane [3,4]. With late-line treatment, efficacy is lower and toxicities accumulate. The development of new therapeutic agents in MBC, such as eribulin mesylate, is an important issue. This review explains the development of eribulin mesylate and its mechanisms of action, and describes its currents applications in breast cancer and future outlook.

Preclinical data

Eribulin mesylate (E7789; Halaven™, EISAI) is a synthetic analog of halichondrin B, a natural macrolide isolated from the marine sponge, *Halichondria Okadai*. In 1986, halichondrin B was identified in these sponges and showed antitumor activity [5]. However, the very limited availability of this compound represented a major barrier to its development. In the early 1990s, scientists successfully synthesized halichondrin B and discovered that its cytotoxicity was a function of the macrocyclic lactone C_1–C_{38} moiety [6]. Since this discovery, a large number of analogs, including eribulin mesylate, have been developed.

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Eribulin mesylate is a tubulin- and microtubule-targeted antitumor drug. Microtubules are intracellular structures and components of the cytoskeleton. Microtubules, which are formed by the polymerization of α- and β-tubulin, realize the mitotic spindle, allowing separation of daughter cells in mitosis. Because of the essential role of the microtubule dynamics in tumor growth, many cytotoxic drugs targeting these structures have been developed. Eribulin mesylate is one of these and its mechanisms of action have not been fully elucidated, but its main mechanism of action is microtubule polymerization suppression. Eribulin mesylate binds with high affinity to a very small number of saturable tubulin sites at the end of microtubules (vinca-site binding), suppressing dynamic instability [7,8], stopping microtubule growth and inducing irreversible mitotic blockade (arrest in Phase G2/M) [9–11] and apoptosis [12]. In addition, it binds soluble tubulin and induces nonproductive tubulin aggregates. These aggregates compete with the soluble tubulin remaining in the cell and bind to microtubule ends, causing malfunction.

Eribulin mesylate has a triphasic elimination (rapid distribution phase in the plasma, slow elimination and low renal excretion) [13–15]. In studies, the terminal half-life of eribulin mesylate ranges from 36 to 48 h [15]. This drug binds to plasma proteins and is predominantly metabolized by CYP3A4, but did not appear to affect the metabolism of other treatments by CYP3A4 [16].

The cytotoxic activity of halichondrin B analogs has been tested in a wide range of cancer cell lines. In MDA-MB-435, a breast cancer cell line, eribulin mesylate inhibits cell growth with greater potency than vinblastine or paclitaxel [9]. In MCF7, another breast cancer cell line, it has been shown that eribulin mesylate blocks mitosis and, therefore, cell proliferation by binding to microtubule ends or aggregating soluble tubulin [17]. Human breast tumor xenograft models have been developed in mice and, in these models, eribulin mesylate inhibits tumor growth [9].

Clinical efficacy

■ Phase I studies

Four Phase I studies have examined eribulin mesylate as monotherapy in advanced solid tumors, and particularly in advanced or MBC.

The first one, directed by Synold, studied weekly administration of eribulin mesylate. A total of 40 patients (38 assessable) with refractory or advanced solid tumors have received eribulin mesylate on days 1, 8 and 15 on a 28-day cycle (by intravenous [iv.] bolus injection). This study used an accelerated titration design. The study ended with two dose-limiting toxicities (DLTs) at 2 mg/m²/week: one grade 3 febrile neutropenia and one grade 4 neutropenia. The maximum tolerated dose (MTD) was 1.4 mg/m²/week. There were two partial responses (PRs): one non-small-cell lung cancer and one bladder cancer, three marker responses and 12 stable diseases (SDs) [13].

A second Phase I study, managed by Mukohara, evaluated iv. bolus administration. Fifteen patients received eribulin mesylate on days 1 and 8 of a 21-day cycle. The observed DLTs were febrile neutropenia and grade 4 neutropenia. Other toxicities were often mild, such as asthenia, alopecia, nausea and neuropathy. The recommended schedule was a dose of 1.4 mg/m² on days 1 and 8 every 3 weeks. In this study, three patients had a PR and four had a SD [18].

Goel studied eribulin mesylate as monotherapy (1 h iv. infusion) on days 1, 8 and 15 of a 28-day cycle. Thirty-two patients with advanced solid tumors were included. The DLT was 1.4 mg/m² with two patients with grade 4 neutropenia and one grade 3 asthenia. The MTD was 1 mg/m². One patient with cervical cancer had an unconfirmed PR and ten patients had a SD [14].

In the fourth study, reported by Tan, 21 patients with advanced solid tumors received eribulin mesylate as a 1-h infusion every 21 days. Three patients experienced a DLT with febrile neutropenia on day 7 at 4 mg/m². The dose was reduced to 2.4 mg/m², where two out of three patients experienced febrile neutropenia. The MTD was defined as 2 mg/m². Nonhematological toxicities were mild and included fatigue, alopecia and nausea. One patient with lung cancer had a PR and 12 had a SD [15].

These trials demonstrate the feasibility of eribulin mesylate in solid tumors, particularly in advanced breast cancer. The weekly schedule provides a slightly higher dose density than the 3-week schedule (0.75 vs 0.67 mg/m²/week) and appears more feasible. Phase II trials are based on this weekly schedule.

■ Phase II studies

Three Phase II trials have studied eribulin mesylate as monotherapy in advanced or MBC.

The first trial, conducted by Vahdat, investigated the effect of eribulin mesylate in previously treated MBC, particularly with anthracycline and taxane [19]. Patients received a median of four prior chemotherapy regimens (one to 11 regimens). A total of 103 patients were included in this study and received two eribulin mesylate schedules of administration. At the beginning, eribulin mesylate was given at 1.4 mg/m² as a 2- to 5-min iv. infusion on days 1, 8 and 15 of a 28-day cycle. Due to neutropenia on day 15, a protocol amendment was made and a second group of patients received eribulin mesylate at the same dose on days 1 and 8 of a 21-day cycle. The primary end point was overall response rate. In the per-protocol population, the objective response rate (ORR) (complete response [CR] and PR) was 11.5% (95% CI: 5.7–20.1) and all of the responses were PRs. The clinical benefit rate (CBR; CR and PR and SD ≥6 months) was 17.2% (95% CI: 10.0–26.8). The secondary objectives were duration of the response, progression-free survival (PFS) and OS, and were respectively 171 days (44–363 days), 79 days (2.6 months or 1–453 days) and 275 days (9 months or 15–826 days). The 21-day schedule was associated with a more favorable tolerability profile (Table 1) [19].

In the second Phase II trial, eribulin mesylate was studied in a population with locally advanced breast cancer or MBC previously treated with anthracycline, taxane and capecitabine. Eribulin mesylate was administered as a 2- to 5-min iv. infusion on days 1 and 8 of a 21-day cycle. The primary end point was the ORR and secondary end points were duration of the response, PFS, OS and adverse events (AEs). A total of 299 patients were enrolled and 269 of these met key inclusion criteria for the primary efficacy analysis. Patients had received a median of four prior chemotherapies. In the eligible population, ORR was 9.3% (95% CI: 6.1–13.4, all of which were PRs) and CBR was 17.1% (95% CI: 12.8–22.1). Median duration of response was 4.1 months (1.4–8.5 months), PFS was 2.6 months (0.03–13.1 months) and OS was 10.4 months (0.6–19.9 months) (Table 1) [20].

Another trial analyzed the efficacy and safety of eribulin mesylate in a Japanese population with locally advanced breast cancer or MBC. Patients were pretreated with anthracycline and taxane and had received at least three prior chemotherapy regimens in a metastatic setting. Eribulin mesylate was administered at the same dose and with the same schedule as in the Phase II trial conducted by Cortes. The primary objective was ORR. 84 patients were enrolled and 80 were included in the eligible population. Patients received a median of three prior chemotherapy regimens. ORR was 21.3% (95% CI: 12.9–31.8) and CBR was 27.5% (95% CI: 18.1–38.6). Median duration of response was 3.9 months (95% CI: 2.8–4.9), median PFS was 3.7 months (95% CI: 2.0–4.4) and median OS was 11.1 months (95% CI: 7.9–15.8). The toxicity profile was the same as in the other Phase II trials: neutropenia was the most common AE (Table 1) [21].

These trials showed the feasibility of eribulin mesylate (1.4 mg/m²) as a 2- to 5-min iv. infusion on days 1 and 8 of a 21-day cycle. Indeed, in these heavily pretreated patients, eribulin mesylate had manageable tolerability. This schedule has activity with an ORR of 10–20% in heavily pretreated MBC. Phase III trials in advanced and MBC were based on these results.

■ Phase III studies in late-stage breast cancer

The EMBRACE study or 305 study was a Phase III global, multicenter, randomized, open-label study of eribulin mesylate versus treatment of physician's choice (TPC) in women with pretreated locally recurrent disease or MBC [22]. Patients had to have received between two and five previous chemotherapy regimens including anthracycline and taxane for locally recurrent or MBC. Patients were randomized between eribulin mesylate and TPC with a 2:1 ratio in favor of eribulin mesylate. TPC could be chemotherapy, hormonal or biological treatment, radiotherapy or symptomatic treatment. Eribulin mesylate was used following the same schedule as the Phase II studies (1.4 mg/m² during a 2- to 5-min iv. infusion on days 1 and 8 of a 21-day cycle). The primary objective was OS between the two groups and the secondary objectives were comparison of PFS, ORR and duration of response.

From November 2006 to November 2008, 762 patients were randomized. A total of 508 received eribulin mesylate and 254 received the TPC. Patients had previously received a median of four chemotherapy regimens. 16% had HER-2 positive disease and 19% were triple negative. Among the TPC patients

Table 1. Response rate, median progression-free survival and median overall survival in Phase II studies with eribulin mesylate as monotherapy in advanced breast cancer.

Study (year)	Schedule	ORR (%) (95% CI)	CBR (%) (95% CI)	Median PFS (months)	Median OS (months)	Ref.
Vahdat *et al.* (2009)	E bolus: 1.4 mg/m² d 1, 8, 15/28 d, protocol amendment: d 1, 8/21 d	11.5 (5.7–20.1)	17.2 (10–26.8)	2.6	9	[19]
Cortes *et al.* (2010)	E bolus: 1.4 mg/m² d 1, 8/21 d	9.3 (6.1–13.4)	17.1 (12.8–22.1)	2.6	10.4	[20]
Aogi *et al.* (2011)	E bolus: 1.4 mg/m² d 1, 8/21 d	21.3 (12.9–31.8)	27.5 (18.1–38.6)	3.7	11.1	[21]

CBR: Clinical benefit rate (CR, PR and SD ≥6 months); d: Day; E: Eribulin mesylate; ORR: Objective response rate (CR and PR); OS: Overall survival; PFS: Progression-free survival.

(247 patients): 238 had received chemotherapy (25% vinorelbine, 19% gemcitabine, 18% capecitabine, 15% taxane, 10% anthracycline and 10% other chemotherapies) and 4% had received hormonal therapy. No TPC patients had received supportive care alone. Baseline characteristics were well-balanced across treatment groups.

The median duration of eribulin mesylate treatment was 3.9 months (0.7–16.3), with TPC the median duration treatment was 2.1 months (0.03–21.2) for patients receiving chemotherapy and 1 month (0.8–6.2) with hormonal therapy. Results showed a significant increase in OS with eribulin mesylate compared with TPC: hazard ratio (HR): 0.81 (95% CI: 0.66–0.99; p = 0.041). Median OS was 13.1 months (95% CI: 11.8–14.3) with eribulin mesylate and 10.6 months (95% CI: 9.3–12.5) with TPC. In the investigator review, the difference in terms of PFS was significant: median PFS was 3.6 months (95% CI: 3.3–3.7) with eribulin mesylate and 2.2 months (95% CI: 2.0–2.6) with TPC (HR: 0.76; 95% CI: 0.64–0.9; p = 0.002). In the independent review, median PFS was 3.7 months (95% CI: 3.3–3.9) with eribulin mesylate and 2.2 months (95% CI: 2.1–3.4) with TPC (HR: 0.87; 95% CI: 0.71–1.05; p = 0.137). In terms of ORR, the difference was significant. In the independent review, objective response was recorded in 57 of 468 patients (12%) treated with eribulin mesylate (1% CR and 12% PR) and ten of 214 patients (5%) treated with TPC (p = 0.002; 5% PR). Median duration of response for eribulin mesylate was 4.2 months (95% CI: 3.8–5.0) and for TPC was 6.7 months (95% CI: 6.7–7.0). Three patients have had a CR (1%) with eribulin mesylate. The CBR were 23% (18.9–26.7) with eribulin mesylate and 17% (12.1–22.5) with TPC (Table 2).

Table 2. Results of the Phase III EMBRACE study (independent review): tumor response, objective response rate, clinical benefit rate, median duration response, progression-free survival and overall survival.

	Eribulin mesylate	TPC	HR (95% CI) p-value
Population (n)	508	254	
Tumor response			
CR (n)	3 (1%)	0	
PR (n)	54 (12%)	10 (5%)	
SD (n)	208 (44%)	96 (45%)	
PD (n)	190 (41%)	105 (49%)	
Not evaluable (n)	12 (3%)	3 (1%)	
ORR (n)	57 (12%)	10 (5%)	
CBR (n)	106 (23%)	36 (17%)	p = 0.02
Median DR months (95% CI)	4.2 (3.8–5.0)	6.7 (6.7–7.0)	p = 0.159
Median PFS months (95% CI)	3.7 (3.3–3.9)	2.2 (2.1–3.4)	0.87 (0.71–1.05) p = 0.137
Median OS months (95% CI)	13.1 (11.8–14.3)	10.6 (9.3–12.5)	0.81 (0.66–0.99) p = 0.041

CBR: Clinical benefit rate (CR, PR and SD ≥6 months); CR: Complete response; DR: Duration response; E: Eribulin mesylate; HR: Hazard ratio; n: Number; ORR: Objective response rate (CR and PR); OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; TPC: Treatment physician's choice.

In conclusion, this Phase III trial showed that eribulin mesylate improved OS in heavily pretreated (particularly with anthracycline and taxane) MBC patients with manageable AEs. Median duration of response seemed longer in the TPC group, but comparison between groups was inappropriate (only ten patients responded to TPC). This study leads to other issues: do any patients or tumor subtypes particularly benefit from eribulin mesylate? Why is the improvement in OS better than the improvement in PFS with eribulin mesylate? How would eribulin mesylate stack up against other new chemotherapeutic agents or targeted therapies? [23].

A second Phase III study, the 301 study (NCT00337103), completed recruitment [24]. This study was an open-label, multicenter, randomized Phase III trial evaluating the efficacy and safety of eribulin mesylate as monotherapy versus capecitabine in patients with locally advanced or MBC who had received up to three prior chemotherapy regimens including anthracycline and taxane. The primary objective was to compare eribulin mesylate versus capecitabine in terms of OS and PFS.

A total of 1102 patients were enrolled with a 1:1 ratio between September 2006 and September 2009 and received either eribulin mesylate (1.4 mg/m² in a 2- to 5-min iv. perfusion on days 1 and 8 of a 21-day cycle) or capecitabine (2.5 g/m²/day in two equal doses on days 1 to 14 of a 21-day cycle). The reporting date is January 2012 [24].

Safety & tolerability

Neutropenia is the most common AE with eribulin mesylate. In fact, dose escalation in Phase I trials has been stopped by the onset of febrile or nonfebrile neutropenia [13–15,18]. In addition, due to the onset of neutropenia on day 15, an amendment was made to avoid the latter in the Phase II study conducted by Vahdat *et al.* [19]. In Phase I and II studies, other common AEs have been fatigue, alopecia, nausea and anemia. Neuropathy has been rare and mild.

In the Phase III EMBRACE study, the AEs were similar to those found in the Phase I and II trials. In this study, AEs occurred in 99% of 503 patients receiving eribulin mesylate and 93% of 247 patients receiving TPC. The most common AEs were asthenia and neutropenia. In terms of grade 3 and 4 AEs, neutropenia, leucopenia and peripheral neuropathy occurred more often with eribulin mesylate than with TPC. Neutropenia was the most common grade 3 (21%) and grade 4 (24%) AE. However, the incidence of febrile neutropenia was low (5%). Fatal AEs occurred in 4% of patients treated with eribulin mesylate and 7% of patients treated with TPC. The occurrence of peripheral neuropathy was similar to the subgroup with taxane (grade 3: 8% and grade 4: <1%). Approximately half of the patients had moderate alopecia. Hypersensitivity reactions occurred in four patients treated with eribulin mesylate (1%) [22].

In conclusion, eribulin mesylate is well-tolerated. Neutropenia is the most common AE. The occurrence of neuropathy remains moderate (Table 3).

Table 3. Most common adverse events with eribulin mesylate as monotherapy in the EMBRACE study.

		Grade	
Adverse events	All grades	Grade 3	Grade 4
Neutropenia	52	21	24
Febrile neutropenia	5	–	–
Leucopenia	23	12	2
Asthenia	54	8	1
Alopecia	45	–	–
Peripheral neuropathy	35	8	<1
Nausea	35	1	0
Hypersensitivity reaction	1	–	–

Conclusion

Eribulin mesylate, a new microtubule dynamics inhibitor, has been developed in breast cancer. This synthetic analog of halichondrin B, a marine sponge extract, was studied in pretreated (particularly with anthracycline and taxane) locally advanced and MBC patients. Preliminary studies showed that eribulin mesylate as monotherapy at 1.4 mg/m² in a 2- to 5-min infusion on days 1 and 8 in a 21-day cycle was manageable and gave an objective response in heavily pretreated MBC. The EMBRACE study confirmed improvement in OS with eribulin mesylate in this context and this drug was approved by the US FDA on 15 November 2010 [101] and the European Medicines Agency on 17 March 2011 [102] for patients with MBC who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline and taxane. Eribulin mesylate is well-tolerated and, unlike other antimicrotubule drugs, has moderate neurotoxicity. Hypersensitivity reactions were observed in four patients (1%) with eribulin mesylate. Neutropenia and asthenia are the most common AEs and are manageable.

Future perspective

Eribulin mesylate, a new microtubule inhibitor, has shown its efficacy and safety in MBC. Only two other chemotherapy agents, anthracycline and taxane, have, such as eribulin mesylate, improved OS in advanced breast cancer. As a result, eribulin mesylate is a new option in late-stage breast cancer treatment. Moreover, this drug is currently being developed as monotherapy or in combination in various stages of breast cancer treatment.

One avenue worth exploring is the study of eribulin mesylate in adjuvant or neoadjuvant settings in combination with anthracycline or alone. Otherwise, the significance of eribulin mesylate is already being studied in earlier stages of MBC. A Phase II trial (NCT01268150) investigated the efficacy and safety of eribulin mesylate as first-line therapy for locally recurrent or metastatic HER2-negative breast cancers [103]. Lastly, new combinations should be studied: eribulin mesylate and chemotherapy drugs or target therapies.

Executive summary

- Anthracycline and taxane are the main chemotherapy drugs in breast cancer treatment.
- Eribulin mesylate (E7389, HALAVEN™) is a simplified synthetic analog of halichondrin B. It inhibits microtubule dynamics by suppressing microtubule polymerization and aggregating soluble tubulin.
- In Phase II trials, eribulin mesylate has proven effective as monotherapy in pretreated (including anthracycline and taxane) advanced and metastatic breast cancer (MBC).
- The EMBRACE study, a Phase III trial, was the first study that demonstrated an improvement in overall survival in heavily pretreated MBC with a chemotherapeutic agent. This study validated the schedule of 1.4 mg/m² eribulin mesylate as 2- to 5-min infusions on days 1 and 8 of a 21-day cycle.
- Eribulin mesylate was approved by the US FDA on 15 November 2010 and by the European Medicines Agency on 17 March 2011 for patients with MBC who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline and taxane.
- The most common adverse events are neutropenia and asthenia. Neuropathy is less frequent than with ixabepilone and taxane.
- Future breast cancer research should include studies in earlier metastatic settings or in adjuvant settings, and combinations with other chemotherapy agents or target therapies such as trastuzumab.

Preclinical studies have investigated synergistic action between eribulin mesylate and chemotherapy agents. *In vitro*, in breast cancer cell lines, there is synergistic activity between eribulin mesylate and gemcitabine, cisplatin, epirubicin, docetaxel and vinorelbine [25]. A Phase Ib/II trial (NCT01323530) studied the feasibility and efficacy of eribulin mesylate in combination with capecitabine in MBC. This study is currently recruiting [103]. In a preclinical study, eribulin mesylate had synergy with trastuzumab [25]. Currently, a Phase II trial (NCT01269346) is recruiting participants to evaluate the safety and efficacy of eribulin mesylate with trastuzumab as first-line treatment in patients with locally recurrent or metastatic HER2-positive breast cancers. This study started in November 2010 and its primary end point is the ORR [103].

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