Clinical Study

Oncology

Oncology 2018;94(suppl 1):29–33
DOI: 10.1159/000489066

Published online: July 24, 2018

Activity of Eribulin Mesylate in Brain Metastasis from Breast Cancer: A Stone in a Pond?

Giovanna Catania Paola Malaguti Simona Gasparro Francesco Cognetti
Antonello Vidiri Alessandra Fabi

Division of Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy

Keywords
Eribulin · Brain metastasis · Breast cancer

Abstract
Background: Brain metastases develop in approximately 10–25% of patients with metastatic breast cancer (MBC) and are associated with a very poor prognosis. ***Case Report:*** We report the case of a 40-year-old woman with MBC and associated lung, bone, liver, and brain metastases, who experienced a time to progression of several months with eribulin after whole-brain radiotherapy (WBRT), 2 lines of chemotherapy, and 1 line of hormonal therapy, maintaining a good toxicity profile. ***Discussion:*** Eribulin, in association with local treatment such as WBRT, can be well tolerated and effective in achieving a long progression-free survival and a good control of brain metastases in patients with MBC who have received multiple lines of treatment. The vascular remodeling properties of eribulin, combined with brain radiotherapy, might facilitate the passage of eribulin across the blood brain barrier, improving brain response. ***Conclusion:*** Our anecdotal experience suggests that eribulin may have a potentially beneficial effect on brain metastases while maintaining a good systemic control of the disease in patients with MBC.

Background

Breast cancer (BC) is the most common malignant disorder in women. Although treatable, metastatic BC (MBC) remains an incurable disease with a median overall survival (OS) of 2–3 years and a 5-year survival of only 25% [1–3]. In the last decade, slow progress has been made in terms of improved outcomes, quality of life, awareness, and information regarding the biology and heterogeneity of BC [4].

There is no standard regimen for patients with MBC who recur after treatment with an anthracycline and a taxane, both in the adjuvant and metastatic setting, and who are not eligible for combination chemotherapy or endocrine therapy. In this setting of patients, single agent capecitabine, eribulin, vinorelbine, gemcitabine, platinum agents, taxanes, or liposomal anthracyclines are the preferred options. Treatment choice should be individualized and take into account different toxicity profiles, previous treatments, and also patient's preferences [5].

Eribulin mesylate (eribulin) is a microtubule dynamics inhibitor approved by the European Medicines Agency (EMA) in March 2011 for the treatment of MBC in pa-

KARGER

E-Mail karger@karger.com
www.karger.com/ocl

Dr. Alessandra Fabi
Division of Medical Oncology, Regina Elena National Cancer Institute
Via Elio Chianesi, 53
IT–00144 Rome (Italy)
E-Mail alessandra.fabi@virgilio.it

tients who had received 2 or more prior chemotherapy regimens for their disease.

This approval was based on results from the EMBRACE study, a phase III, open-label, randomized clinical trial, in which eribulin was compared with treatment of physician's choice (TPC) in patients with locally recurrent or metastatic BC who had received 2–5 prior chemotherapeutic regimens (including an anthracycline and a taxane for early or advanced disease), with ≥2 chemotherapies for advanced disease [6]. In this study, the median OS was significantly longer with eribulin than with TPC (hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.67–0.96; $p = 0.014$]. There was also a significant difference in favor of eribulin in progression-free survival (PFS), as assessed by the investigators (HR 0.76; 95% CI 0.64–0.90; $p = 0.002$), but not by independent reviewers (HR 0.87; 95% CI 0.71–1.05; $p = 0.137$). Frequent toxicities included neutropenia (52% with eribulin vs. 30% with TPC), fatigue (54 vs. 40%), nausea (35 vs. 28%), and peripheral neuropathy (35 vs. 16%).

Support for this indication also came from Study 301, which compared eribulin and capecitabine as first-, second-, or third-line therapy in women with locally advanced or metastatic BC who had previously received an anthracycline and a taxane. In this study, a significant survival benefit for eribulin over capecitabine was not demonstrated in the overall population (HR 0.88; 95% CI 0.77–1.00; $p = 0.056$); however, prespecified subgroup analyses showed a longer OS for eribulin compared with capecitabine in patients with human epidermal growth factor receptor 2 (HER2)-negative disease or triple-negative BC [7].

A pooled analysis of these two phase III trials reported an overall OS benefit of 2.4 months with eribulin compared to control therapy (HR 0.85; 95% CI 0.77–0.95; $p = 0.003$) and an overall PFS benefit of 0.6 months (HR 0.90; 95% CI 0.81–0.997; $p = 0.046$) [8]. All analyzed patient's subgroups favored treatment with eribulin compared to control, with particular OS benefit observed in patients with HER2-negative disease (HR 0.82; 95% CI 0.72–0.93; $p = 0.002$), triple-negative BC (HR 0.74; 95% CI 0.60–0.92; $p = 0.006$), and patients with >2 affected organs (HR 0.77; 95% CI 0.66–0.89; $p < 0.001$). Several previously published case reports and other real-life clinical experiences have shown the efficacy of treatment with eribulin in highly pretreated patients with MBC and have also shown its good manageability and good toxicity profile [9]. In 2015, a case report of an MBC patient who achieved a very long time to progression (23 months) with eribulin was reported [10].

Brain metastases develop in approximately 10–25% of patients with MBC and are associated with worst prognosis [11, 12]. Whole-brain radiotherapy (WBRT) or stereotactic radiation therapy (depending on the number and sites of brain metastasis) is considered the standard treatment for brain metastasis [13, 14]. This case report describes a patient with MBC and brain metastases who experienced a time to progression of several months with eribulin after brain radiotherapy, 2 lines of chemotherapy and 1 line of hormonal therapy, maintaining a good toxicity profile.

Case Report

In July 2013, a 40-year-old woman underwent breast conserving surgery and was diagnosed with a moderately differentiated (G2) infiltrating ductal carcinoma of the right breast (estrogen receptor [ER] 90%, progesterone receptor [PgR] 60%, HER2–, Ki67 10%), at the pT1bpN0 M0 stage.

Based on the disease stage and prognostic factors, adjuvant hormonal therapy with tamoxifen was administered starting from August 2013. Between August and September 2013, she also received 25 radiotherapy sessions (50 Gy). In February 2015, after 18 months of disease-free survival, a CT scan and PET showed bilateral lung metastatic lesions.

In March 2015, she underwent atypical resection of the right lung. Pathological evaluation revealed lung metastasis of adenocarcinoma sharing immunophenotypic features with ductal carcinoma of the breast (ER 90%, PgR 15%, HER2–, Ki67 30%).

In April 2015, the patient started a first-line chemotherapy with nab-paclitaxel (125 mg/m^2; days 1, 8, and 15 of a 21-day cycle) and nonpegylated liposomal doxorubicin (20 mg/m^2; days 1, 8, and 15 of a 21-day cycle) for 4 cycles and achieved a partial response of disease. In September 2015, a CT scan after 7 cycles of chemotherapy confirmed a partial response of disease. In January 2016, a CT scan after 10 cycles of chemotherapy showed a further partial response. Given the good response observed, in February 2016 chemotherapy was discontinued after 10 cycles, and the patient started hormonotherapy with fulvestrant (500 mg; days 1 and 14 of a 28-day cycle) as maintenance treatment.

In May 2016 and in October 2016, CT scans showed a stable disease after 4 cycles and 10 cycles of fulvestrant as maintenance, respectively. In January 2017, after a PFS of 21 months, scintigraphy scan, CT scan, and MRI showed a systemic progressive disease including increased lung metastasis, appearance of bone metastasis (right acetabulum, sacrum, iliac spine, left rib, and D9 vertebral body) and brain metastasis (right angular gyrus 7 mm; left occipital region 7 and 5 mm). There were no neurological symptoms.

Because of progressive disease, fulvestrant was discontinued, the patient received WBRT (total 30 Gy), and oral steroid was administered. After WBRT, in February 2017 she started second-line chemotherapy with capecitabine (2,000 mg/m^2 die, per os on days 1–14, with a 1-week withdrawal period, every 3 weeks). In April 2017, she also started treatment with denosumab (120 mg every 4 weeks). In July 2017, a CT scan, after 6 cycles of capecitabine, showed partial response of brain metastasis but also disease pro-

gression in bone (C5–D2 and D9–D11 vertebral body) and lung, and appearance of liver metastasis (target lesions: II segment 8 mm; IV segment 10 mm; I–III segment 30 + 27 mm). Due to the high risk of fracture, the patient received vertebral radiotherapy. In August 2017, after a PFS of 6 months, she started third-line chemotherapy with eribulin at a dosage of 1.23 mg/m^2 on days 1 and 8 every 21 days. We decided to use granulocyte colony-stimulating factor prophylaxis because of previous treatments, and the patient continued denosumab therapy at the same schedule.

In November 2017, MRI showed stable disease according to the RANO criteria for brain with the presence of two metastases (Fig. 1a, b), while a CT scan showed stability in bone metastasis and partial response in liver metastasis (target lesions: II segment 5 mm; IV segment 10 mm; I–III segment 23 + 20 mm). The treatment was well tolerated, and the patient experienced G1–G2 anemia, alopecia, and moderate fatigue.

Given the partial remission in extracranial disease, eribulin treatment was administered for 3 more cycles. In January 2018, MRI showed a reduction of the dimensions of both brain lesions (right angular gyrus 2 mm; left occipital region 2 mm) (Fig. 1c, d), while metastases on the left occipital area were stable. CT scan documented no change of bone metastasis and a further decrease in the volume of liver metastasis (target lesions: II segment 5 mm; IV segment 8 mm; I–III segment 17 mm).

Based on further partial remission reported by the patient, the treatment has been continued and it is still ongoing. Until now, no serious adverse event was reported during eribulin treatment and no treatment cycle was delayed for hematological toxicity. Moreover, until now, we obtained a PFS of 6 months, which is greater than median PFS resulting from the EMBRACE study [6]. Of course, this represents a great success in a patient with brain metastasis and in the third line of treatment.

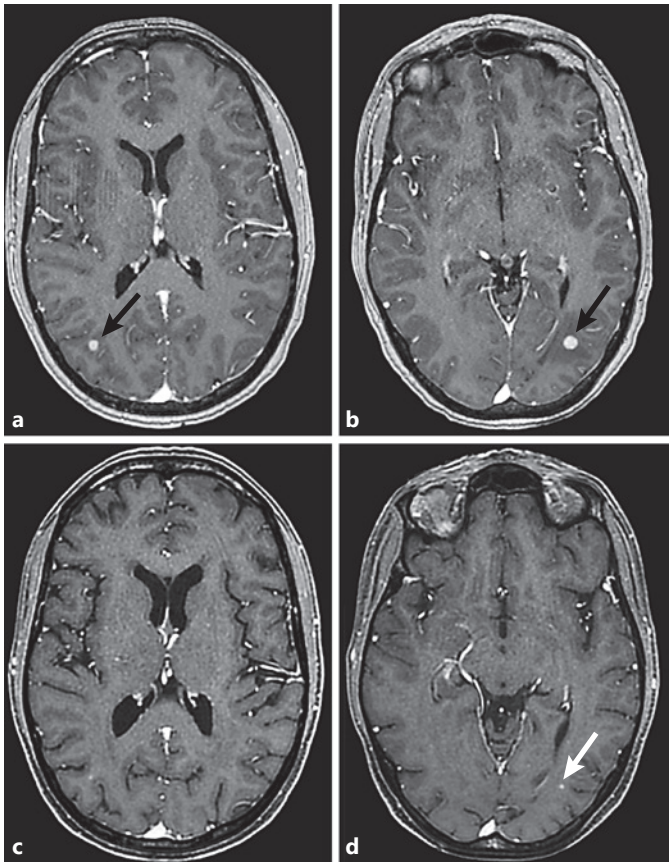

Fig. 1. MR T1 sequences in axial planes after contrast medium infusion. **a**, **b** Pre-treatment MR shows two lesions (black arrows) in the right angular gyrus and in the left occipital lobe, with vasogenic edema. **c**, **d** MR after 6 cycles of eribulin shows a reduction of the dimension of the lesions (white arrow) in relation to response to treatment.

Discussion

In our case report, a patient affected by MBC showed sustained disease control, lasting 12 months after the appearance of brain metastasis and still ongoing thanks to a combination of multiple therapies that included WBRT and chemotherapy. In particular, WBRT followed by eribulin led to a continuous control of brain metastasis, with systemic disease stability for 6 months until now.

The prognosis associated with brain metastasis is very poor. Chemotherapeutic agents do not easily cross the blood-brain barrier, while radiation therapy is known to compromise the barrier function [15] by reducing the expression of the efflux transporter P-glycoprotein [16]. Evidence suggests that this effect may last for as long as several years after postradiation therapy [15]. A number of case reports and other small studies have demonstrated that patients with brain metastasis arising from HER2-negative BC may benefit from capecitabine treatment [17, 18].

In our case report, treatment with WBRT and subsequent capecitabine chemotherapy led to a good response on brain metastasis that was maintained even when systemic disease progression was evident. Subsequent treatment with eribulin has shown a sustained control of brain disease, lasting over 6 months after the end of WBRT, and also a continuous partial response of visceral disease, especially in the liver.

Patients with brain metastasis are poorly represented in the EMBRACE study; indeed presence of brain metastases often leads to exclusion from clinical trials. However, there have been a number of reports describing response to eribulin in BC patients with brain metastases.

In 2013, a case report showed the efficacy of eribulin in a 57-year-old woman with brain metastases arising from BC [19]. This patient received radiotherapy for brain metastases and then treatment with lapatinib and capecitabine. After 3 months, she experienced progres-

sion of brain and liver metastases and was treated with eribulin. After 1 month, brain lesions decreased significantly in size, and this decrease was maintained for at least 4 months.

Eribulin does not cross the healthy blood-brain barrier, but could have the potential to do so after WBRT [20]. Indeed, brain radiotherapy may have facilitated eribulin passage across the blood-brain barrier in our patient, by decreasing the activity of P-glycoprotein. The antiangiogenic action of eribulin could have also contributed to this process. In fact, data on eribulin's antivascular activity have already been reported, showing how eribulin can influence the remodeling of tumor vasculature [21, 22].

In our opinion, although this is only an anecdotal experience, eribulin proved to be a well-tolerated active monotherapy after previous regimens. Eribulin ensured a clinically significant survival improvement, with control of brain metastases, reduction of visceral metastasis and clinical benefit.

With the limits of its anecdotal nature, this experience also confirms the positive results obtained with eribulin in brain metastasis, as reported in other previously published case reports.

The benefit observed with eribulin after multiple lines of therapy also suggests that an earlier introduction of this agent might have been associated with a longer disease control compared with other drugs used in this patient.

In our experience, eribulin treatment was associated with a good toxicity profile, and patient's quality of life was preserved. The standard schedule of eribulin was administered without any difficulties; thanks to the support of granulocyte colony-stimulating factor, the patient did not suffer from neutropenia or febrile neutropenia, and peripheral neuropathy was not reported. These results suggest that eribulin, in association with local treatments such as radiotherapy, can be well tolerated and effective in achieving a long PFS and a good control of brain metastasis in patients with MBC who have received multiple lines of treatment.

Conclusion

Our anecdotal experience suggests that eribulin may have a potentially beneficial effect on brain metastases while maintaining a good systemic control of the disease in patients with MBC. Future studies are warranted to evaluate the activity of eribulin and its mechanism of action in BC-associated central nervous system metastases.

Acknowledgments

Editorial assistance was performed by Luca Giacomelli, PhD, Ambra Corti, and Aashni Shah on behalf of Content Ed Net; this assistance was supported by Eisai. The supporting company was not offered the opportunity to review the manuscript, and had no role in the decision to submit.

Disclosure Statement

The authors declare no conflict of interest.

References

1 Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordström EB, Pagani O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E; European School of Oncology; European Society of Medical Oncology: ESO-ESMO 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2). Breast 2014;23:489–502.

2 Global Status of Advanced/Metastatic Breast Cancer 2005–2015 Decade Report. www.breastcancervision.com and www.abc-lisbon.org (accessed October 27, 2016).

3 Sundquist M, Eriksson Z, Tejler G, Brudin L: Trends in survival in metastatic breast (abstract 453). Cancer Eur J Cancer 2010;8:191.

4 Kobayashi K, Ito Y, Matsuura M, Fukada I, Horii R, Takahashi S, Akiyama F, Iwase T, Hozumi Y, Yasuda Y, Hatake K: Impact of immunohistological subtypes on the long-term prognosis of patients with metastatic breast cancer. Surg Today 2016;46:821–826.

5 Cardoso F, Bedard PL, Winser EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, Kyriakides S, Costa A, Cufer T, Albain KS; ESO-MBC Task Force: International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 2009;101:1174–1181.

6 Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Diéras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators: Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914–923.

7 Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, Olivo MS, He Y, Dutcus CE, Cortes J: Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015;33:594–601.

8 Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA, Awada A: Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat 2014;148:553–561.
9 Gamucci T, Michelotti A, Pizzuti L, Mentuccia L, Landucci E, Sperduti I, Di Lauro L, Fabi A, Tonini G, Sini V, Salesi N, Ferrarini I, Vaccaro A, Pavese I, Veltri E, Moscetti L, Marchetti P, Vici P: Eribulin mesylate in pretreated breast cancer patients: a multicenter retrospective observational study. J Cancer 2014;5:320–327.
10 Borgonovo K, Petrelli F, Cabiddu M, Ghilardi M, Coinu A, Seghezzi S, Barni S: Long response to eribulin in breast cancer: a case report. Future Oncol 2015;11:3–8.
11 Dawood S, Gonzalez-Angulo AM: Progress in the biological understanding and management of breast cancer-associated central nervous system metastases. Oncologist 2013;18:675–684.
12 Minisini AM, Moroso S, Gerratana L, Giangreco M, Iacono D, Poletto E, Guardascione M, Fontanella C, Fasola G, Puglisi F: Risk factors and survival outcomes in patients with brain metastases from breast cancer. Clin Exp Metastasis 2013;30:951–956.
13 McTyre E, Scott J, Chinnaiyan P: Whole brain radiotherapy for brain metastasis. Surg Neurol Int 2013;4:S236–S244.
14 Soliman H, Das S, Larson DA, Sahgal A: Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. Oncotarget 2016;7:12318–12330.
15 Qin DX, Zheng R, Tang J, Li JX, Hu YH: Influence of radiation on the blood-brain barrier and optimum time of chemotherapy. Int J Radiat Oncol Biol Phys 1990;19:1507–1510.
16 Bart J, Nagengast WB, Coppes RP, Wegman TD, van der Graaf WT, Groen HJ, Vaalburg W, de Vries EG, Hendrikse NH: Irradiation of rat brain reduces P-glycoprotein expression and function. Br J Cancer 2007;97:322–326.
17 van Vulpen M, Kal HB, Taphoorn MJ, El-Sharouni SY: Changes in blood-brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? (review). Oncol Rep 2002;9:683–688.
18 Ekenel M, Hormigo AM, Peak S, Deangelis LM, Abrey LE: Capecitabine therapy of central nervous system metastases from breast cancer. J Neurooncol 2007;85:223–227.
19 Fabi A, Vidiri A, Ferretti G, Felici A, Papaldo P, Carlini P, Mirri A, Nuzzo C, Cognetti F: Dramatic regression of multiple brain metastases from breast cancer with capecitabine: another arrow at the bow? Cancer Invest 2006;24:466–468.
20 Matsuoka H, Tsurutani J, Tanizaki J, Iwasa T, Komoike Y, Koyama A, Nakagawa K: Regression of brain metastases from breast cancer with eribulin: a case report: BMC Res Notes 2013;6:541.
21 Nieder C, Aandahl G, Dalhaug A: A case of brain metastases from breast cancer treated with whole-brain radiotherapy and eribulin mesylate. Case Rep Oncol Med 2012;2012:537183.
22 Funahashi Y, Okamoto K, Adachi Y, Semba T, Uesugi M, Ozawa Y, Tohyama O, Uehara T, Kimura T, Watanabe H, Asano M, Kawano S, Tizon X, McCracken PJ, Matsui J, Aoshima K, Nomoto K, Oda Y: Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. Cancer Sci 2014;105:1334–1342.