Eribulin as a Feasible and Safe Monotherapy in a Dialytic Pretreated Woman with Metastatic Breast Cancer: A Case Report

Raffaele Nettuno Carmine Menditto

Department of Oncology, P.O. A.G.P. di Piedimonte Matese, Caserta, Italy

Keywords

Eribulin · Metastatic breast cancer · Taxanes · Chemotherapy · Dialysis

Abstract

Eribulin, a non-taxane inhibitor of microtubule dynamics, is approved for the treatment of metastatic breast cancer patients after progression with anthracyclines and taxanes. Nevertheless, to our knowledge, information on its use in dialytic patients is not available to date. This report describes the case of a chemo-pretreated dialytic woman with lung, bone, and liver metastasis from breast cancer, who experienced stable disease with a response <20% with eribulin in fifth line after 3 hormonal lines and 1 chemotherapy line. This case suggests the feasibility and good tolerability of eribulin in this peculiar setting.

© 2018 The Author(s)
Published by S. Karger AG, Basel

Introduction

Metastatic breast cancer (MBC) is still an incurable disease with a median life expectancy after recurrence of 24–30 months or less. Anthracycline- and taxane-based

chemotherapy represents the mainstay of treatment in this setting. However, resistance to these agents often occurs.

Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs. By inhibiting the microtubule growth phase without affecting the shortening phase and causing tubulin sequestration into non-productive aggregates, it has a distinct mode of action from the other tubulin-targeting agents [1–5].

The global randomized multicenter phase III trial EM-BRACE underlined that eribulin prolongs significantly overall survival in patients with MBC previously treated with both anthracycline and taxane [6] compared with treatment of physicians' choice (13.2 vs. 10.5 months; hazard ratio 0.81; 95% confidence interval 0.67–0.96; $p = 0.014$) with a manageable toxicity profile: limited grade 3 (G3) and 4 (G4) non-hematological events (10% G3 fatigue and 7% G3 peripheral neuropathy), and only 5% incidence of febrile neutropenia [7].

Patients with end-stage renal disease represent a distinct challenge in oncology. Many anticancer drugs and their metabolites are excreted by the kidney, but data to guide dose and schedule adjustments in renal dialysis are scant [8] as this population is typically excluded from clinical trials.

Eribulin has minimal urinary excretion, with 5–6% of the administered dose eliminated in urine over a 72-h period after a single dose. Eribulin has linear kinetics, with terminal half-life of 2 days, rapid extensive volume of distribution, slow-to-moderate clearance and slow elimination, with non-renal clearance ($\approx 7\%$ of the drug excreted unchanged in the urine) [6]. However, information on the use of eribulin in patients with renal dysfunction, and in particular in those on dialysis, is still scant.

This report describes the case of a chemo-pretreated dialytic woman with lung, bone, and liver metastasis from breast cancer who achieved a stable disease response with eribulin in fifth line after 3 hormonal lines and 1 chemotherapy line, and showed good tolerability.

Case Presentation

In February 2011, a white Caucasian woman born in 1942 was admitted to our hospital for the appearance of multiple lung nodules, identified by a computed tomography (CT) scan during a previous admittance to the Nephrology Department due to the worsening of chronic renal failure.

The patient, a usual smoker of about 20 cigarettes per day until 2001, had multiple comorbidities including sclerotic fibrillating cardiomyopathy, overweight class III, beta thalassemia minor, and chronic renal failure in dialytic therapy since 2013.

The patient had been submitted to radical mastectomy on the left side in October 1999, with ipsilateral axillary lymph node dissection for infiltrating ductal carcinoma, highly positive estrogen receptor, progesterin receptor, and cErB2. The pathological tumor node metastasis (pTNM) stage was pT2 (3 cm) pN1 (8/18) M0.

From November 1999 to June 2000, the patient received adjuvant chemotherapy with 4 cycles of epirubicin 75 mg/m² followed by 6 cycles of cyclophosphamide 600 mg/m², methotrexate 40 mg/m², and 5-fluorouracil 600 mg/m² (CMF) and then hormonal therapy with tamoxifen 20 mg per day for 5 years.

In the following 6 years, clinical and radiological follow-up was oncologically negative, until January 2011 when the CT scan revealed the appearance of multiple suspected malignant lung nodules, later confirmed by a positron emission tomography scan. A CT-guided biopsy diagnosed the lesions as lung metastasis of breast cancer with positive estrogen receptor. The tumor marker dosages, such as carcinoembryonic antigen, carbohydrate antigen 15.3 (CA-15.3) and 125 (CA-125) were normal. In May 2011, the patient started a first-line hormonal therapy with exemestane subsequently replaced by letrozole in 2012. No information is available on the reason for this change, as at the time the patient was followed by another center.

In October 2013, a new clinical-instrumental evaluation showed progression at both the clinical (dyspnea) and instrumental level (bilateral pleural effusion and increased lung nodule dimension, and suspect thickening of bone lesions at CT scan in costovertebral, lumbar, and basin bones), and therefore letrozole was replaced by fulvestrant.

In late January 2014, a CT scan revealed a quantitative and dimensional progressive disease in the lung, as well as a slight increase in the tumor marker dosages CA-15.3 (58.3 U/mL) and CA-125 (82.4 U/mL).

The patient underwent first-line chemotherapy with weekly paclitaxel 80 mg/m² obtaining an instrumental and biotumoral partial response after 6 cycles. However, due to the occurrence of high-grade hematological (G4 neutropenia) and neurological toxicities, appearance of superior cava vein subocclusive thrombosis at the site of porth-a-cath central venous catheter, and poor treatment adherence, the patient stopped chemotherapy and started hormonal therapy with exemestane alone.

In April 2015, an abdominal ultrasound and a new CT scan revealed progression in I and V–VI liver segments. From May 2015 until December 2015, the patient stopped exemestane and underwent a second line of chemotherapy with eribulin in monotherapy at the classic dose of 1.23 mg/m² on days 1 and 8, every 21 days. During this period, the patient experienced fatigue and anorexia G2, anemia G2, and neuropathy G1 (according to CTCAE 4.0).

The interim reevaluation performed after 11 cycles of therapy in January 2016 documented a marked worsening of the clinical status (uncontrolled basin pain), of the tumor marker dosage (CA-15.3 180 U/mL, carcinoembryonic antigen 85.8 U/mL) and of the radiological picture with bone, lung, and liver progression at the total body positron emission tomography/CT scan and CT scan. The best response obtained with eribulin was a stable disease with mild reduction of the lesions. The patient was therefore treated with right basin antalgic radiotherapy and palliative progesterone acetate therapy 160 mg every 12 h until exitus, which occurred in March 2016.

Discussion

Approximately 6% of patients undergoing dialysis have malignancies [9], and the number of those who at the same time are undergoing chemotherapy continues to increase. Chemotherapy in dialysis patients is challenging because drug excretion differs from that of non-dialysis patients. Drugs that are excreted by dialysis may show reduced efficacy, while those that are not excreted may cause adverse events [10].

Plasma concentrations of eribulin mesylate increase linearly in a dose-dependent manner with rapid distribution, slow-to-moderate clearance, and slow elimination. A shorter infusion achieves higher peak plasma concentrations compared with the 1-h infusion. At the maximum tolerated dose, plasma levels of eribulin are above the concentration required for *in vitro* cytotoxicity for > 1 week. Eribulin demonstrates triphasic elimination with a half-life ranging from 36 to 48 h, and it is eliminated primarily by biliary excretion. Renal excretion is minimal, with 5–11% of the administered dose eliminated in the urine. To our knowledge, no literature data are available on the use of eribulin in dialytic patient settings [11].

This case report is emblematic because of the use of eribulin in the second-line setting in a dialytic and cardiopathic patient with both anthracycline and capecitabine contraindications. In our patient, the standard schedule of eribulin, together with granulocyte colony-stimulating factor prophylaxis, was administered without any severe toxicity. Instrumental reevaluations documented a stable disease with a slight decrease in lesions.

In our opinion, although this is only a single case, eribulin proved to be a feasible, active, and well-tolerated monotherapy also in dialytic patients. Further validation in distinct subtypes of breast cancer is needed to confirm the use of eribulin in this setting.

Acknowledgements

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

Disclosure Statement

All authors declare no conflict of interest.

References

- 1 Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, Welsh S, Zheng W, Seletsky BM, Palme MH, Habgood GJ, Singer LA, Dipietro LV, Wang Y, Chen JJ, Quincy DA, Davis A, Yoshimatsu K, Kishi Y, Yu MJ, Littlefield BA: In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. *Cancer Res* 2001;61:1013–1021.
- 2 Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L: The primary antimetabolic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. *Mol Cancer Ther* 2005;4:1086–1095.
- 3 Kuznetsov G, Towle MJ, Cheng H, Kawamura T, TenDyke K, Liu D, Kishi Y, Yu MJ, Littlefield BA: Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. *Cancer Res* 2004;64:5760–5766.
- 4 Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA: Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. *Mol Cancer Ther* 2008;7:2003–2011.
- 5 Smith JA, Wilson L, Azarenko O, Zhu X, Lewis BM, Littlefield BA, Jordan MA: Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. *Biochemistry* 2010;49:1331–1337.
- 6 Swami U, Chaudhary I, Ghalib MH, Goel S: Eribulin – a review of preclinical and clinical studies. *Crit Rev Oncol Hematol* 2012;81:163–184.
- 7 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.
- 8 Chang R, Shirai K: Safety and efficacy of pembrolizumab in a patient with advanced melanoma on haemodialysis. *BMJ Case Rep* 2016;2016:bcr2016216426.
- 9 Eneman JD, Philips GK: Cancer management in patients with end-stage renal disease. *Oncology (Williston Park)* 2005;19:1199–1212.
- 10 Niikura R, Serizawa T, Yamada A, Yoshida S, Tanaka M, Hirata Y, Koike K: Safety of regular-dose imatinib therapy in patients with gastrointestinal stromal tumors undergoing dialysis. *Case Rep Gastroenterol* 2016;10:17–23.
- 11 Jain S, Vahdat LT: Eribulin mesylate. *Clin Cancer Res* 2011;17:6615–6622.