Utidelone combined with anti-angiogenic therapy for the treatment of anthracycline/taxane-treated and endocrine-resistant HR$^+$/HER2$^-$ refractory breast cancer with brain metastases: A case report

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Received April 25, 2024; Accepted September 13, 2024

DOI: 10.3892/ol.2024.14771

Abstract. For patients with hormone receptor-positive (HR$^+$) and human epidermal growth factor receptor 2-negative (HER2$^-$) metastatic breast cancer (mBC), the treatment choices become more complex after progression on first-line CDK4/6 inhibitors combined with endocrine therapy. Currently, there are no guidelines that provide a unified standard protocol for this situation. Almost half of patients with mBC develop brain metastases (BMs), and once BMs occur, the survival of the patient is often significantly reduced. An anti-angiogenic drug and chemotherapy combination of has demonstrated synergistic effects in an mBC cell line. Anti-angiogenic drugs have shown therapeutic efficacy in the treatment of mBC, and utidelone has shown the ability to cross the blood-brain barrier and achieve a high concentration in brain tissue in preclinical studies. The present case report describes a patient with HR$^+$/HER2$^-$ mBC and BMs that developed resistance to two CDK4/6 inhibitors and treatments with anthracyclines/taxanes. The patient received a fourth-line treatment regimen combining utidelone with a small-molecule anti-angiogenic drug, namely apatinib or anlotinib. The patient achieved a partial response with this combined regimen, and a progression-free survival (PFS) of 7.6 months, which was the best therapeutic outcome in the entire course of the illness. This result was superior to the second-line treatment with nab-paclitaxel, which resulted in a PFS of 8 months and best overall response of stable disease with slight shrinkage. The present case indicates that a combination of utidelone with apatinib/anlotinib exhibited antitumor activity in a patient with HR$^+$/HER2$^-$ mBC with BMs. Therefore, this combination offers a promising therapeutic option for the clinical treatment of patients with breast cancer and BMs.

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Key words: refractory metastatic breast cancer, brain metastases, utidelone, small molecule anti-angiogenic drugs

Introduction

Breast cancer is the most common malignant tumor in women. Female breast cancer surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases (1). Although advancements in diagnostic and therapeutic methods have significantly improved the prognosis of breast cancer, the prognosis for patients with metastatic breast cancer (mBC) remains poor, with a 5-year survival rate of only ~30% (1,2). Therefore, extending the survival period for patients with advanced-stage breast cancer remains a major challenge in the field.

In patients with hormone receptor-positive (HR$^+$) and human epidermal growth factor receptor 2-negative (HER2$^-$) mBC, CDK4/6 inhibitors combined with endocrine therapy (ET) are the main treatment approach. However, at present, there are no standardized guidelines for the treatment of patients following progression on first-line CDK4/6 inhibitors combined with ET. According to a meta-analysis of 8 studies, including the MONALEESA-2/7, MONARCH-3 and PALOMA-1/2 clinical trials, ~65% of patients receive ET-based treatments, 44% of patients undergo chemotherapy, and 38% of patients continue to receive CDK4/6 inhibitors (3). There are various treatment approaches after the use of CDK4/6 inhibitors, but it remains unclear whether these significantly impact patient prognosis (3).

Among patients who receive first-line CDK4/6 inhibitor treatment, ~20% experience rapid progression, and the prognosis for these patients is generally poor (4). Therefore,

it is necessary to focus increased attention on the search for new treatment strategies for patients with rapid progression. Chemotherapy, as a foundational treatment method for mBC, has seen few new drug developments in the past decade. This may imply that further innovation and research are necessary to discover more effective therapeutic drugs and treatment approaches for the treatment of mBC.

Utidelone is one of a new generation of epothilone-class microtubule inhibitors. It was independently developed in China, and is the only microtubule inhibitor with a novel molecular structure approved globally in the past decade. Notably, it serves as a breakthrough in China, which has not seen the introduction of any novel chemotherapy drugs other than paclitaxel for nearly 30 years, and serves as a new treatment option for patients with mBC (5,6).

In mBC, depending on the molecular subtype, up to 49% of patients may develop brain metastases (BMs), and the occurrence of BMs significantly shortens the survival duration of the patient (7). In a retrospective study of 4,118 patients from the French Epidemiological Strategy and Medical Economics research program who were diagnosed with breast cancer brain metastasis (BCBM) (7), the median overall survival (OS) time was 7.1 months for $HR^+/HER2^-$ cases. In this study, the poorer prognosis observed for $HR^+/HER2^-$ disease compared with $HR^+/HER2^+$ and $HR^-/HER2^+$ disease may be attributed to the development of BMs typically being a late event as metastatic disease progression persists and tumors are almost resistant to ET and chemotherapy (8). There is a clear requirement for an effective clinical treatment for $HR^+/HER2^-$ BCBM. BMs derived from breast cancer are characterized by highly vascular and morphologically malformed vessels. Anti-angiogenesis therapy has the potential to normalize the blood vessels within tumors, thereby facilitating the delivery of antitumor drugs. Consequently, when combined with chemotherapy, it may be able to reverse multidrug resistance (9,10). Previous research has shown that a combination of an anti-angiogenic drug and chemotherapy has synergistic effects in an mBC cell line (11). Anti-angiogenic drugs include both large-molecule biologics and small molecules. The latter category includes apatinib and anlotinib. Apatinib is a highly selective and potent VEGFR tyrosine kinase inhibitor (TKI) with high affinity for VEGFR2. Its low molecular weight facilitates its ability to cross the blood-brain barrier (BBB), potentially offering superior efficacy for BMs compared with other drugs (12). Anlotinib is a small-molecule, multi-targeted TKI that was developed in China and effectively inhibits VEGFR1-3, platelet-derived growth factor receptor-α/β, fibroblast growth factor receptors 1-4, c-Kit, and other targets. It has the ability to inhibit tumor angiogenesis, growth and migration. Anlotinib has also been suggested to be able to cross the BBB, and therefore, to have potential in combating BMs (13).

In a preclinical study of utidelone, it was found using animal models that utidelone has a higher concentration in various tissues than in plasma, and can easily pass through the BBB, maintaining a high concentration in brain tissue (Li *et al*, unpublished data). However, studies on the use of utidelone in BCBMs are lacking. In the present case report, a patient with HR^+ breast cancer that was refractory to CDK4/6 inhibitors combined with ET and progressed after anthracycline/taxane chemotherapy, including the formation of BMs, is described. The patient was treated with utidelone in combination with apatinib/anlotinib, and good therapeutic efficacy was achieved.

Case report

In August 2015, a 37-year-old Chinese female underwent segmental mastectomy of the left breast and sentinel lymph node biopsy of the left axilla at Sun Yat-sen University Cancer Hospital (Guangzhou, China). Postoperative pathology revealed invasive ductal carcinoma of the left breast, grade II, with immunohistochemistry results as follows: Estrogen receptor (ER; 90%$^+$), progesterone receptor (PR; 100%$^+$), HER2 (0) and Ki67 (15%$^+$) (data not shown). The patient received four cycles of adjuvant anthracycline and cyclophosphamide chemotherapy, followed by 32 sessions of radiotherapy and 5 years of tamoxifen as ET. Regular follow-ups were performed, and no signs of metastasis were detected.

In October 2020, a positron emission tomography (PET)/computed tomography (CT) scan indicated the presence of a mass next to the left internal thoracic artery, as well as multiple bone metastases. On October 27, 2020, a biopsy of the mass confirmed it comprised breast cancer tissue. Immunohistochemistry results were as follows: ER (~70%$^+$), PR (<1%$^+$), HER2 (0) and Ki67 (~70%$^+$) (data not shown). The disease-free survival time was 62 months.

From October 2020 to December 2020, the patient received first-line treatment with palbociclib, fulvestrant and goserelin, along with incadronate disodium to protect against bone destruction. Two months later, a CT scan showed enlargement of the mass on the left side of the internal thoracic artery. The efficacy evaluation was progressive disease (PD), with a progression-free survival 1 (PFS1) of 2 months.

In December 2020, the patient received one cycle of second-line chemotherapy with carboplatin and nab-paclitaxel at Fudan University Cancer Hospital (Shanghai, China), which alleviated the pain symptoms. On January 30, 2021, the patient first visited the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Shenzhen, China; henceforth referred to as our hospital), and continued the chemotherapy regimen for one more cycle. A subsequent CT scan showed stable disease (SD), but due to serious side effects and grade III transaminase elevation, carboplatin was discontinued. From February 25, 2021 to May 13, 2021, the patient received four cycles of single-agent nab-paclitaxel chemotherapy, achieving the best overall response of SD.

From May 2021 to September 2021, the treatment was switched to vinorelbine tartrate soft capsules (initially 60 mg/m^2, then 80 mg/m^2) on days 1 and 8, every 3 weeks for four cycles, while ET with goserelin and fulvestrant was continued, and denosumab was regularly administered. On August 24, 2021, a magnetic resonance imaging (MRI) scan suggested liver metastasis. On August 27, 2021, a PET/CT scan at our hospital confirmed liver metastasis and multiple bone metastases. The PFS2 was 8 months.

In September 2021, the patient underwent liver biopsy and ablation of the liver metastasis at The First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). Postoperative pathology showed the infiltrative growth of nest-like atypical

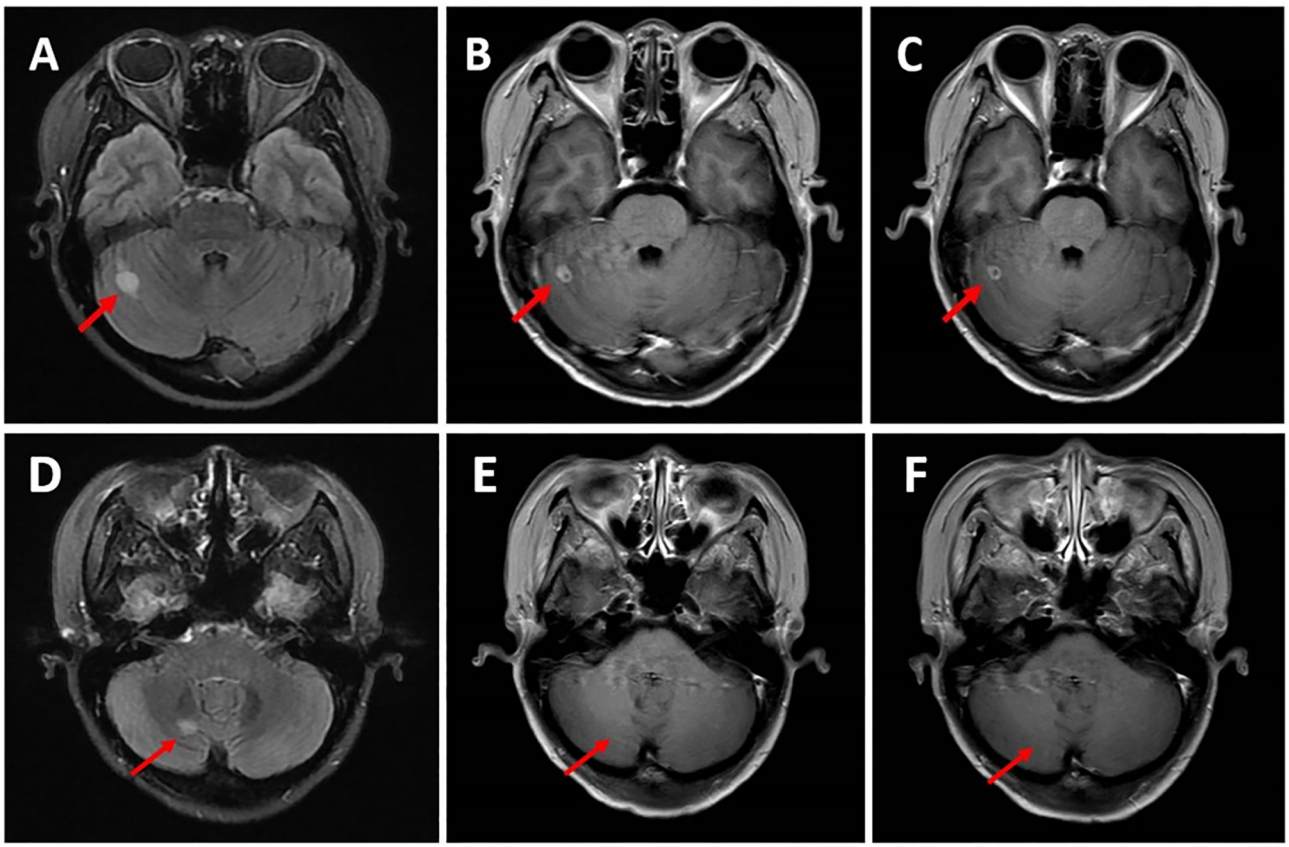

Figure 1. Brain MRI showing the patient response after treatment with utidelone combined with anlotinib. MRI scans (A,D) at baseline, (B,E) after two cycles of treatment and (C,F) after four cycles of treatment. Metastatic size reduction was as follows: (A) 11.5 mm, (B) 6.2 mm and (C) 4.5 mm; (D) 10.0 mm, (E) 0 mm and (F) 0 mm. The red arrows indicate the metastases. MRI, magnetic resonance imaging.

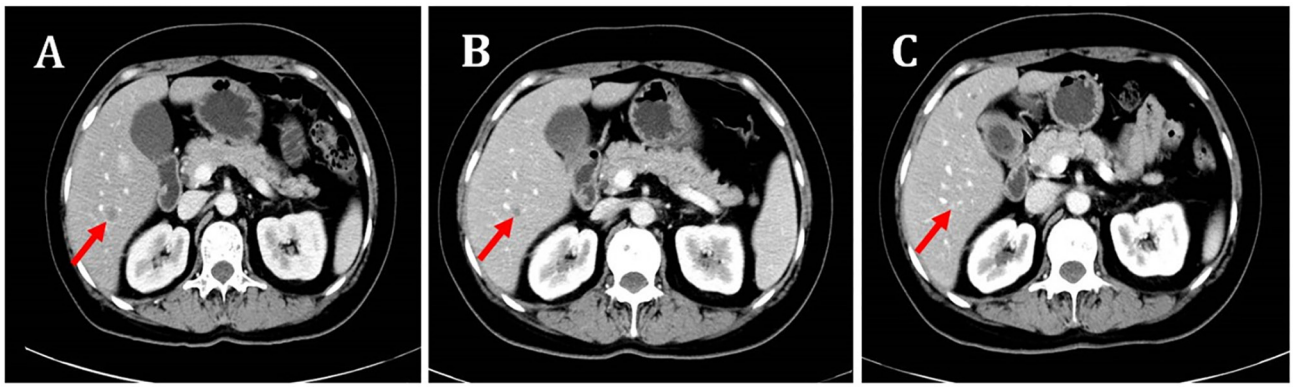

Figure 2. Liver CT results showing the patient response after treatment with utidelone combined with anlotinib: CT scans (A) at baseline, (B) after two cycles of treatment and (C) after four cycles of treatment. Metastatic size reduction was as follows: (A) 12 mm, (B) 8 mm and (C) 4 mm. The red arrows indicate the metastasis. CT, computed tomography.

cells, consistent with mBC in the liver, with the following immunohistochemistry results: ER (~50%+), PR (-), HER2 (0), CK19 (+) and GATA-3 (+).

In September 2021, third-line treatment was initiated with abemaciclib 150 mg twice daily, along with fulvestrant 0.5 g and goserelin 3.6 mg by subcutaneous injection every 28 days. On November 3, 2021, the patient returned to our hospital for a check-up, and a brain MRI scan indicated brain metastasis and new liver metastasis. The PFS3 was 1.4 months. On November 20, 2021, genetic testing revealed mutations in phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit a, paired box 5, SUFU negative regulator of hedgehog signaling, and tumor protein p53. Specifically, circulating tumor DNA (ctDNA) samples were analyzed using the OncoD-C1021B next-generation sequencing (NGS) platform (Beijing Geneplus Technology Co., Ltd.). A 10-ml sample of whole blood was drawn into a standard stabilizing tube (Streck LLC) and centrifuged within 72 h to separate the plasma from peripheral blood cells. ctDNA extraction (QIAseq cfDNA All-in-One Kit; cat. no. 180043; Qiagen GmbH) was performed in a College of

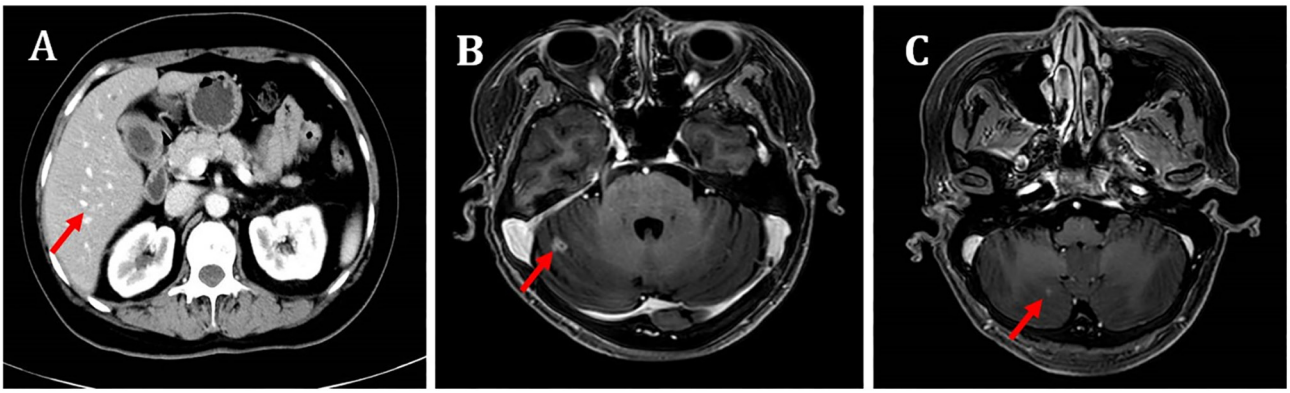

Figure 3. CT and MRI scans showing controlled liver lesions but progressive intracranial lesions. (A) CT scan showing a 5-mm liver lesion (persistent partial response). MRI scans of (B) 9-mm and (C) 2-mm brain lesions. CT, computed tomography; MRI, magnetic resonance imaging.

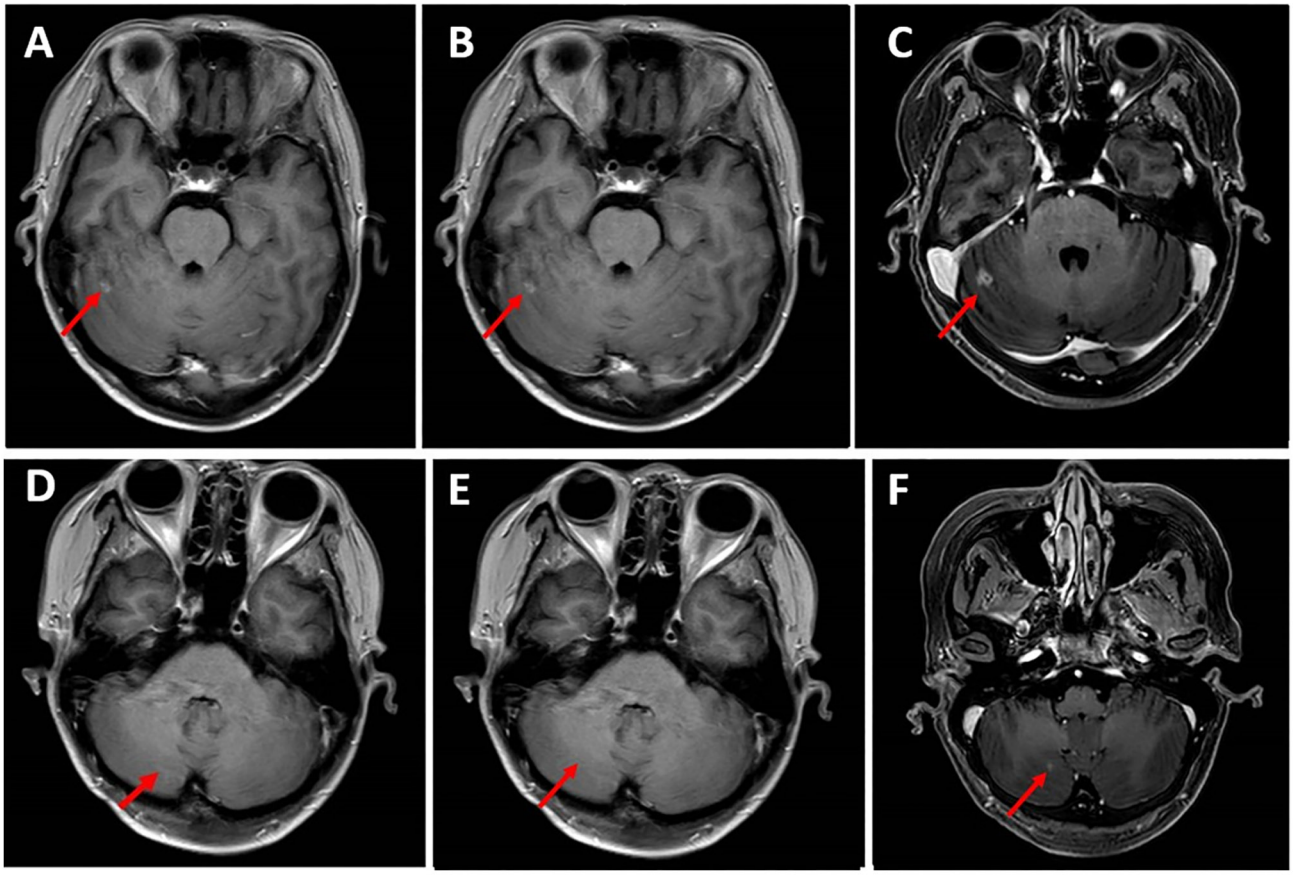

Figure 4. Brain MRI of the patient when the treatment was adjusted to eribulin combined with small-molecule anti-angiogenic therapy. Brain MRI demonstrates a sustained partial response in the largest lesion after treatment with utidelone and small-molecule anti-angiogenic therapy, followed by adjustment to eribulin combined with small-molecule anti-angiogenic therapy. (A and D) Baseline MRI and (B and E) efficacy evaluation showing a partial response after two cycles of treatment and (C and F) disease progression after four cycles of treatment. Metastatic size increased as follows: (A) 4.5 mm, (B) 5 mm and (C) 9.0 mm; (D) 0 mm, (E) 0 mm and (F) 2 mm. MRI, magnetic resonance imaging.

American Pathologists-accredited clinical laboratory, according to the manufacturer's instructions. The DNA concentration was measured using a Qubit™ fluorometer and Qubit dsDNA HS Assay Kit (Invitrogen; Thermo Fisher Scientific, Inc.). Sequencing libraries were prepared from the ctDNA using KAPA DNA Library Preparation Kits (Kapa Biosystems; Roche Diagnostics). NGS was performed using a 1,021 gene panel mutation detection kit (Beijing Geneplus Technology Co., Ltd.) for somatic single nucleotide variants, insertions/deletions, structural variations and copy number variations. The Integrative Genomics Viewer tool (14) was used to verify the candidate variants. Due to the clinical unavailability of PI3K inhibitors, the patient consulted with neurosurgery and radiation oncology specialists, but refused brain radiotherapy and surgery.

A fourth-line chemotherapy regimen with utidelone combined with anti-angiogenic drug therapy was then

Table I. Treatments received by the patient after recurrence and metastasis.

Lines of therapy	Treatment dates	Therapy	Best therapeutic evaluation, extracranial lesions/ intracranial lesions	PFS or duration of therapy[a], months
First	October 2020-December 2020	Palbociclib + fulvestrant	PD/NA	PFS1, 2.8
Second	December 2020-August 2021	Carboplatin + nab-paclitaxel, 2 cycles; nab-paclitaxel, 4 cycles; vinorelbine, 4 cycles	SD/NA	PFS2, 8
Third	September 2021-November 2021	Abemaciclib + fulvestran	PD/PD	PFS3, 1.4
Fourth	November 2021-March 2022	Utidelone + apatinib, 1 cycle; utidelone + anlotinib, 3 cycles	PR/PR	PFS4, 3.7
Fifth	March 2022-July 2022	Eribulin + apatinib, 2 cycles; eribulin + anlotinib, 2 cycles	PR/PR	PFS5, 3.9
Sixth	July 2022-August 2022	Darolutamide + apatinib + exemestane	PD/PD	PFS6, 1.6
Seventh	September 2022-October 2022	Seribantam + anlotinib + exemestane	PD/PD	PFS7, 2.1
Eighth	November 2022	Seribantam + bevacizumab + exemestane	PD/PD	PFS8, 0.3

[a]Utidelone and apatinib/anlotinib can cross the BBB, while eribulin has limited ability to do so. The continued use of antiangiogenic drugs that can cross the BBB after switching from utidelone to eribulin remains effective, leading to a sustained PR. Consequently, the PFS time for the continuous PR of brain lesions during the fourth and fifth lines of therapy is calculated as 3.7 plus 3.9 months, totaling 7.6 months. However, as the disease progresses, the efficacy of what is essentially monotherapy of the brain lesions with antiangiogenic drugs is not long-lasting. PFS, progression-free survival; PFSn, PFS for the nth line of therapy; PD, progressive disease; NA, not applicable; SD, stable disease; PR, partial response; BBB, blood-brain barrier.

established, starting in November 2021. The patient received utidelone 50 mg intravenously on days 1-5 and apatinib 0.25 g orally daily from day 1 to 21 every 21 days for one cycle. The patient experienced grade I peripheral neurotoxicity, grade I hypertension, grade I hyperbilirubinemia and elevated transaminases, which were considered to be associated with apatinib. In the second cycle, which started in December 2021, apatinib was replaced with anlotinib. The patient received utidelone 50 mg intravenously on days 1-5 and anlotinib 8 mg orally daily from day 1 to 21 every 21 days for one cycle, and experienced grade II muscle soreness and numbness of the hands and feet. After two cycles, the efficacy evaluation indicated a partial response to the treatment. Due to muscle soreness, the dose of utidelone was reduced, and the treatment was continued. From January 2022 to February 2022, chemotherapy with the utidelone plus anlotinib regimen was continued, with utidelone 40 mg intravenously on days 1-5 and anlotinib 8 mg orally daily from day 1 to 21 every 21 days for two cycles. After four cycles, the efficacy evaluation indicated that the partial response was maintained (Figs. 1 and 2). However, the patient also had grade II limb soreness, numbness of the hands and feet, abnormal sensations in a 'glove and sock' distribution, and fatigue. The patient, who had a high demand for quality of life and poor compliance, requested adjustment of the medication. The duration of therapy was 3.7 months.

The fifth-line chemotherapy regimen comprising apatinib and eribulin was administered from March 2022 to April 2022. Eribulin 2 mg was dosed intravenously on days 1 and 8, and apatinib 0.25 g was given orally once daily from day 1 to 21 every 21 days for two cycles. The partial response was maintained following this treatment. In April 2022, due to nausea and vomiting, apatinib was switched to oral anlotinib. On May 7, 2022, chemotherapy with the anlotinib and eribulin regimen was initiated, comprising eribulin 2 mg intravenously on days 1 and 8, and anlotinib 8 mg orally daily from day 1 to 21 every 21 days for two cycles. In July 2022, CT and MRI scans showed controlled extracranial lesions but progressive intracranial lesions (Figs. 3 and 4). The PFS5 was 3.9 months.

The sixth-line treatment plan was adjusted to a combination of darolutamide, apatinib and exemestane. In August 2022, a follow-up scan suggested progression of the intracranial lesions, with a PFS6 of 1.6 months.

The seventh-line treatment was a combination of seribantam, anlotinib and exemestane. From September 2022 to October 2022, the patient received whole-brain palliative radiotherapy and local boost radiotherapy at our hospital. The PFS7 was 2.1 months. In November 2022, the patient visited Luohu District People's Hospital (Shenzhen, China) due to pain in the lower limbs and waist, and an eighth-line treatment with seribantam, bevacizumab and exemestane was started,

but the pain did not markedly improve. In November 2022, a follow-up at our hospital revealed multiple nodules in the liver, which were larger and more numerous than before, with an elevated metabolism, suggesting liver metastasis. The PFS8 was 0.3 months.

Subsequently, the patient was admitted to hospice care at Cihai Hospital (Shenzhen, China) and ultimately succumbed to the disease in April 2023. The entire treatment process is depicted in Table I.

Discussion

Currently, the treatment options for BCBM encompass local therapies and/or systemic treatments. Local therapies include surgery, stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT), while systemic therapies comprise chemotherapy and targeted therapies (15). Although surgery has been demonstrated to improve the OS of patients with BCBM, it is typically reserved for those with pronounced symptoms, who are in good general condition and have limited BMs (16,17). The majority of patients with BCBM receive radiotherapy, with patients having a good performance status and localized BMs undergoing SRS, and those with a poorer performance or extensive BMs typically receiving WBRT. However, surgery and radiotherapy can cause serious physical harm to patients. In addition, after local palliative surgery or radiotherapy of the brain, systemic treatment remains necessary (18). Therefore, effective systemic therapy may enable patients with BCBM to avoid the trauma of surgery and the neurotoxicity associated with radiotherapy during advanced treatment.

The role of ET in the treatment of BMs from HR^+ breast cancer is currently supported by limited research and literature. Despite ET being one of the primary treatment modalities for HR^+ breast cancer, further clinical data and studies are required to confirm its application and efficacy in the context of BM. In terms of systemic treatment, the BBB limits the penetration of numerous chemotherapeutic agents, which has limited research into chemotherapy for BCBM (19). Small-molecule anti-angiogenic drugs, such as apatinib and anlotinib, have shown some efficacy in the systemic treatment of triple negative breast cancer with BMs (9,20-24). However, the treatment of patients with HR^+ advanced BCBM remains a considerable clinical challenge. In the present case, the patient had a mass adjacent to the left side of the internal thoracic artery, suspected of being a metastasis, with multiple bone metastases. First-line treatment with the CDK4/6 inhibitor palbociclib combined with fulvestrant resulted in rapid disease progression, with a PFS1 of 2 months. Continued ET provided limited benefit, leading to chemotherapy being considered. Second-line chemotherapy with nab-paclitaxel was administered for six cycles, which achieved SD, followed by oral vinorelbine soft capsule maintenance therapy for four cycles. Following this, liver metastases were detected, with a PFS2 of 8 months. Third-line treatment involved another CDK4/6 inhibitor, abemaciclib, for 'cross-line' use, combined with fulvestrant therapy. Unfortunately, the patient developed new BMs, with a PFS3 of 1.4 months. Due to refusal of brain palliative radiotherapy and surgery by the patient, the selection of drugs that can control BMs by crossing the BBB was crucial. Previous studies have shown that utidelone, apatinib and anlotinib are all able to cross the BBB and may be of benefit in the treatment of intracranial tumors (9,10,12,13).

Utidelone is a recently launched drug of the epothilone class that not only possesses the antitumor effects of traditional microtubule inhibitors but also has a unique mechanism of action that avoids cross-resistance with traditional microtubule inhibitors. The mechanism of paclitaxel resistance has been demonstrated to include the overexpression of P-glycoprotein (P-gp) and changes in microtubule β and α subunits (5). Although the mechanism of action of utidelone is similar to that of paclitaxel, its binding site differs and it does not bind to P-gp on the surface of tumor cells; thus, it effectively evades paclitaxel resistance mechanisms (6).

In the present case, a patient with refractory HR^+ BCBMs was treated with utidelone combined with a small-molecule anti-angiogenic drug, namely apatinib/anlotinib, achieving a PR after two cycles and sustained response after four cycles of treatment. A brain MRI scan showed a marked reduction in the BMs, likely due to the concerted antitumor effect of utidelone and small-molecule anti-angiogenic drugs crossing the BBB. During treatment, the patient experienced grade II limb soreness, hand-foot syndrome and paresthesias, accompanied by fatigue. Due to the patient demanding to maintain a high quality of life and having poor compliance, medication adjustment was requested. Therefore, the treatment was adjusted to eribulin combined with a small-molecule anti-angiogenic drug. After two cycles, the PR was sustained, but after four cycles, the disease progressed, with a therapeutic evaluation of PD. According to preclinical research, eribulin has limited ability to cross the BBB (25). Therefore, it may be inferred that the PR was achieved through the effects of the utidelone and small-molecule anti-angiogenic drug therapy. The continued PR after switching to eribulin and small-molecule anti-angiogenic therapy may have been due to the continued antitumor effect of the anti-angiogenic drug crossing the BBB, although only a single drug reaching the brain is likely to have been less potent than the combined therapy. A previous study indicated that tumor invasiveness may increase in patients who fail CDK4/6 inhibitor therapy, making them more likely to develop resistance to subsequent treatments, ultimately leading to disease progression (26).

Data from the phase III clinical trial of utidelone (registered at ClinicalTrials.gov as trial no. NCT02253459) showed that in comparison with patients treated with capecitabine alone, patients treated with utidelone plus capecitabine had a significant extension in PFS from 4.11 to 8.57 months (27). In this trial, 87% of the 251 HR^+ patients had previously received ET. In the present case report, the PFS of the patient with the fourth-line treatment was 3.7 months, which was lower than the PFS of 8.57 months in the clinical trial. This was mainly because the patient could not tolerate neurotoxicity and stopped taking the drug. The efficacy evaluation was PR. Although combinations of utidelone with anti-angiogenic agents have shown promising efficacy, particularly in patients with BMs, their neurotoxicity should not be ignored. A combination of utidelone and capecitabine was not selected for treatment of the present case due to the lack of imported

capecitabine, and the obvious adverse reactions observed clinically for domestically produced capecitabine, including hand-foot syndrome, abnormal aminotransferase and gastrointestinal reactions. The present case had liver metastasis and mild abnormal aminotransferase. Considering the treatment tolerance and compliance of the patient, combination therapy with apatinib was selected. As both apatinib and utidelone can be neurotoxic, in order to minimize peripheral neurotoxicity, low-dose apatinib was selected for use in the combination therapy. Whether the combination of utidelone with capecitabine or apatinib has greater efficacy and lower toxic side effects requires investigation in future clinical studies.

The most common adverse reactions of utidelone are peripheral neuropathy, hand-foot syndrome, hematological toxicity and gastrointestinal toxicity, with peripheral neuropathy being the primary adverse reaction. The hematological and gastrointestinal toxicities of utidelone are lower than those of other chemotherapy drugs (5,27). Clinical research and practice have demonstrated that utidelone has good safety, with the longest reported use being 34 cycles, which exceeds the use-cycle limitations of traditional chemotherapeutic agents and promotes patient adherence to the medication, thus providing long-term sustained benefits (5). The present patient discontinued utidelone due to peripheral neurotoxicity, primarily because during the year prior to the use of utidelone they had received six cycles of nab-paclitaxel chemotherapy, which also has significant peripheral neurotoxicity, and secondly, because efforts to prevent and manage peripheral neurotoxicity in this patient were inadequate. Strengthening this management in the future will allow patients to benefit from the efficacy of utidelone while also ensuring their quality of life.

As a new-generation microtubule inhibitor, utidelone has been shown in a previous study to evade paclitaxel resistance mechanisms and have the characteristics of high efficacy and low toxicity (5). This makes it a particularly suitable treatment for patients with mBC who have received paclitaxel therapy. To the best of our knowledge, there have been no previous case reports on utidelone combined with small-molecule anti-angiogenic drug therapy in patients with HR^+ BCBM, particularly those with refractory advanced BCBM after two lines of CDK4/6 inhibitors combined with ET and anthracycline/paclitaxel therapy.

In summary, the present case report describes the use of utidelone combined with small-molecule anti-angiogenic drugs to treat a patient with HR^+ advanced BCBMs who was refractory to CDK4/6 inhibitors and progressed after anthracycline/paclitaxel therapy. The effects observed in this patient demonstrate the efficacy of utidelone, even after progression on prior paclitaxel therapy. The present case illustrates the potential of utidelone combined with small-molecule anti-angiogenic drugs in the treatment of BCBM. On this basis, clinical research to elucidate the role of utidelone combined with small-molecule anti-angiogenic drugs in the treatment of patients with BCBM has been initiated.

Acknowledgements

Not applicable.

Funding

The study was supported by Shenzhen Key Medical Discipline Construction Fund (grant no. SZXK013).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The raw sequencing data generated in the present study have been deposited in the Genome Sequence Archive (Genomics, Proteomics and Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences under accession number HRA008225 or at the following URL: https://ngdc.cncb.ac.cn/gsa-human/browse/HRA008225.

Authors' contributions

XB and CD designed the study and wrote the manuscript. XX, XL, LC and JH gathered medical images and examined patient information. XB, XX, ML, JH, XC, LS, QS, JZ, XL and LC contributed to the conceptualization, general design and quality assurance of the study. XB, ML, XC, LS, JZ and QS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Since the patient is deceased, her husband provided written informed consent for the publication of this case report and the associated images.

Competing interests

The authors declare that they have no competing interests.

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