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Case Report

Palbociclib and Fulvestrant Combined Regimen Induced Prolonged Bone Metastasis Control of Stage IV HR+/HER2- Breast Cancer: A Case Report ☆,☆☆

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ABSTRACT

The management of advanced metastasized breast cancer (BC) is a clinically challenging entity with a wide spectrum of novel therapeutics being introduced to the market. Such agents have remodeled BC treatment landscape and prolonged patients' survival. Over the past decade, a growing body of literature has shed lights on CDK4/6 involvement in oncogenesis and the role of its inhibitors in clinical use with palbociclib being the prototype drug. We present a case of a 58-year-old post-menopausal Middle-Eastern woman diagnosed with stage IV HR+/HER2- breast cancer with extensive bone metastasis. The lesions were widely distributed across the axial skeleton including base of the skull, sternum, ribs, left iliac bone, right inferior pubic ramus, cervical, thoracic, and lumbosacral vertebrae. The patient was started on therapeutic doses of letrozole and zoledronic acid in conjunction with adjuvant radiotherapy. A significant partial response was achieved reaching 70% remission followed by sternum disease progression. A decision was made to switch letrozole for tamoxifen which resulted in disease stability. Due to postmenopausal bleeding, tamoxifen was held and letrozole was reintroduced leading to regimen failure and disease advancement. Palbociclib and fulvestrant were started accordingly, yielding a remarkable metabolic response

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of all bone metastatic lesions (stable disease) after three months of the regimen initiation. The aforementioned stable disease status continued for approximately three years up to this point.

Introduction

Breast cancer (BC) is the most common malignancy in women worldwide and is one of the leading causes of cancer-related mortality [1,2]. Of the 4 molecular subtypes of BC, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)- negative BC represents the most common subtype, accounting for 60%-70% of all cases [2]. Hormone therapy is the mainstay treatment for these patients. However, endocrine resistance is a commonly encountered issue when treating this subtype of BC, which prompted further studies and research for new lines of treatment [3].

Dysregulated cyclin-dependent kinases 4 and 6 (CDK4/6) have been implicated in the pathogenesis of BC as they play a crucial role in prompting tumor growth in HR+ BC alongside estrogen-receptor (ER) pathway activation [3]. Due to certain stimulating signals, such as active ERs, CDK4/6 bind to cyclin-D1 and induce hyperphosphorylation of the retinoblastoma (*RB*) gene product. This process inactivates the *RB* gene and facilitates the progression through the G1 checkpoint to the S phase of the cell cycle [4,5]. Thus, the neoteric drug class CDK4/6 inhibitors have been introduced as a treatment modality of HR+/HER2- metastatic breast cancer (MBC). Three CDK4/6 inhibitors have been approved for the treatment of MBC including: palbociclib, ribociclib, and abemaciclib. Such drugs are used in conjunction with aromatase inhibitors or fulvestrant [2]. This report presents the unusual case of a 58-year-old female patient diagnosed with stage IV BC, who achieved prolonged stable disease on palbociclib and fulvestrant.

Case presentation

A 58-year-old post-menopausal Middle-Eastern woman without significant past medical and surgical history presented to our center, complaining of progressive neck pain of one-month duration. The pain was localized, did not radiate to other areas, and was not associated with reduced neck mobility or headaches. Concurrently, the patient observed a growing mass in the right breast. A non-pruritic, erythematous skin rash over the right breast and abdomen has developed three days before the presentation. The pain remained unresolved despite taking paracetamol, eperisone hydrochloride, and etoricoxib. Her review of symptoms was negative except for the complaints mentioned above. Physical examination revealed a left-sided hard, immobile breast mass with speculated margins and multiple enlarged left-sided axillary lymph nodes. Erythematous skin rash was noted over the right breast and abdomen.

Laboratory results included a normal complete blood count and normal comprehensive metabolic panel, except for an elevated alkaline phosphatase (ALP) at 452 IU/L (normal range 44-147 IU/L). An ultrasound (US) of the left breast revealed a fungating mass. In contrast, the right breast revealed an irregular, oval-shaped hypoechoic soft tissue mass at the 10 o'clock position, measuring approximately 0.3 × 0.2 cm, with characteristics highly suggestive of a benign nature. Subsequent mammography of the right breast was performed, which exhibited heterogeneous fibroglandular tissue and a well-circumscribed, round, iso-dense mass in the right upper lateral quadrant of the breast, categorized as BI-RADS III.

A comprehensive spinal computed tomography (CT) scan (Fig 1A-C) revealed extensive multilevel metastatic lytic bone lesions. These lesions included the skull base and a substantial portion of the vertebral column, with complete collapse of the T1 vertebra resulting in compression of the subarachnoid space and the spinal cord. Additionally, involvement of the sternum and numerous ribs bilaterally was evident. This was followed by a whole-body (18F)-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan, which exhibited a hypermetabolic multilobulated large left breast mass measuring 4.0 × 6.0 × 3.5 cm, indicative of primary BC. Multiple hypermetabolic enlarged lymph nodes in the left axilla accompanied this. The PET/CT scan revealed multiple hypermetabolic osteolytic bone lesions with destructive characteristics along the axial skeleton, specifically affecting levels C1, C2, C7, T1, T2, T4, T5, T8, T9, T11, L3, L5, and S1. Further osteolytic lesions were identified in the left iliac bone, right inferior pubic ramus, multiple ribs bilaterally, and the sternum, the largest lesion. There was no evidence of abnormal focal uptake elsewhere in the body. Bilateral tru-cut biopsies were conducted on the right and left breasts. Histopathological assessment of the right breast biopsy disclosed the presence invasive mammary carcinoma with ductal carcinoma in situ and comedo necrosis, notably without lymphovascular and perineural involvement. Immunostaining results were ER 90% positive, progesterone receptor 80% positive and HER2 negative expression. Subsequent assessment included the measurement of cancer antigen (CA) 15-3, revealing a value of 45.47 IU/mL (normal value < 30 IU/mL).

The patient's therapeutic regimen commenced with oral letrozole (2.5 mg once daily) and intravenous (IV) zoledronic acid (4 mg IV infusion) administered at 4-week intervals, complemented by palliative radiotherapy. A comprehensive assessment conducted approximately 7 months post-treatment initiation, utilizing PET/CT imaging, indicated a partial response to treatment by 30%. Specifically, the dimensions of the initially identified hypermetabolic lesion within the left breast exhibited a reduction to 5.3 × 3.6 × 3.3 cm. Additionally, a discernible decrease in metabolic activity in the lytic bone lesions and a subtle interval sclerosis pattern were consistent

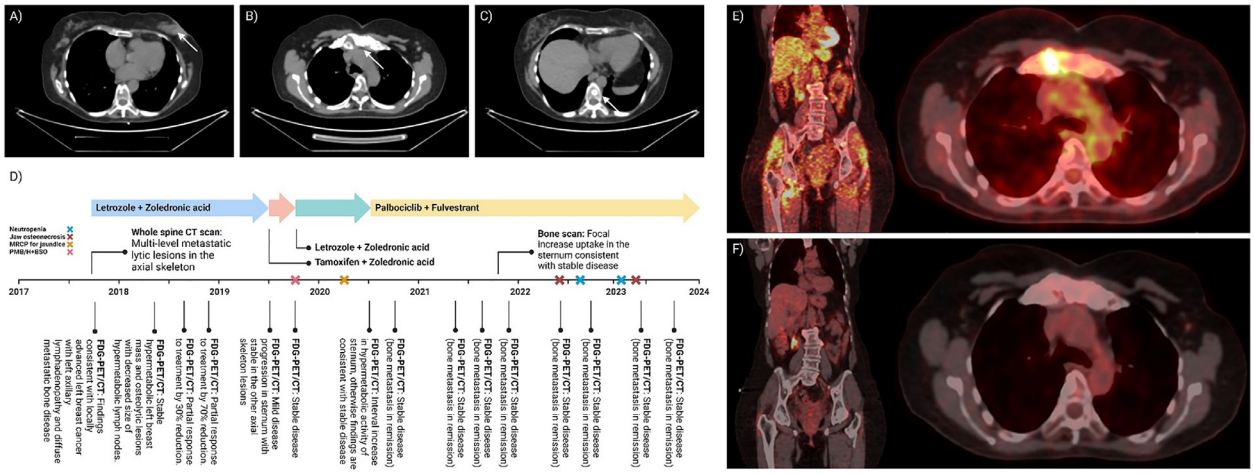

Fig. 1 – CT scans illustrating multilobulated large left breast mass measuring 4.0 x 6.0 x 3.5 cm, indicative of primary BC (A), sternum lesion representing a metastatic deposition (B), and an example of vertebral osteolytic lesion (C). Timeline representing the major clinical events including scans, regimen switching, and adverse events (D). Selected PET-CT scan images illustrating active lesions (E) and stable disease (F).

with the partial response. Concurrently, the patient's CA 15-3 level was measured at 32.03 IU/mL (normal range <30 IU/mL). The subsequent months witnessed continued clinical and radiological improvements, marked by the transition of the axial osteolytic lesions to a non-hypermetabolic state. However, a new osteolytic lesion emerged at the L4 vertebra, while the sternum-based osteolytic lesion retained its hypermetabolic characteristic.

Eighteen months following the initial diagnosis, letrozole therapy was changed to tamoxifen (20 mg orally once daily). While under the regimen of tamoxifen and zoledronic acid, a subsequent PET/CT scan indicated mild disease progression, evident in the slightly hypermetabolic lesions localized in the sternum and the L4 vertebra, accompanied by re-elevation of the CA 15-3 marker to 57.33 IU/mL (normal range <30 IU/mL). Approximately 2 months into tamoxifen treatment, the patient reported post-menopausal bleeding, characterized by minimal volume and mild lower abdominal discomfort. Subsequently, an US investigation was pursued, revealing an enlarged uterus with potential fibroid presence. As a result, the patient underwent a total abdominal hysterectomy with bilateral salpingo-oopherectomy (H+BSO). Letrozole was re-initiated alongside fulvestrant (500 mg intramuscular (IM)) injection with zoledronic acid infusions. Following one month of fulvestrant treatment, there was an observed elevation in liver function test results, with AST levels at 196 IU/L (normal range 8-33 IU/L), ALT at 191 IU/L (normal range 4-36 IU/L), ALP at 159 IU/L (normal range 44-147 IU/L), and GGT at 560 IU/L (normal range 5-40 IU/L). Hepatitis A workup was negative. Subsequent assessments encompassed liver and gallbladder US imaging, which revealed the presence of biliary sludge and multiple gallstones. Additionally, magnetic resonance cholangiopancreatography revealed a dilated common bile duct measuring 9 mm in diameter and a distended gallbladder containing multiple stones, accompanied by pericholecystic fluid suggestive of acute cholecystitis. The later being managed accordingly. An ongoing progression of the hypermetabolic osteolytic lesion in the sternum was observed. Thus, oral administration of palbociclib at a daily dose of 125 mg, with a regimen of 21 days on medication followed by 7 days off, in combination with fulvestrant (500 mg, IM) injection every 28 days and zoledronic acid infusions every 3 months was initiated. After 3 months of treatment with palbociclib, a follow-up PET/CT scan revealed a stable hypermetabolic osteolytic lesion in the sternum and non-hypermetabolic lesions in the axial spine. The disease was determined to be in a state of remission.

During treatment, the patient experienced two episodes of neutropenia. The first occurrence was classified as grade 2 neutropenia, with an absolute neutrophil count (ANC) of 1090 per microliter. The patient was asymptomatic and managed conservatively. One week later, follow-up ANC revealed a count of 1600 per microliter. The second episode was classified as grade 3 neutropenia, with an ANC of 990 per microliter. Subsequently, palbociclib was held. Moreover, two episodes of jaw osteonecrosis occurred and were managed accordingly. A follow-up whole-body PET/CT scan was performed one year later, revealing consistent findings of stable non-hypermetabolic multiple osteoblastic/osteolytic lesions in the axial skeleton and sternum, maintaining the state of remission. The patient exhibits favorable clinical response on palbociclib and fulvestrant therapy, and a follow-up PET/CT scan is recommended every 3 months. Fig. 1D illustrates a timeline of the aforementioned clinical events including scans, regimen switches, and adverse events.

Discussion

This case illustrates the rare attainment of prolonged stable disease of stage IV BC, with the therapeutic regimen of palbociclib and fulvestrant. In the presented case, we describe the clinical course of a 58-year-old woman diagnosed with stage IV HR+/HER2- BC and bone metas-

tases. The patient underwent various therapeutic regimens, including palliative radiotherapy and hormonal therapy involving letrozole and tamoxifen. Zoledronic acid was also used for the management of metastatic bone disease. Although follow-up imaging demonstrated notable improvements in the existing metastatic bone lesions, a new lesion emerged at the L4 vertebra. Thus, the initiation of oral palbociclib along with fulvestrant injection ensued. Remarkably, three months after the commencement of palbociclib therapy, the patient achieved prolonged stable disease.

Palbociclib is a member of the novel drug class CDK4/6 inhibitors. The CDKs are serine-threonine kinases that are pivotal in regulating cell-cycle progression. CDK4/6 interact with cyclin-D1, a transcriptional target of ER, forming an active complex. This interaction facilitates the hyperphosphorylation of the RB tumor suppressor protein, hindering its inhibitory effect. This process enables cells to progress from the G1 checkpoint to the S phase of the cell cycle [4,5]. HR+/HER2- BC pathogenesis included a disrupted CDK4/6 pathway with an overexpressed cyclin-D1. Inhibition of the CDK4/6 by palbociclib will induce complete dephosphorylation of the RB protein, halting the cell cycle progression at the G1 checkpoint [5]. Therefore, palbociclib is administered with letrozole as a first-line therapy for MBC based on the results of the PALOMA clinical trials. It could also be combined with fulvestrant for MBC that has advanced despite prior endocrine therapy based on PALOMA-3 trial [6]. The most common adverse events documented for palbociclib are neutropenia, leukopenia, fatigue, and nausea [3].

The addition of palbociclib in PALOMA-2 and PALOMA-3 trials resulted in an improved objective response rate (ORR) compared to the control population. ORR is the percentage of patients with a confirmed complete or partial response. The palbociclib plus letrozole arm in PALOMA-2 had a rate of 42.1%, compared to 34.7% for the control arm. Furthermore, the palbociclib plus fulvestrant arm in PALOMA-3 had a 19% rate versus 9% for the control arm. However, complete pathological response, defined as the disappearance of any residual cancer cells on histopathological examination of a previously affected tissue after neoadjuvant chemotherapy, was not tested for nor mentioned in the results of PALOMA-2 and PALOMA-3 trials [4,7].

Bone metastasis from BC represents a prevalent manifestation, constituting approximately 75% of MBC cases [8]. BC metastasis typically results in osteolytic, osteoblastic, or mixed lesions, often characterized by simultaneous sclerotic and lytic processes within the affected bones. Given that the axial skeleton is the predominant site for bone metastasis, multiple potential complications may ensue, including pain, pathological fractures, spinal cord compression, and humeral hypercalcemia of malignancy [8,9]. Diagnostic modalities used to identify bone metastasis include bone scintigraphy, CT imaging, and FDG-PET/CT scan, with the latter being acknowledged as the most superior approach [10]. Therapeutic options for bone metastasis include bisphosphonates and denosumab, a monoclonal antibody targeting receptor activator of nuclear factor kappa-B ligand (RANKL) [8].

The use of palbociclib for treating HR+/HER2- BC has been described in multiple case reports with remarkable results. The combination of palbociclib and letrozole was mentioned as a first-line treatment in a 60-year-old woman, showing a complete metabolic response [11]. It has also been beneficial in cases with resistant cancer, such as the case of a locally advanced BC resistant to multiple cycles of Adriamycin and Docetaxel, achieving residual cancer burden class 1 when switched to this regimen [12]. Another report detailed the case of a 40-year-old woman with bone and lung metastases refractory to radiochemotherapy and tamoxifen, experiencing a complete response within 8 months of palbociclib and letrozole therapy [13].

Palbociclib has also been used in cases of BC recurrence, as two reports described the recurrence after 13 and 14 years with lymph node involvement. When treated with palbociclib and letrozole, the first patient exhibited disease stabilization and improved lymph node swelling within a year of treatment, while the second patient achieved a complete clinical response [14,15]. Another report mentioned the use of palbociclib with anastrozole in stage IV BC with liver metastases, achieving a state of stable disease after three years [16]. Yoneto et al. described the case of a 74-year-old woman diagnosed with stage IV BC featuring multiple lung and liver metastases. She was treated with palbociclib and fulvestrant and achieved a state of stable disease. After 1 year, palbociclib was switched to abemaciclib due to strong myelosuppression, and the patient maintained a stable disease state with no adverse events [17]. Two interesting reports mentioned the use of palbociclib as a single agent for treatment. The first case was of a 73-year-old woman with extensive liver metastases undergoing multiple therapeutic regimens and 2 separate hepatectomies, which only resulted in disease progression. Switching her to palbociclib resulted in near-complete metabolic resolution. However, the progression free survival was only maintained for 20 months due to the progression of the hepatic lesions [18]. The other case was described by Droubi et al. as an 85-year-old woman with cutaneous metastases, who exhibited a complete disappearance of the metastatic lesions within a month of starting palbociclib, and maintained a disease-free state of more than 2 years [19].

Two cases were presented by Inoue et al. about male BC. The first case is of a 53-year-old man with stage IIB BC who experienced failure of primary treatment with radiochemotherapy, total mastectomy, and tamoxifen. He presented with cutaneous metastasis on the chest, and further evaluation revealed metastasis to the sternum. When switched to palbociclib and fulvestrant, he achieved a stable disease state for at least 9 months. The second case is of an 82-year-old man who presented with a new onset of hoarseness of voice. Physical examination revealed a thyroid mass and multiple enlarged cervical and axillary lymph nodes after sixteen years of treatment of primary BC. Pathology reports exhibited papillary thyroid carcinoma and MBC, with the latter being prioritized for treatment. After the failure of tamoxifen therapy, he was started on palbociclib and letrozole. He achieved a partial response with no disease progression or adverse events [20]. Another report documented the unusual treatment of HR+/HER2+ MBC in a 50-year-old woman with palbociclib, added to letrozole, trastuzumab, and leuprorelin, displaying a partial response to treatment after 21 months [21]. Our case

demonstrates that extensive bone metastases from stage IV HR+/HER2- BC can be put into a state of prolonged stability by using palbociclib in combination with fulvestrant.

Conclusion

In this report, we presented the unusual case of prolonged stable disease of metastatic breast cancer on combination therapy of palbociclib and fulvestrant. This showcases the importance of CDK4/6 inhibitors in the management of resistant cases of BC, and paves the way for their broader utilization in advanced BC treatment.

Availability of data and materials

Not applicable.

Authors contribution

Data curation, R.K.J and S.M.A.; writing – original draft preparation, R.K.J, A.H.A, S.M.A, J.M.A, and M.S.B.; writing – review and editing, A.H.A, and O.A.; visualization, R.K.J, A.H.A, and O.S.; supervision, O.S.; project administration, O.S. All authors have read and agreed to the published version of the manuscript.

Ethics approval

This report has been conducted and written in accordance with the ongoing regulations for case reports and case series in the King Abdullah University Hospital (KAUH). Case reports are exempted from institutional ethical approval by the institutional review board (IRB).

Patient consent

Informed consent was obtained from the patient for publication of this report and any associated images.

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