Clinical Study

Oncology

Oncology 2018;94(suppl 1):34–44
DOI: 10.1159/000489067

Published online: July 24, 2018

Eribulin Treatment in Patients with Liver Metastatic Breast Cancer: Eight Italian Case Reports

Guido Giordano[h, i] Antonio Febbraro[a] Erica Quaquarini[b] Anna Turletti[c]
Rebecca Pedersini[d] Mimma Raffaele[e] Federica Villa[f] Rosalba Rossello[g]
The Italian Eribulin Working Group

[a]Medical Oncology Unit, "Sacro Cuore di Gesù Fatebenefratelli" Hospital, Benevento, Italy; [b]Operative Unit of Medical Oncology, ICS Maugeri-IRCCS, Pavia, Italy; [c]ASL Città di Torino, Ospedale Martini, Turin, Italy; [d]Breast Unit-Oncology Department, Spedali Civili Hospital, Brescia, Italy; [e]UOSD Oncologia Presidio Cassia, Sant'Andrea-Dipartimento Oncologico ASL, Rome, Italy; [f]S.C. Oncologia Medica, Dipartimento Oncologico Aziendale, ASST Lecco, Lecco, Italy; [g]Oncologia Medica dell'Ospedale S. Vicenzo di Taormina, Taormina, Italy; [h]Medical Oncology Unit, San Filippo Neri Hospital, Rome, Italy; [i]Oncology Division, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Keywords
Eribulin · Metastatic breast cancer · Liver metastasis · Quality of life

Abstract
Liver metastases are very common in metastatic breast cancer (MBC); current treatments for these lesions are based on systemic chemotherapy, endocrine- or human epidermal growth factor receptor 2 (HER2)-targeted therapy, and palliative therapy. However, no standard approach has been clearly identified for second and further chemotherapy lines in MBC patients. In the phase III clinical trial EMBRACE, eribulin was particularly effective in reducing liver lesions and improving both overall survival and progression-free survival in liver MBC patients. In this series, we collected 8 case reports of Italian clinical practice in which eribulin has shown significant efficacy in reducing liver metastases in MBC patients: complete response was reported in 2 patients, and 4 patients achieved partial response. The treatment was well tolerated, thus confirming that eribulin is a suitable therapeutic option for elderly patients and for those who have metastatic HER2-negative disease. In the setting of MBC, the sequencing of therapeutic agents should consider expected response, side effects, tumor characteristics, and patient's preferences, in order to successfully tailor the most appropriate therapy beyond earlier lines.

Introduction

Breast cancer is the most frequently diagnosed cancer in women [1]. Between 15 and 20% of patients present with metastatic breast cancer (MBC), and currently around 50% of patients with operable breast cancer relapse with metastatic disease. Despite the progress achieved

Members of the Italian Eribulin Working Group are listed in the Appendix.

KARGER

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

Dr. Guido Giordano
Oncology Division, IRCCS Casa Sollievo della Sofferenza
viale Cappuccini 1
IT–71013 San Giovanni Rotondo (Italy)
E-Mail giordano.guido81@gmail.com

in the systemic treatment of MBC, treatment approaches have symptomatic-palliative goals, on one hand prolonging the time to progression and survival, and on the other hand improving quality of life (QoL) by reducing and delaying the onset of symptoms [2–4]. However, in the last years, the potential of new drugs (biological response modifiers as well as new chemotherapeutic agents) to prolong survival when used in the appropriate sequence has partially changed the landscape of this condition. According to international guidelines [5], in anthracycline and taxane pre-treated patients, single agent capecitabine, vinorelbine, or eribulin are the preferred choices. Additional options include gemcitabine, platinum-based agents, taxane re-challenge, and liposomal anthracyclines. Nonetheless, effective treatment options for patients with MBC resistant to anthracyclines and taxanes are limited.

Eribulin is a new anticancer agent, approved for patients with MBC already treated with at least 2 chemotherapeutic regimens, including anthracyclines and taxanes in either adjuvant or metastatic setting [6]. Eribulin is a synthetic analogue of the natural product halichondrin B isolated from the marine sponge *Halichondria okadai*. Its mechanism of action is unique among microtubule poisons and involves binding to polymerized tubulin, without affecting depolymerization but promoting tubulin sequestration in nonfunctional polymers. This determines cell cycle arrest in the G2-M phase in vitro in several human cancer cell lines, including p-glycoprotein-expressing and taxane-resistant lines, when incubated in the presence of nanomolar concentrations of the drug [7–9]. In the clinical setting, the phase III EMBRACE study demonstrated the efficacy of eribulin in terms of prolonging overall survival (OS) versus the treatment of physician's choice (TPC) [10]. This trial included almost 60% of patients with liver metastases who achieved important benefit from eribulin in terms of reduced lesions and improved clinical outcomes [11]. Liver metastases are very common in MBC [12]; current treatments for these lesions are based on systemic chemotherapy, endocrine- or human epidermal growth factor receptor 2 (HER2)-targeted therapy [depending on estrogen receptor (ER), progesterone receptor (PgR) and HER2 status], and palliative therapy. Nevertheless, no standard approach has been clearly identified for second and further chemotherapy lines in MBC patients [13].

This series of case reports describes the therapeutic approach used in 8 patients with MBC treated in different Italian centers, focusing on the activity of eribulin treatment in hepatic disease. All patients gave consent to publish these reports.

Case Reports

Case 1

In August 1996, a 45-year-old woman noticed a lump of about 1 cm in the right breast. In anamnesis, she reported pharmacologically treated hypertension and no family history of breast or gynecological cancer. After surgery, histological examination revealed the presence of a G3, pT1 N0 invasive ductal carcinoma (IDC), ER 90%, PgR 90%, Ki67 15%, HER2 3+. From November 1996 until October 2001, the patient underwent adjuvant hormonal therapy with a luteinizing hormone-releasing hormone (LH-RH) analogue (3.75 mg every 28 days) and tamoxifen (20 mg daily). In October 2004, during the follow-up visit, the patient reported worsening dyspnea and cough: chest radiography and a subsequent computed tomography (CT) scan confirmed the presence of pleural effusion associated with pleural thickening and increased Ca-125 (221 UI/mL) and Ca 15.3 (52 UI/mL), with normal carcinoembryonic antigen (CEA 4 ng/mL). Approximately 1 L of citrine yellow liquid was drained from the patient during thoracentesis. Pleural fluid cytology tested positive for cancer cells compatible with the disease in medical history. From November 2004 until February 2005, she performed first-line chemotherapy based on anthracyclines and taxanes (epirubicin 75 mg/m^2, docetaxel 75 mg/m^2 every 21 days for 6 total cycles), achieving a complete response (CR). Then, she continued with hormone therapy with letrozole 2.5 mg until December 2011, when she decided, on her own, to discontinue the drug, having to endure a long follow-up. In January 2014, she came to the follow-up visit complaining of pain in the upper right abdominal quadrant, unresponsive to analgesics. A positron emission tomography-CT (PET-CT) scan highlighted multiple nodules in the liver, then evaluated by needle biopsy. Histological examination documented the presence of metastases compatible with mammary primary disease, significantly changed from previous histological examination (ER 30%, PgR 25%, Ki67 35%, HER2 negative). Hematological examinations showed increased Ca 15.3 (70 UI/mL) with normal CEA (4 ng/mL). From January to March 2014, the patient was treated with second-line nab-paclitaxel 260 mg/m^2 every 3 weeks for 4 infusions without showing any response, with volumetric increase in liver metastases and tumor markers. Therefore, we opted for third-line treatment with capecitabine 2,000 mg/m^2, on days 1–14, every 3 weeks and vinorelbine 25 mg/m^2 on days 1 and 8, every 3 weeks. After 2 cycles of treatment, the patient discontinued capecitabine for grade 3 hand-foot syndrome and continued with vinorelbine single agent for other 2 cycles, achieving progression of liver disease, as evidenced by PET-CT (the bigger lesion in the right liver being 39 mm large, standardized uptake value [SUV] max. 17.5) (Fig. 1).

Furthermore, the pain in the right upper quadrant increased (visual analogue scale [VAS] = 7) and Ca 15.3 increased (120 UI/mL). Therefore, the patient initiated a fourth-line treatment with eribulin 1.23 mg/m^2 on days 1 and 8 of a 21-day cycle. The first reevaluation of disease was performed after 4 cycles of treatment. The radiological examination confirmed stability of liver metastases. The treatment was very well tolerated: the patient reported only grade 2 paresthesia of hands and arms after 6 cycles, managed with α-lipoic acid. At the next revaluation after 8 cycles, partial remission was described at the PET-CT with a reduction of the large right liver lesion size to 1 cm, with SUV 8 (Fig. 2). Ca 15.3 levels also decreased (58 UI/mL).

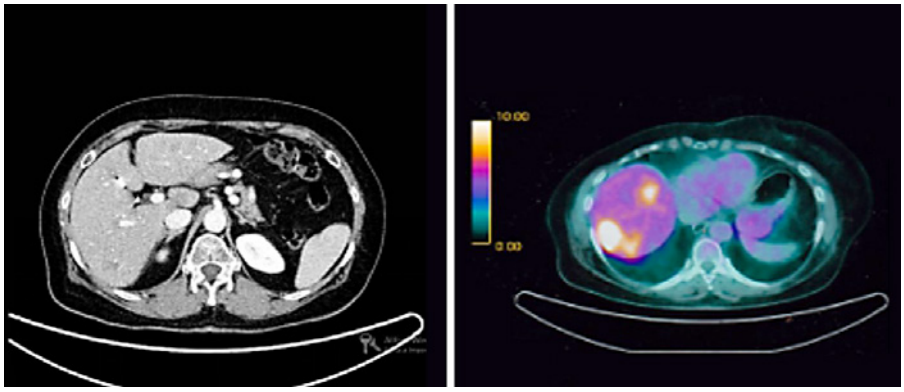

Fig. 1. PET-CT (August 2014) shows multiple liver lesions, the biggest measuring 39 mm, in the right liver (SUV max. 17.5).

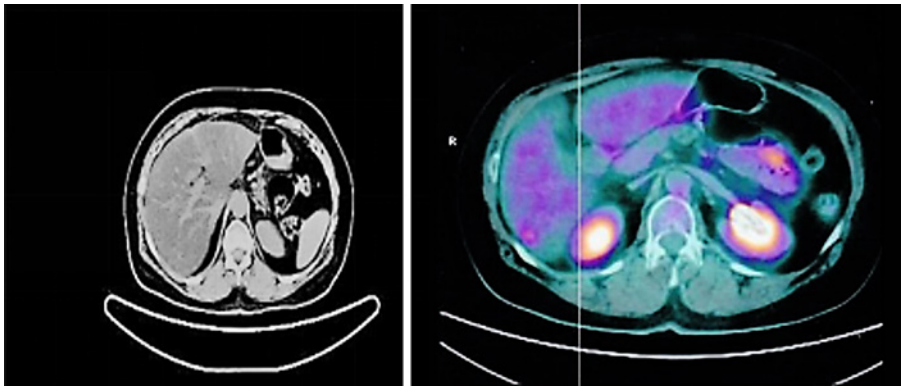

Fig. 2. PET-CT (April 2015) after 8 cycles of eribulin shows dimensional reduction of the hepatic lesions (10 mm, SUV max. 8).

Therefore, the patient continued treatment with eribulin, successfully completing 18 courses of treatment until February 2016. Both tumor markers and radiological examinations confirmed partial response (PR) on the liver. No dosage adjustment was needed during therapy. In addition, even after the first cycles, the performance status improved and, importantly, the dose of opioid analgesics was decreased (VAS = 0). In February 2016, at the appearance of new hepatic lesions, treatment with eribulin was discontinued. Currently, the patient is being treated with pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks as sixth line of therapy after the disease had progressed further in the liver after a fifth line with letrozole and palbociclib 125 mg daily for 21 consecutive days followed by 7 days off treatment (compassionate use).

Case 2

In 2002, a 46-year-old premenopausal woman, with uneventful past medical history and no familiarity with breast or ovarian cancer, underwent a right quadrantectomy with sentinel lymph node biopsy for a lobular carcinoma (staging pT2 pN0 M0, grade 2 [G2], hormonal receptors and cellular marker status: ER negative, PgR negative, Ki67 17%, HER2 negative). The patient started 6 cycles with epirubicin, 5-fluorouracil, and cyclophosphamide as adjuvant therapy, in addition to complementary radiotherapy. In 2006, a right mastectomy was performed due to local recurrence; the histological exam confirmed the diagnosis of lobular carcinoma, infiltrating the pectoral muscle (pT2 Nx M0, G2, ER 40%, PgR< 1%, Ki67 15%, c-erbB 1+). A further adjuvant treatment with 6 cycles of tri-weekly paclitaxel was prescribed, followed by hormonal therapy with tamoxifen 20 mg/die and LH-RH analogues. In 2010, she had a subcutaneous relapse in the right breast removed. Following the resection, she switched hormonal therapy from tamoxifen to letrozole 2.5 mg/die, continuing LH-RH analogue injections.

In 2012, a flare of CEA and Ca 15.3 became evident; a whole-body CT scan revealed systemic progression with pleural, liver, and skin (right breast) metastases. Due to the preserved performance status (Eastern Cooperative Oncology Group – ECOG PS = 0), absence of disease-related symptoms and organ failure, a first-line treatment with exemestane 25 mg/die and everolimus 10 mg/die was prescribed in the context of a research protocol. The treatment was continued for 11 months with PR, and it was well tolerated, except for G3 mucositis according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTC version 4.0) [14]. In November 2013, a second line with fulvestrant 500 mg was started for asymptomatic pleural and liver progression. After 5 months, a further pleural, hepatic, nodal, skin, and bone disease progression occurred.

Considering the short progression-free survival (PFS) interval with the last hormonal treatment, the patient started a first-line chemotherapy with tri-weekly nab-paclitaxel 260 mg/m^2 and zoledronic acid. The treatment produced PR in the skin and liver and disease stabilization at the other sites; the patient complained only of G1 peripheral neuropathy and G2 alopecia. The therapy was continued for 10 months until February 2015, when skin progression occurred. CEA and Ca 15.3 were 9.1 U/mL and 145 ng/mL, respectively.

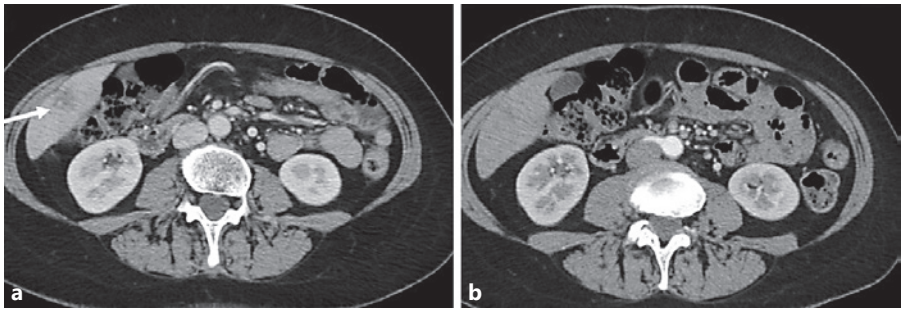

Fig. 3. a CT scan showing liver metastasis before eribulin treatment; the white arrow indicates the lesion. **b** Complete liver response after 6 cycles of eribulin treatment.

Eribulin mesylate 1.23 mg/m^2 on days 1 and 8 of a 21-day cycle was then started; after 6 cycles, a complete skin and liver response became evident (Fig. 3), with PR of the pleural lesions and stability of bone disease. The treatment was well tolerated, with G2 asthenia, G2 alopecia and without worsening of G1 peripheral neuropathy. No administration delays occurred for hematological toxicity. The treatment was continued for 11 months; in January 2016, at the end of the twelfth cycle, a CT scan showed an increase in pleural, skin, and bone disease; the liver complete remission was still ongoing. CEA was 3.8 U/mL and Ca 15.3 48 ng/mL. The patient underwent skin chest 3D conformational radiotherapy for a total of 45 Gy (1.8 Gy/fraction for 25 fractions) with complete regression of metastatic nodules.

In April 2016, the patient started a third-line systemic CT with capecitabine 1,000 mg/bid on days 1, 14, and 21; in addition, in January 2017, for a further disease progression, a fourth-line treatment with metronomic vinorelbine was started. At present, the patient is alive, and the treatment is ongoing with substantial disease stabilization.

Case 3

In 2006, a 37-year-old woman underwent lumpectomy plus axillary dissection for IDC G2 pT 2(m) pN1a, ER 80%, PgR 60%, Ki67 18%, c-erb2 negative. No distant metastasis was reported. She started chemotherapy (epirubicin and cyclophosphamide + paclitaxel), followed by radiotherapy and hormonal therapy with tamoxifen. In 2009, during follow-up examination, vertebral metastases were detected; therefore, the patient started a treatment with aromatase inhibitors, LH-RH analogues, and zoledronic acid, achieving a PR until June 2011 when a new skeletal progression disease was reported. Ca 15.3 was 80 U/mL and the ECOG PS was 0; the patient initiated capecitabine for 8 cycles. In November 2011, a new skeletal progression of disease was noticed with Ca 15.3 82 U/mL and ECOG PS 0; the patient was treated with fulvestrant + LH-RH analogues, achieving CR after 12 months, but after 18 months, a further progression in the bone was observed. Then, in May 2013, the patient started oral vinorelbine, radiotherapy on days 11 and 12, and denosumab monthly with an initial CR, but subsequent disease progression in bone after 6 cycles. In October 2013, the disease progressed to the liver. Hepatic biopsy did not show any difference between primary cancer and liver metastasis: IDC G2, ER 75%, PgR 55%, Ki67 22%, c-erbB2 2+, fluorescence in situ hybridization (FISH): negative. Ca 15.3 was 100 U/mL and ECOG-PS was 0. The patient started docetaxel 75 mg/m^2, achieving a PR (CT scan and bio-humoral) after 4 cycles, but the disease progressed after 9 cycles (Fig. 4). In July 2014, a new hepatic progression was observed with concomitant increase in transaminases (alanine aminotransferase [ALT] 120 U/L and aspartate aminotransferase [AST] 108 U/L), but normal bilirubin. Ascites was not detectable, and Ca 15.3 was 120 U/mL. The patient was determined to continue treatment and was showing good PS (0); therefore, she started eribulin 0.97 mg/m^2 because of heavy previous chemotherapy. A rapid normalization of altered parameters was observed; the patient did not experience toxicities and had an improved QoL. She received 10 cycles of eribulin, when a new increase in Ca 15.3 indicated again hepatic progression of disease (Fig. 4). In April 2015, the patient initiated liposomal epirubicin (weekly schedule), with PR and good QoL. In December 2015, after 9 cycles, ascites and jaundice appeared: CT scan showed massive hepatic involvement, and hepatic failure was reported. Chemotherapy was stopped and the patient died on January 31, 2016.

Case 4

In 2006, a 58-year-old woman was admitted to hospital because of a large, painful, solid mass located in the left breast; mammography and ultrasound examination confirmed a 15-cm maximum diameter lesion. Axillary ultrasound was negative for solid lesions. Core biopsy was performed, and final examination was diagnostic for poorly differentiated (G3) infiltrating ductal carcinoma. Immunohistochemistry showed hormone receptor positivity (ER 90%, PgR 75%; Ki67 25%; HER2 status: 2+, and FISH test showed no amplification), while contrast-enhanced CT scan and bone scintigraphy were negative for distant metastases. CEA and Ca 15.3 levels were within normal range. The patient started 3 cycles of neoadjuvant chemotherapy with fluorouracil + epirubicin + cyclophosphamide (FEC regimen). In July 2006, she underwent radical left mastectomy and axillary lymphadenectomy, with the final histological examination confirming IDC stage pT1cpN1M0. Adjuvant treatment was continued with 3 further cycles of FEC chemotherapy and, then, hormonotherapy with anastrozole was started.

In October 2009, during follow-up examination, a solid nodule located in the upper external region of the right breast was detected by ultrasound. This nodule was surgically resected (histological examination: well differentiated IDC pT1c G1), but due to positive surgical margins, the patient underwent right radical mastectomy and sentinel node biopsy (final stage: pT1cpN1M0 G1; immunohistochemistry: ER 90%, PgR 90%, Ki67 10%, HER2 1+). CEA and Ca 15.3 levels were within normal range. CT scan was negative for distant metastases. After surgery, adjuvant treatment was completed with 6 cycles of chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF schedule), and then hormonotherapy with tamoxifen.

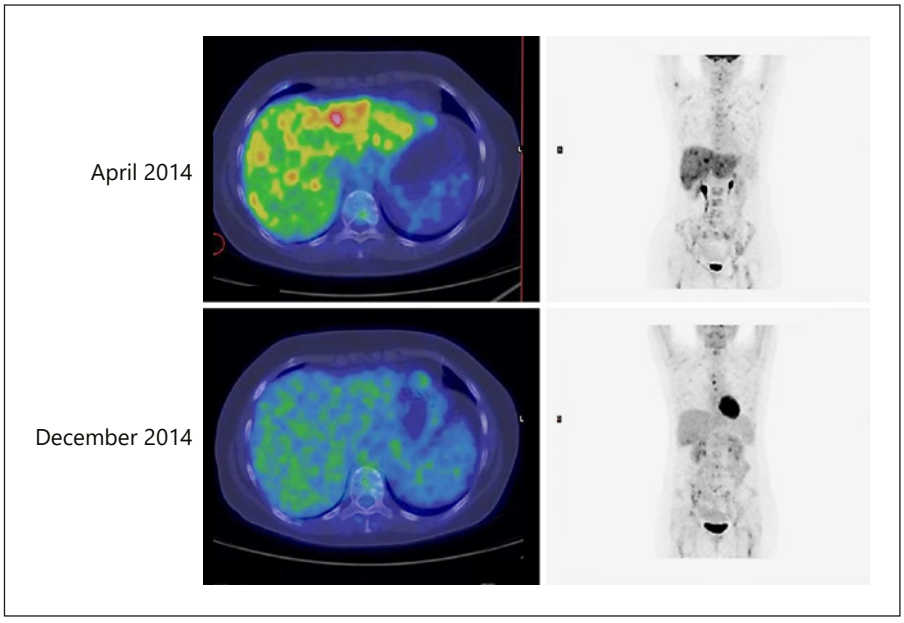

Fig. 4. CT scans before starting eribulin (April 2014) and during treatment (December 2014).

In December 2012, a contrast-enhanced CT scan detected several right lung metastases with a maximum diameter of 4 cm extended to the pleural surface; CEA was 38.7 U/mL; Ca 15.3 was 39 U/mL. A first-line treatment with paclitaxel + bevacizumab was started and performed for 14 cycles, achieving as best response a PR on lung metastases. Treatment was stopped in January 2014, and the patient underwent a follow-up period (CEA 4.2 U/mL; Ca 15.3: 12 U/mL).

In November 2014, a contrast-enhanced CT scan showed disease progression in lung and pleural metastases, but liver lesions were stable. A second-line treatment with vinorelbine 25 mg/m^2 on days 1 and 8 every 21 days was started (4 cycles). In February 2015, 2 liver lesions, located in the VI segment were detected, and pulmonary lesions increased in size (maximum diameter 2.5 cm) and number; pleural metastases also increased in size (3 vs. 1.5 cm), with right pleural effusion. CEA was 42 U/mL and Ca 15.3 121 U/mL. The ECOG PS was 1, due to chest pain and dyspnea. Laboratory exams were within normal range. In March 2015, a third line with eribulin 1.23 mg/m^2 on days 1 and 8 of a 21-day cycle was started. The patient experienced an immediate clinical benefit with reduction of opioid consumption for pain control and reduced dyspnea. G2 neutropenia occurred on day 8 of the second cycle, but no dose reduction was needed. After the second cycle, AST and ALT increased to 82 U/L and 94 U/L, respectively (upper normal limits were 37 and 40 for ALT and alanine aminotransferase, respectively) and γ-glutamyl transferase (GGT) levels increased to 175 U/L (upper normal level according to our laboratory was 50 U/L). Bilirubin levels and other liver-related examinations were still within normal ranges. For this reason, we started ursodeoxycholic acid and glutathione treatment up to the first day of cycle 3. After 10 days of treatment, both aminotransferase and GGT levels decreased to 55, 59, and 91 U/L, respectively. Treatment with full-dose eribulin was continued without delays, and after 3 cycles a PR was observed by CT scan on pleural and lung lesions. No more pleural effusion was detected and the liver lesions disappeared. CEA and Ca 15.3 level rapidly decreased to 3.2 and 28 U/mL, respectively. Chemotherapy was continued, and ursodeoxycholic acid was administered daily up to cycle 15. Patient's ECOG PS progressively improved to 0, and no more episodes of dyspnea or chest pain occurred. Twenty-one cycles of eribulin treatment were successfully completed and instrumental examinations as well as tumor markers confirmed a CR on the liver metastases and a PR on the lung.

In January 2017, a contrast enhanced CT scan showed bone metastases located to the pelvis, and the decision to suspend eribulin chemotherapy was undertaken. The patient underwent radiation on the pelvis and hormonotherapy with fulvestrant that is still on course. Globally, eribulin showed a very high activity in this patient and a good tolerability; in fact, no limiting toxicities occurred, and no dose reductions were needed. Despite an increase in aminotransferase and GGT levels after cycle 2, liver function remained well preserved. Liver ultrasounds performed during the treatment showed "bright liver" images, indicating steatosis that was also confirmed by the CT scan evaluations.

Case 5

In September 1996, a 60-year-old woman was admitted to hospital because of a nodule of 1.5 × 1 cm in the right breast detected by a control mammography. In anamnesis, she reported previous acute hepatitis B, chronic bronchitis, hypothyroidism, hypertension, and hypercholesterolemia. In October 1996, she underwent right quadrantectomy and axillary lymphadenectomy. The tumor was staged as T1N0M0. Histological examination indicated an IDC G2 (ER and PGR positive, c-erbB2 0). In December 2012, the patient was referred to the oncology division for lumbar pain radiating to the legs (numerical rating scale 6), treated in the previous months with nonsteroid anti-inflammatory drugs and steroids. She underwent a CT scan, which documented multiple macroadenopathies in the mediastinum, and a subsequent biopsy. The histological examination revealed neoplastic finding compatible with

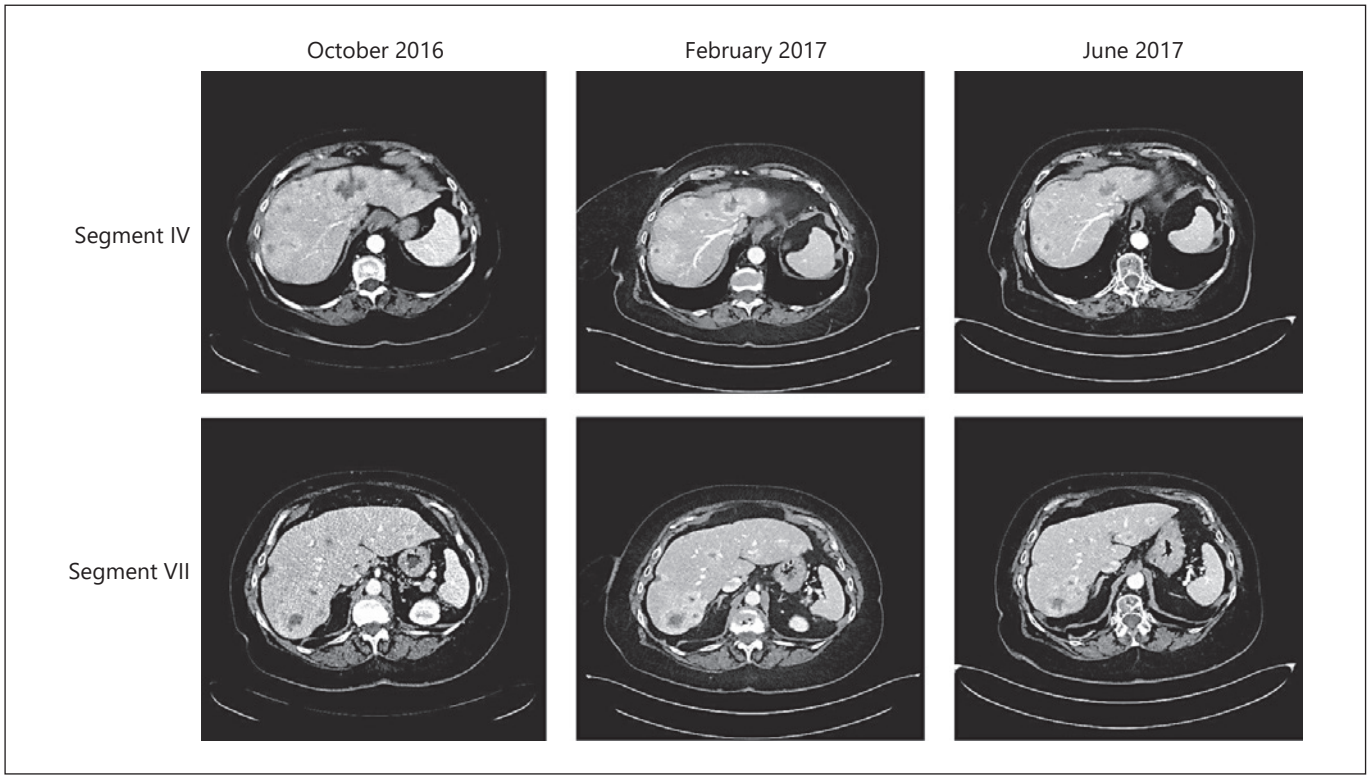

Fig. 5. CT scans of liver lesions in IV and VII segments.

breast cancer (ER 80%, PgR 30% c-erbB2: 2 + FISH not amplified). In January 2013, the patient began hormone therapy with aromatase inhibitor, letrozole 2.5 mg, achieving a partial remission.

In November 2014, a CT scan revealed an increase in lymph nodes located in the mediastinum; she started fulvestrant high-dose regimen (500 mg every 28 days).

In May 2015, a progression of mediastinal lymph node disease was detected; Ca 15.3 was 38 U/mL and CEA 2 U/mL. Therefore, the patient stopped fulvestrant and began the first-line metronomic capecitabine at 1,500 mg per day.

In October 2015, a CT scan confirmed an increase in mediastinum adenopathies and the presence of liver secondary lesions, with Ca 15.3 as 60 U/mL. The patient stopped capecitabine and started a second line with oral vinorelbine. In February 2016, mediastinum adenopathies increased further, and multiple liver metastases appeared (Ca 15.3 110 U/mL). Therefore, she stopped vinorelbine and started the third line with liposomal doxorubicin every 15 days. In May 2016, after 6 cycles of therapy, a tumor marker increase (Ca 15.3 516 U/mL) and a CT scan documented an increase in both the mediastinum adenopathies and liver multiple lesions and the appearance of adenopathies located to the hepatic ileus. The patient stopped liposomal doxorubicin and underwent a liver biopsy for new biological typing. The histological examination indicated a metastatic lesion compatible with breast cancer (ER 100%, PgR 0%, MIB1 28%, c-erbB2 negative [score 1+] FISH: no amplification of HER2 gene).

In June 2016, the patient started a weekly fourth-line treatment with nab-paclitaxel (days 1, 8, and 15 every 28 days); in October 2016, a tumor marker increase (Ca 15.3 791 U/mL) was noted, and a CT scan documented a progression of the metastatic lesions in the liver (Fig. 5). The ECOG- PS of the patient was 1, and she was asymptomatic except for asthenia G1.

In November 2016, she started a fifth-line chemotherapy with eribulin 1.23 mg/m^2 (days 1 and 8 of a 21-day cycle). Given the advanced patient's age and previous treatments, eribulin dose was reduced to 88% (2 mg) of the standard dose. The patient received 18 cycles of eribulin (10 months); the treatment was well tolerated, and the unique toxicity reported was alopecia G3.

The tumor marker Ca 15.3 progressively decreased during treatment (January 2017 Ca 15.3 392 U/mL, February 2017 Ca 15.3 317 U/mL, April 2017 Ca 15.3 201 U/mL).

In February 2017, a CT scan documented a partial reduction of the multiple liver metastases and the mediastinum and abdominal adenopathies (Fig. 5); in June 2017, despite an increase in the Ca 15.3 level (248 U/mL), multiple liver metastases decreased further at the CT scan (Fig. 5), and eribulin was continued.

In September 2017, after 18 cycles, a further significant tumor marker increase was detected (Ca 15.3 632 U/mL), concomitantly with a progression of liver metastases. Therefore, eribulin was discontinued, and the patient started chemotherapy with carboplatin AUC2 on days 1, 8, and 15 every 28 days.

Case 6

In 1998, a 55-year-old woman underwent left quadrantectomy and axillary lymphadenectomy (histological examination: IDC stage pT1c pN1 Mo; ER 90%; PgR 70%). In anamnesis, she reported a negative familial history of cancer and sigmoid diverticulum. From April 1998 to August 1998, she received 6 cycles of adjuvant chemotherapy with CMF regimen, followed by radiotherapy and adjuvant endocrine therapy with tamoxifen 20 mg/day (September 1998 to September 2003). In May 2010, during follow-up, a hepatic lesion was detected by ultrasound and confirmed by PET-CT, which also showed several peritoneal lesions. Histological examination of the hepatic lesions indicated IDC G3, ER 60%, PgR 20%, Ki67 10%, c-erbB2 status 1+.

In June 2010, the first-line chemotherapy with FEC regimen plus granulocyte colony-stimulating factor (G-CSF) therapy was started and performed for 6 cycles, achieving a CR on hepatic and omental metastases. In November 2011, the patient started a hormonotherapy with anastrazole, until August 2013, when a CT scan revealed a progression of peritoneal disease. In September 2013, she initiated a second-line chemotherapy with docetaxel 75 mg/m^2 1 every 21 days for 8 cycles plus G-CSF therapy, achieving a PR and reporting peripheral neuropathies G3. In May 2014, the treatment was discontinued, and she started hormone therapy with fulvestrant 500 mg. In April 2015, 2 liver lesions in IV and VIII segments (diameter 4.5 and 3.8 cm, respectively) were detected, together with an increase in size and number of omental lesions (CEA 32 U/mL; Ca 15.3 146 U/mL). The patient showed ECOG PS 1 with loss of appetite, fatigue, weight loss; laboratory examinations were in the normal range. In May 2015, the patient initiated eribulin treatment (1.23 mg/m^2 on days 1 and 8 of a 21-day cycle). This therapy was chosen due to the good tolerance and efficacy previously seen in frail and elderly patients, with minimal toxicities that can be managed with dose modifications. Currently, the patient is in her 34th cycle of eribulin. Her performance status has improved to ECOG grade 0 and the only detectable side effects are fatigue, occasional asthenia and G1 neuropathy in the hands and feet. Her white blood cell count is normal: 4 times was it necessary to delay the dose for neutropenia, and only in the last 3 cycles was it necessary to administer GCS-F. Liver function tests did not change. In January 2017, the CA 15.3 level was 58 U/mL and CEA 6 U/mL; therefore, she underwent a restaging-CT alternating with abdominal ultrasound every 3 months. After the sixth cycle, the CT documented hepatic response >50% and a CR on peritoneal disease; in January 2017, CT showed a stable hepatic disease and persistent peritoneal response.

Case 7

In 1995, a 53-year-old woman underwent right quadrantectomy and axillary lymphadenectomy; the histological examination revealed the presence of a 1.8-cm IDC G3, ER 100%, PgR negative, HER2 negative, Ki67 30%, and 9 out of 16 lymph nodes were positive (TNM pT1cN3). She received sequential adjuvant chemotherapy: 3 cycles of adriamycin (60 mg/m^2 every 3 weeks), followed by 4 cycles of CMF regimen. She was also treated with adjuvant locoregional radiotherapy. From September 1996 until September 2001, she received tamoxifen 20 mg, followed by 5 years of letrozole 2.5 mg until 2006. In January 2011, she experienced disease relapse in the right axillary and laterocervical lymph nodes, with bone metastasis. The axillary biopsy confirmed the same biological features of the primary breast cancer.

The patient was initially treated with anastrozole, achieving a complete clinical and radiological response, and the hormone treatment was continued until September 2013, when she experienced progressive disease in the lymph nodes, bones, and liver (2 lesions of 15 and 22 mm in segments V and VI, respectively). Then, she received treatment with fulvestrant for 1 year, with significant PR (> 50%) in lymph nodes and liver. In September 2014, due to further disease progression in the liver, everolimus plus exemestane therapy was started, with an initial CR until May 2015, when a CT scan showed again progression with high-burden hepatic disease.

A subsequent chemotherapy with weekly paclitaxel was administered for about 6 months with an initial PR followed by liver progression. In November 2015, capecitabine was started for another 6 months, with PR after 4 cycles and progression after 8.

In June 2016, the patient started treatment with eribulin (1.23 mg/m^2 on days 1 and 8 of a 21-day cycle). The treatment is currently ongoing; it is well tolerated without relevant adverse events or need for dose reduction. Subsequent restaging CT scans have shown PR after 3, 6, 9, and 12 cycles (Fig. 6).

Case 8

In 1996, a 54-year-old woman underwent right quadrantectomy for IDC (stage pT1cN2(24/27) M0), followed by chemotherapy with anthracyclines and hormone therapy. In anamnesis, she reported arterial hypertension, thyroid disease, and a positive familial history for mammary carcinoma. In October 2008, a subclavicular lymph node relapse occurred (ER 80%, PgR 25%, MIB1 25%, HER2 ++, FISH amplification). The patient received 3 cycles of CMF chemotherapy, followed by resection of the subclavicular lesion. In March 2009, a CT scan revealed disease progression with further right subclavicular adenopathy. Therefore, the patient started a treatment with a combination of LH-RH analogues, anastrozole and trastuzumab, in association with radiotherapy (50 Gy) in December 2009.

In May 2011, a PET-CT scan detected an adenopathy at high activity (SUV 15) in the right axilla and multiple lesions of lower dimension (SUV 5); the fine-needle biopsy was positive for IDC. In July 2011, the patient underwent surgical intervention to remove all lesions that contained lymph nodes and skin metastasis of IDC (ER 80%, PgR 40%, Ki67 20%, HER2 3+). A therapy with fulvestrant and LH-RH analogues was started. In October 2012, PET-CT indicated disease progression in periclavicular lymph nodes and mammary right lymph nodes. In December 2013, the patient underwent radiosurgery with Cyberknife on subclavicular lymph node metastasis. Then, she was treated with capecitabine and lapatinib for 3 cycles. In March 2014, a PET-CT scan revealed that the subclavicular lesion had disappeared, but a novel lesion in the liver was present in the IV and II segments; mammary lesion was stable. In April 2014, the patient received trastuzumab + vinorelbine until October, when PET-CT scan detected CR in the liver and progression in lymph nodes (I and II intercostal space, SUV 1). Then, she again underwent radiotherapy with Cyberknife on mammary lymph node and continued chemotherapy with trastuzumab and cyclophosphamide until June 2015. In July, a PET scan detected a local relapse in the parasternal and paramedian region, by I intercostal space, and a hepatic lesion in the IV segment; previous adenopathies were still present in the I and II intercostal space. In August 2015, trastuzumab emtansine was initiated for 3 cycles, achieving PR in both the hepatic lesion (SUV 4.3 vs. 11.8) and lymph

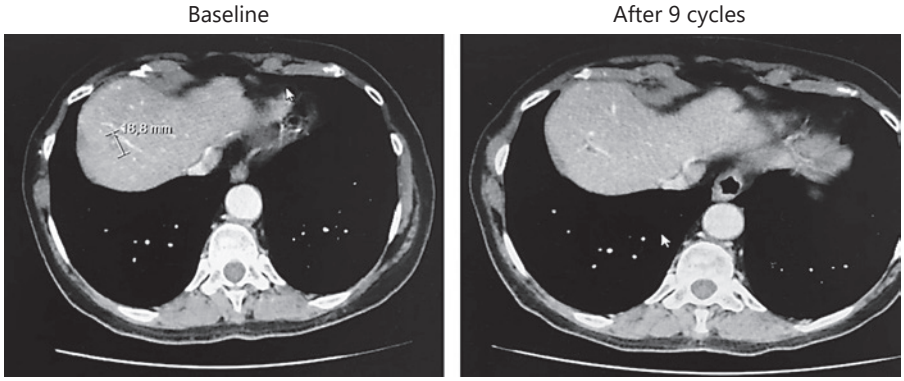

Fig. 6. CT scans at baseline and after 9 cycles of eribulin.

nodes in the mammary region (SUV 4.1 vs. 5.7). The treatment with trastuzumab emtansine continued; as a side effect, increased transaminase G1–2 was noted. In January 2016, PET-CT detected an increase in the hepatic lesion (SUV 9 vs. 4.3) and stable disease in the right axilla and in mammary lymph nodes.

In February 2016, the patient started a treatment with eribulin; after 3 cycles, PET-CT indicated a good metabolic response (CR in the liver, disappearance of lesions in the right axilla, but persistent lesion in the mammary lymph nodes of I intercostal space). In March 2017, the patient underwent 3 treatments with stereotactic radiotherapy with robotic arm on mammary lymph nodes (total dose 24 Gy); the treatment was well tolerated. In June 2017, PET-CT showed a significant reduction of the paramedian lesion (SUV 5.5) and mild captation in the liver (segment VII and VIII). In October 2017, PET-CT detected again stable adenopathies at the paramedian level and a new metabolic activity in the upper pulmonary lobe.

Up to now, the patient has received 25 cycles of eribulin, reporting only asthenia G2 and some episodes of G1 increased transaminase that did not require dose modification.

Discussion

In this series of case reports, a long response to eribulin was obtained in MBC patients with a long history of disease, after failure of previous lines of chemotherapy. Treatment duration ranged from 10 to 23 months, and in 2 patients the therapy is still ongoing at the time of writing this article (Table 1).

Apart from the antimitotic agent eribulin, no other agent has shown a clear advantage in OS in patients with MBC who received chemotherapy with anthracyclines and taxanes, drugs considered as cornerstone of medical therapy in adjuvant and metastatic breast cancer [5]. A pooled analysis of phase III trials shows that eribulin improves clinical outcomes in specific patient subgroups, including women with HER2-negative or triple-negative disease [15].

Eribulin was significantly effective even in reducing liver metastases [11]. In this series, 2 patients benefited from a CR, and 4 patients showed PR. The activity of eribulin on liver metastasis is of crucial clinical importance, because if breast cancer liver metastasis is left untreated, the expected survival time is limited to 4–8 months [16]. A post hoc analysis of the EMBRACE study showed that patients with liver lesions had significantly longer PFS (3.7 vs. 2.0 months) and OS (12.2 vs. 10.1 months), when treated with eribulin rather than TPC; and that among patients with hepatic lesions a clinical response was seen in 31.5% of patients (20 CR and 65 PR out of 270) with eribulin versus 14.6% (5 CR and 16 PR out of 144) with TPC [11]. Women with ER-positive disease and baseline liver metastases appeared to gain a major benefit with eribulin compared with TPC [11].

One patient (case 3) died of hepatic failure: this woman was heavily pretreated and both her ECOG PS and hepatic condition did not allow to use a full dose of eribulin; conversely, in the other cases, dose delay or reduction did not affect the efficacy of treatment. Increased AST (7.7%), ALT (7.6%), GGT (1.7%), hyperbilirubinemia (1.4%) were common adverse events related to eribulin treatment in phase II and phase III trials, but no G4 events had been reported, except for hyperbilirubinemia [10, 15, 17]. In case of hepatic impairment due to liver metastasis, eribulin exposure was increased 1.8-fold with mild impairment and 3-fold with moderate impairment compared to normal liver function; in patients with mild impairment, a dose of 0.97 mg/m^2 resulted in a higher exposure compared to the recommended dose of 1.23 mg/m^2 [18].

Both the disease control of metastatic lesions and the favorable tolerability profile contributed also to guaranteeing a good QoL from the first doses of eribulin. In the setting of MBC, QoL is an objective whose importance is secondary only to OS prolongation; it is a complex parameter, whose

Oncology 2018;94(suppl 1):34–44
DOI: 10.1159/000489067

Table 1. Summary of patient and disease characteristics and treatment outcomes

	Patient							
	1	2	3	4	5	6	7	8
Age, years	67	62	47	70	82	85	76	76
Comorbidities	Hypertension	None	None	Unknown	Acute hepatitis B, chronic bronchitis, hypothyroidism, hypertension, hypercholesterolemia	Sigmoid diverticulum	None	Arterial hypertension, thyroid disease
Disease characteristics								
Age at diagnosis, years	45	46	37	58	60	55	53	54
Site	Right breast	Right breast	Breast	Left breast	Right breast	Left breast	Right breast	Right breast
TNM	pT1 N0	pT2 pN0 M0	pT 2(m) pN1a	pT1cpN1M0	T1N0M0	pT1c pN1 Mo	TNM pT1cN3	pT1cN2(24/27) M0
Grade	G3	G2	G2	G3	G2	–	G3	–
Hormonal status	ER 90%, PgR 90%, HER2 3+	ER negative, PgR negative, HER2 negative	ER 80%, PgR 60%, HER2 negative	ER 90%, PgR 75%, HER2 2+	ER positive, PgR positive, HER2 negative	ER 90%, PgR 70%	ER 100%, PgR negative, HER2 negative	ER 80%, PgR 25%, HER2 2+
Surgery	Lumpectomy	Quadrantectomy	Lumpectomy	Radical mastectomy	Quadrantectomy and axillary lymphadenectomy	Quadrantectomy and axillary lymphadenectomy	Quadrantectomy and axillary lymphadenectomy	Quadrantectomy
Age at metastasis, years	53	54	40	64	76	67	69	59
Sites	Lung, liver	Skin, pleura, liver, nodes, bones	Bone, liver	Lung, liver	Lymph nodes, liver	Liver, peritoneum	Bone, nodes, liver	Nodes, skin, liver
Previous lines								
Number	3	1	2	2	4	2	2	3
Longest PFS	3 months	10 months	6 months	13 months	4 months	22 months	8 months	6 months
Best response	CR	PR	CR	PR	Progression disease	CR	PR	CR
Reason for discontinuation	Progression	Progression	Progression	Progression	Progression	Progression	Progression	Progression
Eribulin								
Number of cycles	18	20	9	21	18	34	Not available	25
Dose intensity, mg/m^2	1.23	1.23	0.97	1.23	1.23	1.23	1.23	1.23
PFS, months	19	13	10	23	11	22	20	21
Liver response	PR	CR	Progression disease	CR	PR	PR	PR	PR
Reason for interruption	Progression	Progression	Death	Progression	Progression	Ongoing	Ongoing	Ongoing

CR, complete response; PR, partial response; PFS, progression-free survival; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

measure relies on definite scales and whose determinants can be deeply subjective [19]. Nevertheless, an effective disease control is the fundamental requirement of a good QoL; in this case series, an extensive regression of metastases in the liver, skin (case 2), and lung (case 4) translated into an evident improvement of patient's QoL, whose daily activities and life satisfaction were ameliorated. Pain control is another important aspect of QoL: in case 1, eribulin treatment reduced both pain (VAS 7–0) and the use of opioid drugs. The performance status even improved during eribulin treatment, thus contributing to adherence to therapy and extending time to progression.

To be acceptable, drug-related toxicities must be tolerable, not interfere with daily living and be coherent with patient's expectation of QoL. In the EMBRACE study, overall toxicity rates were similar between eribulin and TPC, and the majority were G1/2. Grade 3/4 adverse events occurred more frequently with eribulin than with TPC, and the most common were neutropenia (45 vs. 21%), leukopenia (14 vs. 6%), and peripheral neuropathy (9 vs. 2%) [10]. These side effects were also reported in the patients of this series, without compromising, however, the adherence to therapy that was discontinued only for disease progression.

Eribulin confirmed to be a well-tolerated therapy, even in elderly patients. Indeed, in 4 reports, women were older than 65 years when eribulin was started, and 1 of them was 80 years old. An analysis of clinical trial data reported by Muss et al. [20] highlighted the possible use of eribulin in older patients. This study included data collected from 2 phase II studies as well as the phase III EMBRACE study. Toxicity and efficacy data were compared between groups of patients stratified by age. The analysis showed no significant difference in outcome or in toxicity rates based on patient age, thus validating eribulin as an option in patients aged over 70 years [20]. In the real-world setting, eribulin confirmed to be effective and safe in elderly patients as well as in the younger population, the most frequent adverse events being neutropenia, fatigue, and peripheral neuropathy [21].

Another relevant aspect of these case reports is the possibility to obtain disease control also in HER2-positive disease, unresponsive to hormonal agents; this underlines the importance of selecting which patients are suitable for chemotherapy also on the basis of their previous response to the recommended hormonal treatments [22]. The patient described in case 2 obtained a long-lasting disease control with her first-line taxane treatment and a satisfying debulking and PFS with eribulin, thus enforcing the hypothesis that patients who had a disease control with early chemotherapy lines might have higher probability to respond to eribulin therapy in the advanced setting [23]. As previously reported, liver response is still ongoing, after more than 1 year from the end of eribulin treatment, and the patient was able to receive 2 additional chemotherapy lines without worsening of toxic effects.

Conclusion

In the reported cases, eribulin demonstrated good activity and tolerability in pre-treated patients with multiple metastases. A careful agent sequencing – considering expected response, side effects, tumor and patient characteristics and preferences – could help clinicians to successfully tailor the appropriate treatment also beyond earlier lines. Eribulin treatment can lead to an effective disease control and, in some cases, an important debulking in the presence of liver metastases; moreover, it is confirmed as a suitable therapeutic option for elderly patients.

Acknowledgements

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. We thank Elisa Sala, PhD, professional medical writer, for her medical editorial assistance with our report.

Disclosure Statement

The authors declare that they have no conflicts of interest.

Appendix

Members of the Italian Eribulin Working Group

A. Febbraro, *A. Spagnuolo*, *I. Spagnoletti* – Medical Oncology Unit, "Sacro Cuore di Gesù Fatebenefratelli" Hospital, Benevento, Italy; *E. Quaquarini*, *F. Sottotetti*, *R. Palumbo*, *M. Frascaroli*, *B. Tagliaferri*, *G. Massa*, *A. Bernardo* – Operative Unit of Medical Oncology, ICS Maugeri-IRCCS, Pavia, Italy; *A. Turletti* – ASL Città di Torino, Ospedale Martini, Turin, Italy; *G. Giordano, P. Colina, G. Antonelli* – Medical Oncology, San Filippo Neri Hospital, ASL Roma 1, Rome, Italy, and Oncology Division, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; *R. Pedersini*, *L. Vassalli*, *M. Claps*, *V. Amoroso*, *S. Grisanti*, *E. Roca*, *A. Berruti*, *E.L. Simoncini* – Spedali Civili Hospital, Brescia, Italy; *M. Raffaele* – UOSD Oncologia Presidio Cassia, Sant'Andrea-Dipartimento Oncologico, ASL Roma 1, Rome, Italy; *F. Villa, A. Crippa, A. Ardizzoia* – S.C. Oncologia Medica, Dipartimento Oncologico Aziendale, ASST Lecco, Lecco, Italy; *F. Ferraù* – Oncologia medica dell'Ospedale S. Vicenzo di Taormina, Taormina, Italy; Mario D'Andrea – Medical Oncology, San Filippo Neri Hospital, ASL Roma 1, Rome, Italy.

References

1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, Forman D, Bray F: Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–1403.

2 Pal SK, Dehaven M, Nelson RA, Onami S, Hsu J, Waliany S, Kruper L, Mortimer J: Impact of modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer. BMC Cancer 2012;12:435.

3 Jones SE: Considerations in treatment choice for metastatic breast cancer. Breast Cancer 2008;15:35–39.

4 Bonotto M, Gerratana L, Poletto E, Driol P, Giangreco M, Russo S, Minisini AM, Andreetta C, Mansutti M, Pisa FE, Fasola G, Puglisi F: Measures of outcome in metastatic breast cancer: insights from a real-world scenario. Oncologist 2014;19:608–615.

5 Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Penault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L, Winer E: ESO-ESMO 3nd international consensus guidelines for advanced breast cancer (ABC3). Ann Oncol 2017;28:16–33.

6 Doherty MK, Morris PG: Eribulin for the treatment of metastatic breast cancer: an update on its safety and efficacy. Int J Womens Health 2015;7:47–58.

7 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.

8 Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C, Littlefield BA, Wilson L: The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005;4:1086–1095.

9 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.

10 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: Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a Phase III open-label randomised study. Lancet 2011;377:914–923.

11 O'Shaughnessy J, Cortes J, Twelves C, McCutcheon S, He Y, Olivo M, Wanders J, Goldstein L, Barrios C: Efficacy of eribulin versus treatment of physician's choice for metastatic breast cancer based on localization of specific secondary metastasis (poster). 31st Annu Miami Breast Cancer Conf, March 2014.

12 Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, Abbruzzese JP: Metastatic patterns in adenocarcinoma. Cancer 2006;106:1624–1633.

13 Diamond JR, Finlayson CA, Borges VF: Hepatic complications of breast cancer. Lancet Oncol 2009;10:615–621.

14 National Cancer Institute Common Terminology Criteria for Adverse Events. Bethesda, National Cancer Institute, 2016. http://ctep.cancer.gov/reporting/ctc.html.

15 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;148:553–5561.

16 Adam R, Aloia T, Krissat J, Bralet MP, Paule B, Giacchetti S, Delvart V, Azoulay D, Bismuth H, Castaing D: Is liver resection justified for patients with hepatic metastases from breast cancer? Ann Surg 2006;244:897–907.

17 Kaufman P, Awada A, Twelves C,Yelle L, Perez E, Velikova G, Olivo MS, He Y, Dutcu 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.

18 Devriese LA, Witteveen PO, Marchetti S, Mergui-Roelvink M, Reyderman L, Wanders J, Jenner A, Edwards G, Beijnen JH, Voest EE, Schellens JH: Pharmacokinetics of eribulin mesylate in patients with solid tumors and hepatic impairment. Cancer Chemother Pharmacol 2012;70:823–832.

19 Wood R, Mitra D, De Courcy J, Iyer S: Patient-reported quality of life and treatment satisfaction in patients with HR+/HER2– advanced/metastatic breast cancer. Clin Ther 2017;39:1719–1728.

20 Muss H, Cortes J, Vahdat L, Cardoso F, Twelves C, Wanders J, Dutcus CE, Yang J, Seegobin S, O'Shaughnessy J: Eribulin monotherapy in patients aged 70 years and older With metastatic breast cancer. Oncologist 2014;19:318–327.

21 de Nonneville A, Sabatier R, Gonçalves A, Extra JM, Tarpin C, Launay S, Tassy L, Viens P, Rousseau F: Safety and efficacy of eribulin for "real-world" older patients with metastatic breast cancer. J Geriatr Oncol 2018;9:281–283.

22 Palumbo R, Sottotetti F, Riccardi A, Teragni C, Pozzi E, Quaquarini E, Tagliaferri B, Bernardo A: Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians. Ther Adv Med Oncol 2013;5:334–350.

23 Quaquarini E, Sottotetti F, D'Ambrosio D, Malovini A, Morganti S, Marinello A, Pavesi L, Frascaroli M: Eribulin across multiple lines of chemotherapy: a retrospective study on quality of life and efficacy in metastatic breast cancer patients. Future Oncol 2017;13:11–23.