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# First-line endocrine therapy combined with CDK 4/6 inhibitor in disseminated carcinomatosis of bone marrow (DCBM) luminal breast cancer: a case report

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## Abstract

**Background** Metastatic breast cancer especially in disseminated carcinomatosis of bone marrow (DCBM) poses a life-threatening risk, often requiring systemic chemotherapy. This situation lacks a cure, emphasizing symptom relief and quality of life. The documented occurrence of DCBM is merely 0.17% in metastatic breast cancer and ranges from 0.6 to 1.7% in solid tumors. Until now, there is no official medical guideline for treating patients with luminal breast cancer (LBC) who have DCBM. This case report highlights LBC patient with DCBM, treated at diagnosis with first-line therapy combining endocrine therapy (ET) and a CDK4/6 inhibitor.

**Case presentation** A 36-year-old premenopausal female of Javanese ethnicity with advanced de novo luminal breast cancer diagnosed in 2020. The immunohistochemistry showed estrogen receptor (ER)+ (90%), progesterone receptor (PR)+ (20%), human epidermal growth factor receptor 2 (HER-2) negative, and a high Ki-67 staining result at 60%. The patient had visceral crisis, which involved bone marrow infiltration and liver metastasis with preserved liver function. After intolerance of side effects from first line treatment with tamoxifen, the treatment plan was adjusted to letrozole, ribociclib, and leuprorelin injection. After completing the sixth cycle of treatment, blood parameters in the laboratory were found to have returned to normal. The patient's response to this regimen was remarkable, with significant alleviation of symptoms and improvement in quality of life observed.

**Conclusion** Notably, the combined approach of ET and CDK4/6 inhibitor represents a novel intervention in managing DCBM in patients with LBC.

**Keywords** Breast cancer, CDK 4/6 inhibitor, Chemotherapy, Endocrine therapy, Visceral crisis

## Background

Breast cancer is the most common type of cancer in women. While metastatic disease, which is often considered incurable, is rarely present at the time of the initial diagnosis, approximately 20% of women with initially treatable breast cancer eventually experience relapses, with 70% of these relapses involving distant metastases [1]. It is important to highlight that while patients with breast cancer frequently experience the spread of cancer to their bone marrow, the occurrence of substantial

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pancytopenia owing to full bone marrow metastasis is relatively rare in this population [1–3]. Disseminated carcinomatosis of the bone marrow (DCBM) is a life-threatening condition, potentially leading to a visceral crisis (VC), for which systemic chemotherapy is recommended [4, 5]. VC has a grim prognosis, with an overall survival (OS) of merely 3.7 months. The emergence of symptomatic bone marrow metastasis is an uncommon phenomenon in metastatic breast cancer. The documented occurrence of bone marrow metastasis is merely 0.17% in metastatic breast cancer and ranges from 0.6 to 1.7% in solid tumors. Approximately 70% of patients with VC tested positive for hormone receptors (HR). However, the overall survival (OS) of these patients did not show a significant increase when receiving chemotherapy as opposed to palliative care. Moreover, chemotherapy adversely affects the quality of life for these patients. There is no conclusive treatment for bone marrow metastasis, which presents a significant risk to patients' survival [5, 6].

Despite the availability of numerous therapeutic modalities, achieving a cure for hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer remains a rare outcome [6]. The present therapeutic approach for HR+/HER2− advanced breast cancer entails a sequential administration of ET, targeted therapy, and/or chemotherapy with the overarching objectives of extending patient survival, delaying disease progression, and mitigating cancer-related symptoms [6, 7]. The landscape of this treatment regimen has been significantly impacted by the introduction of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. Currently, three CDK4/6 inhibitors—namely, palbociclib, ribociclib, and abemaciclib have received approval from the US Food and Drug Administration (FDA). Several studies have indicated that CDK4 inhibitors are effective in the treatment of metastatic breast cancer in bone marrow [7, 8].

In one randomized phase II trial (RIGHT Choice study), in 222 pre- or perimenopausal patients with aggressive, hormone receptor-positive, HER2-negative breast cancer (half of whom had VC), initial ET plus ribociclib improved progression-free survival relative to combination chemotherapy [24.0 versus 12.3 months, hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.36–0.79], with similar response rates (65% versus 60%) and fewer grade 3 to 4 adverse events (0.9% versus 7.0%), although the overall survival result is still pending [9, 10]. Although these results support frontline ET plus a CDK 4/6 inhibitor for patients with aggressive luminal type HER2-negative disease, we note that most patients in this trial had *de novo* metastatic disease [9]. Here, we present a case of a patients with LBC with a DCBM at the diagnosis, treated with a combination of ET and CDK4/6 inhibitor as first line therapy.

## Case presentation

A 36-year-old premenopausal female of Javanese ethnicity with a family history of advanced breast cancer in her mother, first noticed a lump and changes in the size and shape of her left breast nipple in 2020. She experienced psychological denial for over 3 years and did not undergo early detection screening, even after acknowledging the presence of the lump.

In May 2023, the patient was admitted to the hospital following fainting episodes, suffering from severe anemia (hemoglobin 3.6 g/dL), thrombocytopenia (24,000/uL), and leukocytosis (26,000/uL). The left breast appeared hardened and was prone to bleeding. Laboratory tests showed elevated lactate dehydrogenase (LDH) levels of 2616 U/L and uric acid levels of 10.4 mg/dL. The histopathology and immunohistochemistry of the breast core biopsy revealed invasive luminal B breast cancer with estrogen receptor (ER)+ (90%), progesterone receptor (PR)+ (20%), HER-2 negative, and a high Ki-67 staining result at 60%. The decision-making process for the diagnostic strategy in this case was guided by the necessity to accurately characterize the breast cancer subtype and assess the extent of metastasis, particularly to the bone marrow. The initial step involved histopathological examination of tissue samples obtained through a core biopsy, followed by immunohistochemistry (IHC) to evaluate the expression of specific markers on tumor cells. The markers chosen for assessment played pivotal roles in informing the treatment plan. ER and PR expression levels were assessed to determine the hormone receptor status of the tumor. With high ER expression (90%) and positive PR expression (20%), the tumor was identified as hormone receptor-positive (HR+), rendering it suitable for ET. Additionally, HER-2 expression was evaluated to determine HER-2 status, which was found to be negative, suggesting limited benefit from HER-2-targeted therapies. The high Ki-67 index (60%) indicated rapid tumor growth and potential aggressiveness, further influencing treatment decisions.

Liver function tests found abnormalities with Child–Pugh class A. From contrast enhanced MSCT-scan abdominal disclosed metastases to the liver with multiple nodules, the largest of which has a size of approximately 1.6 cm in both the right and left lobes (segment II and VIII), (Fig. 1) and lytic lesion in thoracolumbar vertebrae (Fig. 2). As her hematological condition worsened, a bone marrow biopsy conducted in May 2023 revealed metastatic adenocarcinoma originating from invasive breast carcinoma of the non special type (Fig. 3). Therefore, it was concluded that the patient had advanced breast

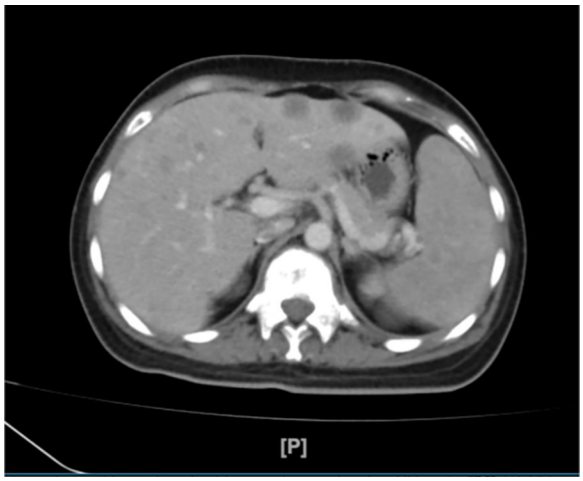


**Fig. 1** Liver metastasis

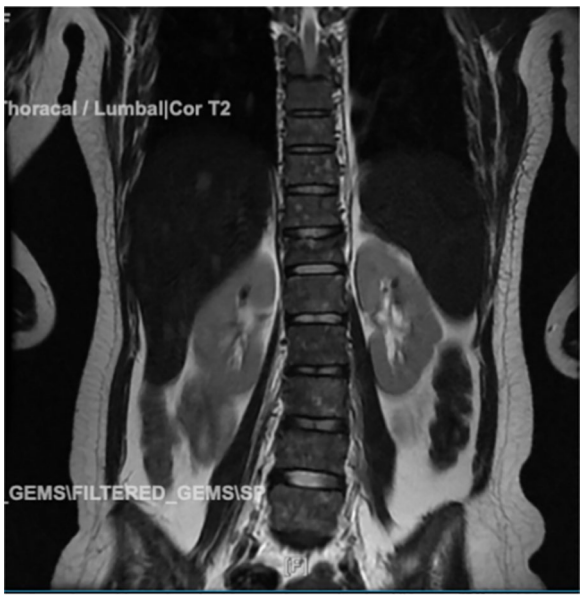


**Fig. 2** Bone metastasis

cancer with metastases to the bone, liver, and bone marrow, along with hematological complications.

The first planned treatment option was chemotherapy, but further evaluation was needed owing to the critical hematological condition. The patient had symptomatic cytopenia. Additionally, the patient subsequently experienced melena, a complication of severe thrombocytopenia. We considered treatments that offer good morbidity and survival outcomes without exposing the patient to the risk of severe hematological complications. The patient was then initially planned to receive 20 mg of tamoxifen and 3.75 mg of leuprorelin. However, she exhibited poorly tolerated clinical side effects, such as hot flushes, nausea, and joint pain. At that period, the patient's condition deteriorated; she experienced severe pain and was bedridden. Consequently, the therapeutic regimen was adjusted to injection of 3.75 mg of leuprorelin monthly in combination with 2.5 mg of letrozole, and 600 mg of ribociclib every 4 weeks, and zoledronic acid as for bone sparring agent. On the basis of literature, the combination of ET and CDK4/6 inhibitors especially ribociclib holds promise for yielding favorable outcomes in patients with metastatic breast cancer, particularly in cases involving bone marrow metastasis. On the basis of meta-analysis study by Hermansyah *et al*., the arms utilizing CDK 4/6 inhibitors demonstrated superior overall response rates (ORR) compared with other treatment groups, as evidenced by the relative risk (RR) according to the randomized-effect model (REM) of 1.59 [95% confidence interval (CI) 1.37–1.86] and $p$ value of $<0.00001$. Additionally, the combination regimen showed higher clinical benefit rates (CBR) with a RR of 1.22 (95% CI 1.13–1.32) as per the REM, with $p$ value of $<0.00001$ in patients with HR+/HER2− breast cancer. Furthermore, this combined treatment approach effectively reduced the rate of progressive disease (PD) within the intention-to-treat (ITT) group, with a RR of 0.46 (95% CI 0.39–0.54) according to the fixed-effect model (FEM), and $p$ value of $<0.00001$. Although the incidence of adverse effects, particularly hematological reactions, was significantly lower in the arm receiving ET alone, the occurrence of other systemic reactions was relatively similar between treatment groups [11, 12].

At the outset of treatment, the patient experienced hot flushes, fatigue, and chills but tolerated them well. After two cycles, the patient showed significant clinical improvement; pain was reduced, the frequency of transfusions decreased, and she even began to ambulate. By the end of the fourth cycle, her hematological profile showed improvement with hemoglobin of 10.4 g/dL and platelets of 76.000/uL, and she could walk and engage in daily activities. After completing the sixth cycle of treatment, blood parameters in the laboratory were found to have returned to normal. The patient's response to this regimen was remarkable, with significant alleviation of symptoms and improvement in quality of life observed. On the basis of previous literature, the combination of ET and CDK 4/6 inhibitors in patients with breast cancer has shown promising outcomes with minimal side effects. The patient was advised to undergo monthly follow-up appointments. To date, the patient has shown no clinical symptoms of metastatic breast cancer and continues to maintain a sustained complete remission for 4 months under this treatment regimen (September–December 2023). The clinical timeline, diagnostic examination

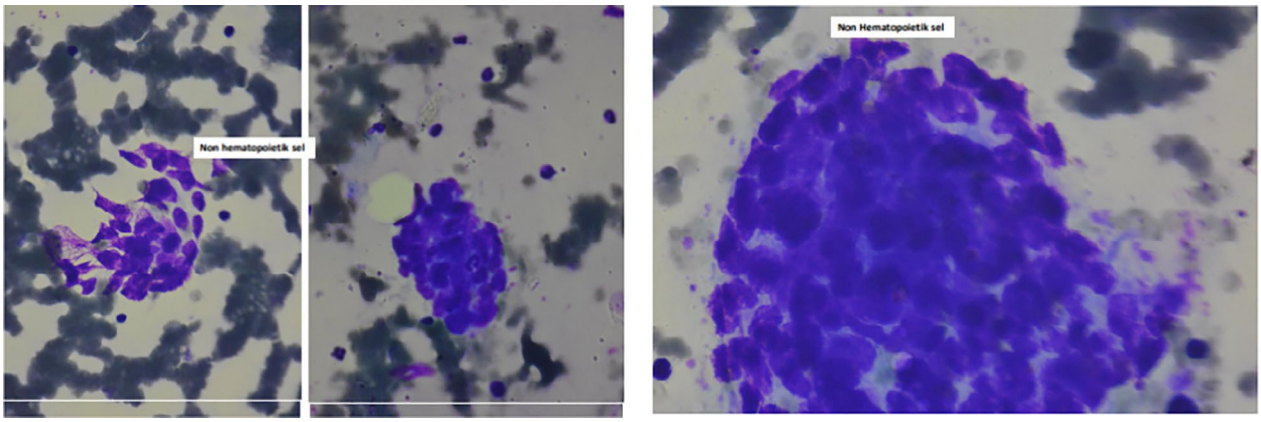


**Fig. 3** Bone marrow biopsy showed metastatic adenocarcinoma originating from invasive breast carcinoma of the non-special type

findings, and therapeutic interventions are illustrated in Fig. 4. Data on the changes in hematological parameters are presented in Fig. 5.

## Discussion

Advanced breast cancer with bone marrow infiltration can be considered as a VC [13]. The experts from the French Breast Cancer Intergroup Unicancer (UCBG) also classified symptomatic cytopenia, irrespective of its grade as VC [14]. In the current clinical instance, the patient had invasive lobular carcinoma at the diagnosis and widespread infiltration of cancerous cells in the bone marrow [15]. Anemia and thrombocytopenia are frequently the initial clinical signs and symptoms in patients with DCBM. The emergence of clinically significant marrow involvement reflects an uncommon occurrence [15, 16]. Regardless of how long it took between the diagnosis of DCBM and the first diagnosis of breast cancer, the prognosis for DCBM is poor, and the therapy is complex owing to cytopenias [5]. Although cytopenia is a common feature of DCBM, systemic therapy can achieve long-lasting disease control despite a higher risk of hematological complications without affecting the disease control or median survival of patients treated with

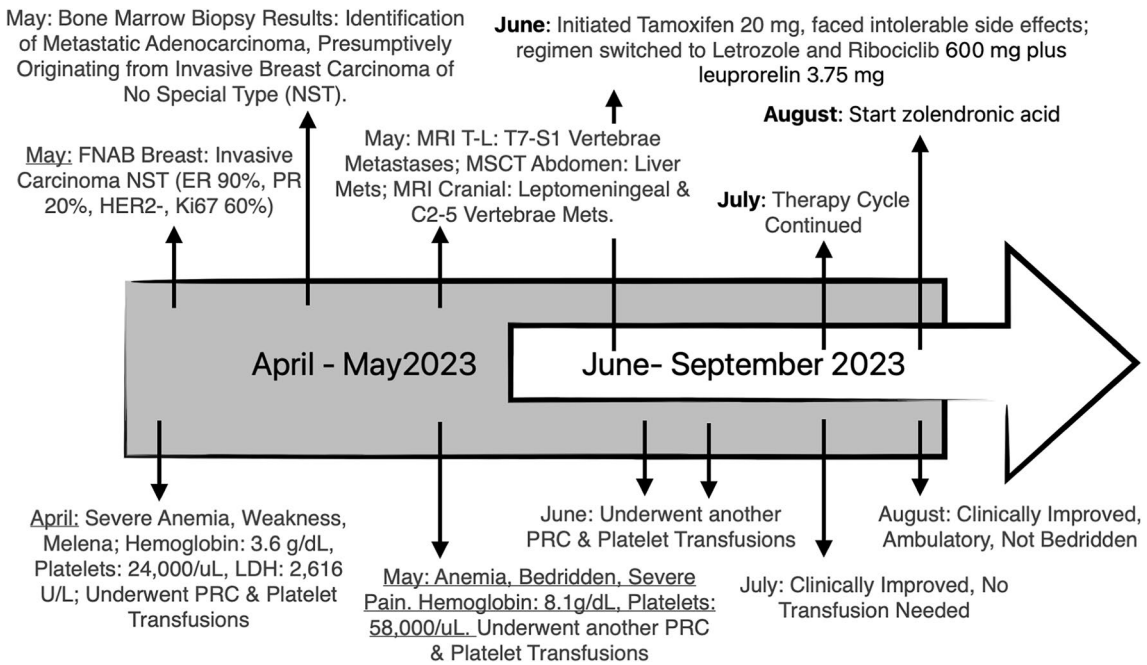


**Fig. 4** Clinical timeline, diagnostic examination findings, and therapeutic interventions

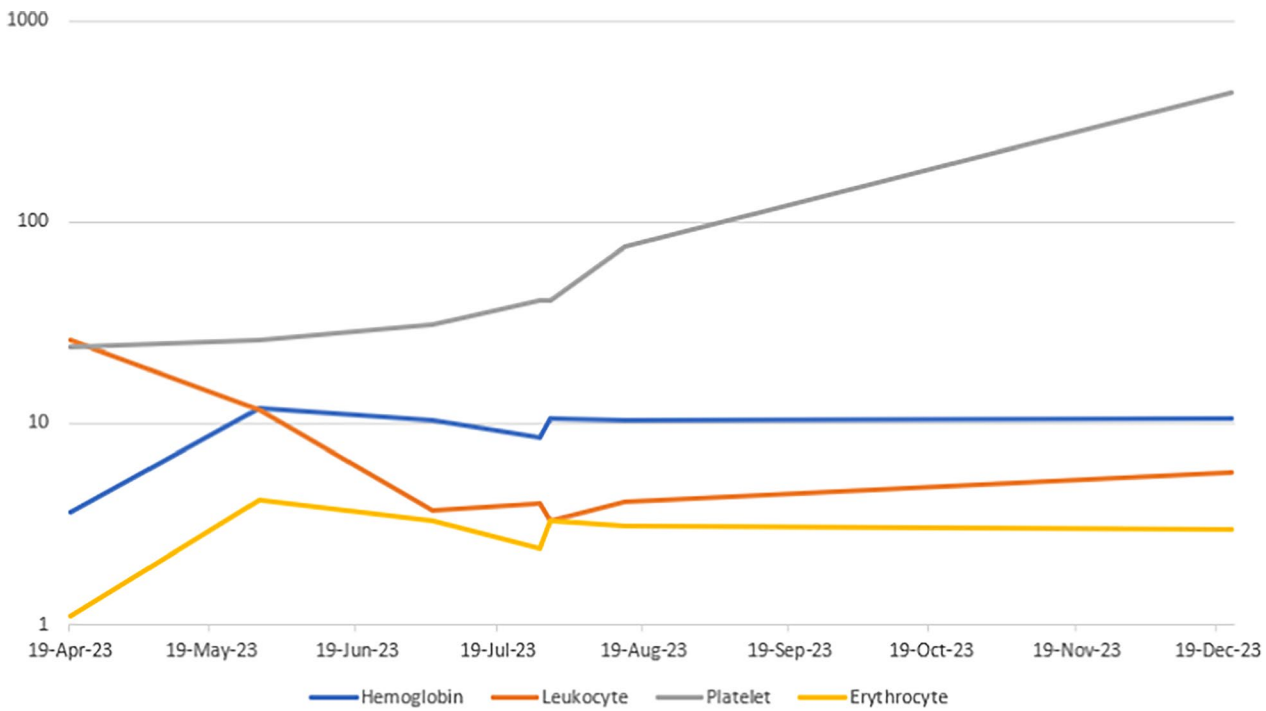


**Fig. 5** Hematological parameter changes occur within the progression of the disease and during treatment

single-agent chemotherapy or polychemotherapy regimens [17, 18].

Zoledronic acid, a potent bisphosphonate, is commonly described as a bone-sparing agent owing to its critical role in inhibiting osteoclast-mediated bone resorption, particularly in patients with metastatic bone disease. It functions by suppressing osteoclast activity, thereby preserving bone density and reducing the incidence of skeletal-related events (SREs), such as fractures, hypercalcemia, and bone pain. This bone-stabilizing effect is particularly valuable in metastatic settings, where the maintenance of skeletal integrity is essential for improving patient quality of life and alleviating symptoms associated with bone metastases. There are limited data that combining ET (with or without targeted agents) with chemotherapy improves overall survival, and therefore we do not use this strategy [10]. International guidelines state that the administration of combination of ET and CDK4/6 inhibitors is the first line of treatment for advanced breast cancer with positive hormone receptor but HER2-negative, excluding patients with life-threatening conditions or VC as disease presentations. CDK4/6 inhibitors represent a recently developed category of therapeutic agents for treating LBC. The disruption of the cyclin D-CDK4/6 signaling pathway has been identified as a significant factor in breast cancer biology. CDK4/6 enzymes are serine/threonine kinases whose activity is regulated through interaction with a cyclin regulatory subunit [6–8]. These enzymes are pivotal in driving cell cycle progression, a fundamental process in cell proliferation. Within this context, cyclin D proteins (D1, D2, and D3) act as regulators of CDK4 and CDK6 by forming active complexes with them [19]. Notably, cyclin D1, which is excessively expressed in roughly half of breast cancers, is controlled transcriptionally by the ER. The ER signaling pathway enhances the cellular abundance of D-class cyclins, particularly cyclin D1. This event results in the inactivation of the retinoblastoma (Rb) tumor suppressor protein, leading to the progression of the cell cycle and overcoming the G1/S transition phase [7, 19].

As this patient is classified as having a VC, according to international guidelines, the recommended treatment involves chemotherapy. However, in this case, we decided that it is too risky to undergo chemotherapy with hematological parameters in disarray owing to metastasis. The choice of ET plus CDK4/6 inhibitor is considerably rational as per our thought. This was inline with the phase II RIGHT Choice study (NCT03839823). The study enrolled 222 premenopausal or perimenopausal individuals diagnosed with hormone receptor–positive, HER2-negative aggressive breast cancer [20]. More than 50% of these patients were identified by the investigators as having VC. Out of this cohort, 112 participants were randomly allocated to be administered ribociclib alongside an aromatase inhibitor—either letrozole or anastrozole—combined with goserelin. The remaining 110

patients were designated to undergo a chemotherapy regimen chosen by their physicians. Patients who underwent treatment with ribociclib in combination with ET experienced a progression-free survival of 24 months, approximately 1 year longer than their counterparts treated with chemotherapy (12.3 months) [11, 21]. Moreover, the median time to treatment failure was notably extended for those receiving ribociclib plus ET, with a duration of 18.6 months compared with 8.5 months for those treated with chemotherapy [11].

Although the overall response rate was comparable between the two treatment groups (65.2% for ribociclib plus ET and 60% for chemotherapy), the incidence of symptomatic adverse events, including diarrhea and fatigue, varied significantly. Serious treatment-related adverse events were observed in 1.8% of patients in the ribociclib plus ET group, contrasting with 8% in the combination chemotherapy group. Likewise, treatment discontinuation owing to treatment-related adverse events occurred in 7.1% of patients treated with ribociclib plus ET and in 23% of patients treated with chemotherapy, highlighting a notable difference in tolerability between the two approaches [9]. This study is one of the considerations in determining the treatment for this patient.

Hematologic toxicity is a well-documented adverse effect associated with inhibiting cyclin-dependent kinase 6 (CDK4/6). While all three CDK4/6 inhibitors can induce cytopenia to varying degrees, study analysis revealed a statistically significant and substantial reduction in the likelihood of experiencing severe (grade 3–4) neutropenia with abemaciclib compared with palbociclib when used in conjunction with either an aromatase inhibitor (AI) [7, 19]. Notably, there was no discernible difference in the occurrence of grade 3–4 infections between these two CDK4/6 inhibitors. Febrile neutropenia episodes could not be compared owing to inconsistent reporting in abemaciclib trials. Ribociclib exhibited a more favorable hematologic toxicity profile than palbociclib, with a lower incidence of grade 3–4 neutropenia (OR: 0.39–0.41 depending on the ET backbone) and anemia (OR: 0.45–0.79 depending on the ET backbone) [6, 7]. In this case we did not find any hematological toxicities owing to CDK4/6 inhibitors [22].

The combination of CDK4/6 inhibitors and hormonal therapy for advanced luminal breast cancer with VC is not yet established in recent guidelines. However, this approach has shown promise, as indicated by other case reports with similar situations [23]. Remarkably, VC stands out as the sole exception in the utilization of CDK4/6 inhibitors in combination with ET as a first-line treatment, despite the evident limitations of chemotherapy in this scenario. Nevertheless, the identified shortcomings of chemotherapy in this context, coupled with the promising outcomes, have naturally sparked increased interest in the use of CDK4/6 inhibitors for VC, challenging the established role of chemotherapy in this crucial subgroup [24]. Insights in this direction have emerged from retrospective analyses revealing that a noteworthy proportion of clinicians (18% and 12%, respectively) prefer CDK4/6 inhibitors over chemotherapy even for VC [25].

According to a retrospective study conducted at a large tertiary UK cancer center from 2017 to 2021, Behrouzi *et al*. aimed to compare outcomes in patients with ER+/HER2− advanced breast cancer (ABC) experiencing VC or impending VC when treated with CDK4/6 inhibitors or weekly paclitaxel. The results demonstrated that the CDK4/6 inhibitors cohort exhibited a significantly longer median time to treatment failure (TTF), progression-free survival (PFS), and overall survival (OS) compared with the paclitaxel cohort: TTF 17.3 versus 3.5 months (HR 0.33, 95% CI 0.17–0.61, $p=0.0002$), PFS 17.8 versus 4.5 months (HR 0.38, 95% CI 0.21–0.67, $p=0.002$), OS 24.6 versus 6.7 months (HR 0.37, 95% CI 0.20–0.68, $p=0.002$). The median time to the first improvement in IVC/VC was similar between the CDK4/6 inhibitors and paclitaxel groups (3.9 versus 3.6 weeks, $p=0.773$), and disease control at 4 months did not significantly differ (77.8% versus 59.4%, $p=0.168$). Multivariate analysis revealed that treatment with CDK4/6 inhibitors was independently associated with a longer PFS compared with paclitaxel (HR 0.31, 95%CI 0.12–0.78, $p=0.015$). From this study, we can conclude that the use of CDK4/6 inhibitors is associated with significantly better survival outcomes compared with chemotherapy [26].

The initial head-to-head trial, The RIGHT Choice, provides the first evidence showcasing ribociclib's superior efficacy and safety compared with conventional chemotherapy (CT) for patients experiencing VC [11]. Several ongoing clinical trials are currently investigating the same issue with alternative CDK4/6 inhibitors. Two single-arm phase II trials, exploring abemaciclib (NCT04681768) and dalpiciclib (NCT05431504) combined with ET, specifically focus on HR+/HER2− advanced breast cancer (ABC) exhibiting clinical features that meet VC criteria. Additionally, the ABIGAIL trial (NCT04603183) is examining the efficacy and safety of abemaciclib in combination with ET, comparing it to the standard approach of upfront chemotherapy with paclitaxel followed by endocrine maintenance therapy (i.e., abemaciclib plus ET) in HR+/HER2− ABC with aggressive disease features. These trials, will contribute valuable insights to guide future treatment decisions for patients with aggressive disease features in HR+/HER2− advanced breast cancer [27].

In considering future research directions and potential impacts on clinical practice, several key considerations emerge from the successful outcomes observed with the combination of ET and CDK 4/6 inhibitors in treating patients with breast cancer. Further investigation into the long-term efficacy and safety profile of this treatment regimen is warranted, particularly in diverse patient populations and across various stages of breast cancer progression. Additionally, comparative studies evaluating the effectiveness of ET and CDK 4/6 inhibitors versus standard chemotherapy regimens could provide valuable insights into optimal treatment strategies, especially in cases of metastatic breast cancer. Furthermore, real-world evidence studies are needed to validate the findings from clinical trials and assess the feasibility and effectiveness of implementing this regimen in routine clinical practice. Overall, continued research efforts in these areas hold the potential to refine treatment guidelines, enhance patient care, and ultimately contribute to better outcomes for individuals affected by bone marrow metastatic breast cancer.

## Conclusion

The combination of ET and CDK4/6 inhibitors shows promising clinical benefits in treating advanced LBC with visceral crisis, surpassing the efficacy of chemotherapy alone. Moreover, this regimen tends to induce fewer adverse effects, thereby enhancing patients' quality of life. This case underscores the importance of considering ET and CDK4/6 inhibitors as a preferred treatment option in similar metastatic cases of LBC. It suggests a potential shift in future clinical guidelines toward incorporating these combinations earlier in the treatment pathway for eligible patients.

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**Author contributions**
All of the authors contributed equally to writing this manuscript.

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**Availability of data and materials**
The article and supplementary material contain the original contributions that were presented in the study. The appropriate author can be contacted for more information.

## Declarations

**Ethics approval and consent to participate**
All procedures used in this study were approved by the ethics committee of Elisabeth Hospital, Semarang, Indonesia.

**Consent for publication**
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**
The authors affirm that they have no known financial or interpersonal conflicts that might have looked to have influenced the research presented in this study.

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## Publisher's Note