Journal of Breast Cancer

J Breast Cancer 2013 March; 16(1): 12-15 http://dx.doi.org/10.4048/jbc.2013.16.1.12

REVIEW ARTICLE

Eribulin for Advanced Breast Cancer: A Drug Evaluation

Alaaeldin Shablak

Department of Medical Oncology, Bradford Royal Infirmary, Bradford, UK

Eribulin is a synthetic microtubule dynamics inhibitor that was developed from a marine natural product halichondrin B. It exhibited *in vitro* and *in vivo* activities against a wide number of malignancies. A number of advanced phase trials showed improved survival following eribulin treatment in pretreated advanced breast cancer patients. This review provides an overview of the background to the therapeutic use of eribulin in oncology, including its pharmacology, pharmacokinetics, clinical efficacy, safety, and potential economic factors.

Key Words: *Breast neoplasms, Eribulin, Microtubule inhibitor*

INTRODUCTION

The microtubules, formed by the polyerization of the cellular protein tubulin, play a crucial role in the cell division process hence any interference in the function of this protein can result in cell separation disruption and causes cellular death by apoptosis which can be used as a cancer treatment modality [1]. A number of the currently available anticancer drugs work by changing the extent of the microtubule polymer mass, either decreasing it for the tubulin polymerization inhibitors (such as vinka alkaloids [2]) or increasing it for the tubulin polymerization promoters (such as the taxanes [3]).

Halichondrin B is a natural product that was originally isolated from the Western Pacific sponge *Halichondria okadai* [4] and later from an *Axinella* sp. [5]. This compound was shown to bind to tubulin at a site close to the vinka site and inhibit tubulin polymerization [6], but unlike other tubulin polymerization inhibitors, halichondrin B inhibits the tubilin growth with no effect on microtubule shortening. It also sequesters tubulin into nonfunctional aggregates [7].

Halichondrin B has also shown antiproliferative effects against a broad range of human cancer cell lines, including breast, prostate, melanoma, and colorectal [8]. Furthermore, it has been associated with tumor regression and elimination in a variety of well established human tumor xenograft models [9] thus it was an excellent candidate for clinical development. To overcome the major obstacle of clinical development of this product, compound supply, a research program at Eisai Research Institute was initiated to develop a synthetically accessible anticancer agent based on the halichondrin B skeleton. As a result of this program, the truncated halichondrin B analog, eribulin (E7389), was discovered and showed activity in the preclinical models of diseases in which microtubule inhibitors already have a therapeutic role such as breast or ovarian cancer and also in other diseases in which they are less relevant such as colorectal cancer [9-11].

Correspondence to: **Alaaeldin Shablak**
Department of Medical Oncology, Bradford Royal Infirmary, Duckworth Lane, BD9 6RJ Bradford, UK
Tel: +44-1274-542-200, Fax: +44-1274-366-745
E-mail: alshiblaq@hotmail.com

Received: January 27, 2013 **Accepted:** March 7, 2013

PHARMACOLOGY

Two phase I trials of eribulin in solid malignancies were designed to assess the maximum tolerated dose (MDT), toxicity profile, preliminary anticancer activity and pharmacokinetics of two different intravenous administration methods; weekly (days 1, 8, and 15 of a 28-days cycle) [12] and 3 weekly (a drip every 21 days) [13] methods.

ADMINISTRATION AND MTD

In the weekly study, 32 patients received doses ranging from 0.25 to 1.4 mg/m^2, with dose-limiting toxicity (DLT) consisting of grade 4 and 3 neutropenia in two and three patients respectively (one with associated grade 3 fatigue) at the higher dose. Thus, the MTD was regarded as 1 mg/m^2, a dose in which only one of six evaluable patients had DLT [12]. In the

3-weekly study 21 patients received doses from 0.25 to 4 mg/m^2, with DLT consisting of neutropenia in all three patients treated at 4 mg/m^2, and in two of three patients at 2.8 mg/m^2. The MTD was 2 mg/m^2, a dose level at which only one of six evaluable patients had DLT [13].

PHARMACOKINETICS

In the weekly schedule, eribulin mesylate pharmacokinetics following a 1-hour intravenous infusion, were linear and dose-proportional over the dosing range of 0.25 to 1.4 mg/m^2. Eribulin exhibited consistent pharmacokinetic parameter estimates between the first and third intravenous doses administered on days 1 and 15 at each dose level. The plasma concentration-time profile exhibited a rapid distribution phase with a mean distribution half-life of ~0.43 hours followed by a slower elimination phase with a half-life of 38.7 hours. The urinary excretion route was thought to play a minor role in the elimination of eribulin. Overall urinary excretion of eribulin was minimal with 5% to 6% of the administered dose eliminated in urine over a 72-hour period after a single dose [12].

On the other hand, the 3 weekly schedule showed that the pharmacokinetic profile of eribulin was characterized by an extensive volume of distribution, a slow-to-moderate clearance, and a slow elimination, with only a small fraction of the drug (~7%) excreted unchanged in the urine. Eribulin exhibited a plasma terminal half-life of ~2 days. Plasma area under the concentration-time curve ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) increased approximately linearly over the dose range studied; the dose-normalized C_{max} and $AUC_{0-\infty}$ values were consistent across dose levels with the exception of the 2 mg/m^2 dose level, where higher values were observed [13].

Adverse events and clinical outcome

From both trials, neutropenia and fatigue were the predominant toxicities. Neutropenia occurred earlier in the 3 weekly schedule with neutropenic fevers occurring as early as day 7 of the first cycle. Alopecia was also reported in 33% of patient in the 3 weekly schedule. Eight patients in the weekly schedule and one in the 3 weekly had reported clinical manifestations of neuropathy. Hyponatremia and nausea were less frequently reported.

From both studies, two unconfirmed partial responses were observed (taxane refractory cervical and taxane naive non-small cell lung cancers). Disease stabilisation was observed in 12 patients of the 3 weekly schedule (duration range, 47-386 days) and 10 patients on the weekly schedule (duration range, 39-234 days) [12,13].

ADVANCED PHASE TRIALS IN BREAST CANCER

Based on the phase I studies results, a number of advanced phase trials were conducted to evaluate the safety and efficacy of this drug. Three phase II trials of eribulin in chemotherapy pretreated advanced breast cancer patients using the weekly schedule (day 1 and 8 of 21 days cycle) were completed. In all these studies, eribulin showed a manageable tolerability profile, with most of the common drug-related adverse events being neutropenia, fatigue, alopecia, nausea, and anaemia and these were similar to the phase I trials findings. Eribulin was also associated with a low incidence of peripheral neuropathy overall and severe peripheral neuropathy was limited to grade 3 only [14-16]. The objective response rates as reported in these studies were 11.5%, 14.1%, and 21.3%. Encouraged by the response rate and toxicity profile from previous studies, a large phase III trial has recently been completed. EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) randomized patients with locally recurrent disease or metastatic breast cancer (MBC) previously treated with 2 to 5 prior chemotherapy regimens (including anthracyclines and taxanes) to eribulin (using phase II schedule) or treatment of physicians' choice (TPC) [17]. This study has shown statistically significant increase in overall survival (hazard ratio, 0.81; 95% confidence interval, 0.66-0.99; p = 0.004) in the eribulin group (13.1 months) compared with TPC group (10.6 months). Grade 3/4 adverse events were reported in both arms. The common adverse events associated with eribulin were asthenia/fatigue (8.2% grade 3; 0.6% grade 4), neutropenia (21.1% grade 3; 24.1% grade 4) and peripheral neuropathy (7.8% grade 3; 0.4% grade 4), demonstrating a manageable tolerability profile for this agent when given as a monotherapy.

A second phase III study is underway to compare the efficacy and safety of eribulin with capecitabine. It contains important quality of life and pharmacokinetic correlates hence this will be the first study to provide a full analysis of the impact of eribulin upon the quality of life [18].

In addition to breast cancer, phase II studies have been conducted to assess the efficacy of eribulin in non-small cell lung cancer [19], sarcoma [20], ovarian cancer [21], pancreatic [22], head and neck [23], and prostate cancers [24].

ECONOMIC IMPACT/COST EFFECTIVENESS

Although eribulin mesylate is approved by the U.S. Food and Drug Administration for the treatment of patients with MBC who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease [25],

it was rejected by NICE in the United Kingdom based on its cost effectiveness. According to the manufacturer documentations following the EMBRACE trial, the estimated cost per cycle of eribulin was £1,738 compared to £1,335, £1,599, £1,429, and £740 for the costs per cycle for TPC, vinorelbine, gemcitabine and capecitabine respectively with incremental costs for eribulin of £5,586, £5,177, £4,041, and £12,779 compared with TPC, gemcitabine, vinorelbine and capecitabine respectively. This resulted in incremental cost-effectiveness ratios (ICERs) for eribulin of £46,050 per quality-adjusted-life year (QALY) gained versus TPC, £27,183 versus gemcitabine, £35,602 versus vinorelbine and £47,631 versus capecitabine. In their application to NICE, the manufacturer estimated the gain per QALY. However, NICE review concluded that the most optimistic ICER for the overall intention-to-treat (ITT) group was £68,600 per QALY gained. Furthermore, given that the mean overall survival gain was 2.7 months from the overall ITT population, the Committee concluded that eribulin could not be considered a cost-effective use of resources for National Health Service (NHS) use even if all of the criteria for being a life-extending, end-of-life treatment were met [26].

CONCLUSION

Eribulin is a novel nontaxane microtubule dynamics inhibitor that has demonstrated therapeutic activity in patients with solid tumors, particularly in heavily pretreated patients with MBC. Moreover, eribulin was shown to have a manageable toxicity and a modest incidence of neuropathy, which appears to be lower than with other microtubule inhibitor agents. Overall, eribulin represents a promising new treatment option as single-agent chemotherapy in patient's solid cancer and in particular, the chemotherapy pretreated breast cancer patients. On the other hand, the cost effectiveness of the drug remains a matter of a debate that will need to be taken in consideration for any future clinical evaluation of this drug.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Kingston DG. Tubulin-interactive natural products as anticancer agents. J Nat Prod 2009;72:507-15.
2. Kingston DG. Taxol and its analogs. In: Cragg GM, Kingston DG, Newman DJ, editors. Anticancer Agents from Natural Products. 2nd ed. Boca Raton: CRC Press; 2005. p.123-35.
3. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. Nature 1979;277:665-7.
4. Hirata Y, Ohya S. Halichondrins: antitumor polyether macrolides from a marine sponge. Pure Appl Chem 1986;58:701-10.
5. Pettit GR, Herald CL, Boyd MR, Leet JE, Dufresne C, Doubek DL, et al. Isolation and structure of the cell growth inhibitory constituents from the western Pacific marine sponge Axinella sp. J Med Chem 1991;34:3339-40.
6. Bai RL, Paull KD, Herald CL, Malspeis L, Pettit GR, Hamel E. Halichondrin B and homohalichondrin B, marine natural products binding in the vinca domain of tubulin. Discovery of tubulin-based mechanism of action by analysis of differential cytotoxicity data. J Biol Chem 1991;266:15882-9.
7. Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005;4:1086-95.
8. Hamel E. Natural products which interact with tubulin in the vinca domain: maytansine, rhizoxin, phomopsin A, dolastatins 10 and 15 and halichondrin B. Pharmacol Ther 1992;55:31-51.
9. Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, et al. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res 2001;61:1013-21.
10. Zheng W, Seletsky BM, Palme MH, Lydon PJ, Singer LA, Chase CE, et al. Macrocyclic ketone analogues of halichondrin B. Bioorg Med Chem Lett 2004;14:5551-4.
11. Seletsky BM, Wang Y, Hawkins LD, Palme MH, Habgood GJ, DiPietro LV, et al. Structurally simplified macrolactone analogues of halichondrin B. Bioorg Med Chem Lett 2004;14:5547-50.
12. Goel S, Mita AC, Mita M, Rowinsky EK, Chu QS, Wong N, et al. A phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. Clin Cancer Res 2009;15:4207-12.
13. Tan AR, Rubin EH, Walton DC, Shuster DE, Wong YN, Fang F, et al. Phase I study of eribulin mesylate administered once every 21 days in patients with advanced solid tumors. Clin Cancer Res 2009;15:4213-9.
14. Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roché H, et al. Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol 2010;28:3922-8.
15. Aogi K, Iwata H, Masuda N, Mukai H, Yoshida M, Rai Y, et al. A phase II study of eribulin in Japanese patients with heavily pretreated metastatic breast cancer. Ann Oncol 2012;23:1441-8.
16. Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2009;27:2954-61.
17. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914-23.
18. Twelves C, Cortes J, Vahdat LT, Wanders J, Akerele C, Kaufman PA. Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. Clin Breast Cancer 2010;10:160-3.
19. Gitlitz BJ, Tsao-Wei DD, Groshen S, Davies A, Koczywas M, Belani CP,

http://dx.doi.org/10.4048/jbc.2013.16.1.12

et al. A phase II study of halichondrin B analog eribulin mesylate (E7389) in patients with advanced non-small cell lung cancer previously treated with a taxane: a California cancer consortium trial. J Thorac Oncol 2012; 7:574-8.
20. Schoffski P, Ray-Coquard IL, Cioffi A, Bui NB, Bauer S, Hartmann JT, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011;12:1045-52.
21. Hensley ML, Kravetz S, Jia X, Iasonos A, Tew W, Pereira L, et al. Eribulin mesylate (halichondrin B analog E7389) in platinum-resistant and platinum-sensitive ovarian cancer: a 2-cohort, phase 2 study. Cancer 2012;118:2403-10.
22. Renouf DJ, Tang PA, Major P, Krzyzanowska MK, Dhesy-Thind B, Goffin JR, et al. A phase II study of the halichondrin B analog eribulin mesylate in gemcitabine refractory advanced pancreatic cancer. Invest New Drugs 2012;30:1203-7.
23. Arnold SM, Moon J, Williamson SK, Atkins JN, Ou SH, LeBlanc M, et al. Phase II evaluation of eribulin mesylate (E7389, NSC 707389) in patients with metastatic or recurrent squamous cell carcinoma of the head and neck: Southwest Oncology Group trial S0618. Invest New Drugs 2011;29:352-9.
24. de Bono JS, Molife LR, Sonpavde G, Maroto JP, Calvo E, Cartwright TH, et al. Phase II study of eribulin mesylate (E7389) in patients with metastatic castration-resistant prostate cancer stratified by prior taxane therapy. Ann Oncol 2012;23:1241-9.
25. U.S. Food and Drug Administration on HALAVEN™ (eribulin mesylate) Injection. U.S. Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201532lbl.pdf. Accessed January 4th, 2013.
26. Final appraisal determination on Eribulin for the treatment of locally advanced or metastatic breast cancer. National Institute for Health and Clinical Excellence. http://www.nice.org.uk/nicemedia/live/13238/57079/57079.pdf. Accessed January 4th, 2013.