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Development of Acute Myeloid Leukemia Following CDK4/6 Inhibitor Therapy for Patient with Metastatic Hormone Receptor Positive Breast Cancer (mHR+BC) and Pre-existing Clonal Hematopoiesis of Indeterminate Potential–A Case Report

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Abstract

Acute Myeloid Leukemia (AML) is an aggressive hematologic malignancy that may arise de novo or secondary to cytotoxic therapies. Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i), such as palbociclib, ribociclib, and abemaciclib are widely used in the treatment of hormone receptor-positive breast cancer (HR+BC) and have a tolerable safety profile compared to conventional chemotherapy agents applied in this space. Although rare, AML has been reported after CDK4/6i exposure; we describe a case occurring after prolonged ribociclib therapy in a 77-year-old female patient with metastatic HR+BC and pre-existing Clonal Hematopoiesis of Indeterminate Potential (CHIP). A pre-treatment bone biopsy for Next Generation Sequencing revealed a sub-clonal IDH2 & DNMT3A mutation. The patient was started on letrozole and subsequently ribociclib, with clear improvements in clinical symptoms during the initial years of therapy, but this was followed by an acute worsening of cytopenias which prompted dose-reductions and eventual discontinuation of ribociclib. Due to a persistent worsening of her pancytopenia and concerns for peripheral blasts on her blood work, a bone marrow biopsy was performed which confirmed the diagnosis of IDH2+ AML. This case illustrates AML temporally associated with CDK4/6 inhibitor exposure in a patient with pre-existing CHIP. While CDK4/6i therapy works through G1 cell-cycle arrest, the long-term impact of this treatment on hematopoietic stem cells (HSCs) is unknown. This case raises important questions regarding this widely used therapy among patients with HR+BC and further studies are needed to investigate potential links between CDK4/6i and myeloid-derived malignancies.

Keywords: AML; breast cancer; CDK4/6 inhibitor; ribociclib; CHIP; acute myeloid leukemia

List of Abbreviations: AML: acute myeloid leukemia; HR+ BC: hormone receptor positive breast cancer; HSC: hematopoietic stem cells; CDK: cyclin-dependent kinase; CHIP: clonal hematopoiesis of indeterminate potential; IHC: immunohistochemistry

Introduction

Acute myeloid leukemia (AML) is a malignancy of myeloid-derived hematopoietic stem cells (HSC) characterized by the clonal expansion of immature myeloid blast cells. AML primarily affects older adults, with a median age at diagnosis in the United States of 68 years with a 5-year overall survival of 28%, which drops sharply with increasing age as patients older than 70 having 5% [1] [2]. The development of AML in patients treated with agents for breast cancer is a recognized but rare complication, primarily associated with cytotoxic chemotherapy agents such as anthracyclines and alkylating agents. AML related to alkylating agents typically occurs 5-7 years after exposure with a shorter latency period of 1-3 years associated with topoisomerase II inhibitors [3].

Multiple large center studies have demonstrated a statistically significant increased risk of developing AML following anthracycline chemotherapy in breast cancer patients. Regarding the anthracycline chemotherapy agents, one study conducted by Lee et al. demonstrated an increased risk of developing AML and myelodysplastic syndrome (MDS) with the use of anthracycline-based adjuvant therapy for early breast cancer patients. A cohort of 153,575 patients who underwent surgery for breast cancer was divided into 3 groups – anthracycline-based adjuvant therapy, non-anthracycline based adjuvant therapy, and no adjuvant chemotherapy. Their results showed that the risk of developing AML and MDS was highest in the group who received anthracycline-based adjuvant therapy compared to patients who did not receive adjuvant therapy (hazard ratio [HR] 9.531; $p < 0.0001$ for AML and HR 2.559 $p < 0.0001$ for MDS) while also having the highest 10-year cumulative incidence among the 3 groups (0.221% for AML and 0.199% for MDS) [4]. Additionally, a study in 2018 specifically assessed for the development of AML and MDS following adjuvant chemotherapy agents for patients with breast cancer (age ≥ 65 years, n = 92,110). Treatment groups consisted of anthracycline-based (A), taxane-based (T), anthracycline- and taxane- based (A+T), or cyclophosphamide, methotrexate, or 5-flurouracil (CMF). Notably, the A and A+T regimens were associated with an increased likelihood of developing AML (HR 1.70, 95% CI [1.16 – 2.50] (A) and HR 1.68, 95% CI [1.22 – 2.30] (A + T)) compared to patients who did not receive chemotherapy [5].

A pooled analysis of 9,679 women from 4 group trials also found a significantly increased risk of developing AML/MDS. 30 patients developed AML (0.3%) and 17 patients developed MDS (0.2%) with 83% of events occurring within 5 years of initiating the study. Multivariable Cox regression and competing risk models revealed an increased risk of developing AML or MDS after receiving anthracycline agents compared to patients who did not receive anthracycline agents (HR = 5.16, 95% CI 1.47-18.19). Notably, among women age ≥ 65, 0.8% developed AML or MDS compared with 0.4% for women age < 65 suggesting a correlation with increased age as well [6].

CDK4/6i such as, palbociclib, ribociclib, and abemaciclib, in combination with endocrine therapy have emerged as a standard of care for treating metastatic HR+BC. These agents selectively inhibit CDK4 and CDK6, preventing phosphorylation of the retinoblastoma (Rb) protein and consequently halting cells in the G1 phase of the cell cycle, preventing the progression to the S phase. Furthermore, the CDK6 gene has been found to be amplified in various lymphomas and leukemias as it serves as a critical regulator of transcription by interacting with transcription factors such as the signal transducer and activator of transcription (STAT) and activator protein (AP-1) family [7]. CDK6 has also been found to regulate vascular endothelial growth factor A (VEGF-A), a known tumor promotor. Unlike cytotoxic chemotherapeutic agents, CDK4/6i are selective agents that trigger growth arrest resulting in reversible effects on proliferating cells. In contrast, traditional cytotoxic therapy induces cell death via direct DNA damage or mitotic disruption and are associated with broader adverse effects as previously discussed.

The safety profile of CDK4/6i is favorable compared to cytotoxic chemotherapy with the most common adverse hematologic event being neutropenia. One study found that Grades 3-4 neutropenia comprised a majority of the adverse effects of palbociclib (66%) and ribociclib (60%), but was notably the second most reported adverse event for abemaciclib at 22% [8]. Importantly, medical literature on CDK4/6i therapy causing AML or MDS is limited in contrast to the established increased risk with anthracyclines and alkylating agents, though isolated reports of AML after CDK4/6i exposure do exist.

Materials and Methods

This case report was prepared using the CARE guidelines for case reporting. Clinical data was obtained through review of the patient's electronic medical record (EMR), including hospital admission records, clinic visits, imaging studies, and laboratory results. Diagnostic confirmation of metastatic HR-BC was based on histopathologic evaluation of breast biopsy specimens.

Next-generation sequencing (NGS) was performed on the bone biopsy specimen to assess for somatic mutations relevant to hematologic malignancies. Cytogenetic and molecular analyses at the time of AML diagnosis included karyotyping, polymerase chain reaction (PCR)–based assays for recurrent fusion transcripts, and targeted sequencing for IDH1/2 and FLT3 mutations.

Serial imaging studies were reviewed to assess disease response, and tumor markers (CA15-3, CEA) were monitored throughout the treatment course and shown in Figure 2. Hematologic parameters were tracked longitudinally from baseline through the onset of pancytopenia and leukemic transformation.

All patient identifiers were removed to maintain confidentiality. Institutional review board (IRB) approval was not required for this single-patient case report, as per institutional policy. This study was a non-interventional retrospective analysis and did not involve the application of experimental treatment involving humans or animal subjects.

Results

Case Presentation: We present a 77-year-old female patient who was diagnosed with recurrent stage IV HR+, HER2- breast cancer with metastases to the bone, lung and liver. Her medical history was significant for atrial fibrillation, hypertension, mitral valve replacement, and heart failure. She was diagnosed with breast cancer in 2014, but her treatment was delayed as she required open heart surgery for repair of her replaced mitral valve due to mitral stenosis. On January 2016, both breasts were biopsied. Her right breast biopsy showed grade 2 HR+ HER2-negative invasive lobular carcinoma with a Ki-67 of 19%. Her left breast biopsy showed intermediate grade HR+ ductal carcinoma in situ (DCIS). The following month, she underwent bilateral breast lumpectomies with positive DCIS margins and a right-sided sentinel lymph node biopsy with negative nodal findings. After her lumpectomies, she declined adjuvant radiation therapy and endocrine therapy at that time. The next time she was seen was in April 2023 when she presented to the emergency department with new neck pain radiating down both arms accompanied with weakness, numbness, and weight loss. A CT scan revealed extensive osseous metastases involving the axial and appendicular skeleton with pathologic fractures of the cervical, thoracic, and lumbar spine with cord impingement noted at C5-C7. At that time, a 2.2 cm mass was noted in the right breast. 6 days after her presentation to the ED, she received palliative radiation therapy to her cervical spine (C1-C7), as well as her lower thoracic spine (T7-T12) for a total of 20 Gy over 5 fractions. She later received additional radiation therapy dosed at 8 Gy in 1 fraction to her lower lumbosacral spine (L3-S4) on 6/23/2023, mid-thoracic spine (T3-T5) at 8 Gy in 1 fraction on 6/28/2023, and to her right hip in 8 Gy in 1 fraction on 7/27/2023. The following month after her visit to the emergency department, she underwent bilateral breast biopsies. The left breast biopsy revealed intermediate grade HR+ DCIS whereas her right breast biopsy showed grade 2 HR+ HER2-negative invasive lobular carcinoma with estrogen receptor (ER) expression of 100%, progesterone receptor (PR) expression of 80%, HER2 IHC of 1-2+, negative FISH testing (ratio 1.85, HER2 copy number 2.43), and a Ki-67 10%. Shortly after, she established care in our clinic on

5/26/2023. While waiting to undergo a bone biopsy, she had significant clinical deterioration due to cancer-related pain. To avoid rapid deterioration, letrozole therapy was initiated on 06/07/2023. She underwent a left iliac bone biopsy on 6/21/2023 which confirmed the presence of metastatic carcinoma of breast origin. Receptor testing showed ER 95%, PR 15%, HER2 IHC 2+, and negative HER2 FISH testing (ratio 1.0, HER2 copy number 2.3). She was started on her first course of bisphosphonate therapy via zoledronic acid on 07/05/2023. 10 days later, she was hospitalized due to acute on chronic heart failure with reduced ejection fraction (HFrEF) and atrial fibrillation with rapid ventricular response (RVR), after which she was started on digoxin (125 mcg), warfarin was discontinued, and she was discharged on 07/20/2023. Following her hospitalization, she was started on ribociclib (200mg daily) on 08/04/2023 while continuing her letrozole therapy. Her dose of ribociclib was increased to 400 mg daily for her 2nd cycle (09/01/2023), then 600 mg daily on 01/19/24 given continued tolerance. During this period, she switched from zoledronic acid to denosumab on 09/29/23 due to a persistent but stable decline in her glomerular filtration rate (GFR) below 50 since initiating therapy to avoid the risk for acute kidney injury. Repeat bone scan imaging on 11/15/23 showed increased sclerotic findings throughout the areas of prior lytic destruction within the bone, though CT imaging showed discordant evidence of mild progression. Short interval imaging was performed on 01/17/24 consistent with stable disease, as was subsequent imaging on 03/11/24, 07/17/24, and 10/01/24. Additionally, pre-treatment tumor biomarker testing on 07/26/23 showed a CA15-3 of 96.2 U/mL which normalized on 10/27/23 and remained normal from 12/20/23 onwards. CEA was also tested, but normal throughout her course. Clinical improvements to her cancer-related pain, fatigue, and mobility were also seen throughout this period of treatment initiation to the fall of 2024. Prior to treatment initiation, her platelet count was between 90-100 K/uL, her hemoglobin was 9-10 g/dL, her WBC count was 4.5-6 K/uL, and her ANC was 2.7-3.9 K/uL. After starting full dose ribociclib (600mg) on 01/19/24, lab work from 02/2024 to 07/2024 showed a platelet count of 91-112 K/uL, a hemoglobin of 11.4 to 12.5 g/dL, a WBC count of 2.3 to 3.0 k/uL, and an ANC of 1.4-1.9 K/uL.

On 09/13/24, ribociclib was dose reduced back down to 400 mg daily due to increased bruising and a low platelet count of 67 K/uL. Repeat testing on 10/23/24 showed a platelet count of now 34 K/uL. Ribociclib was held on 11/08/2024 for 1 week while continuing with letrozole, but her platelet count dropped to 1.9 K/uL, now with worsening anemia and leukopenia as well. A fluoroestradiol positron emission tomography (FES-PET) scan was ordered at this time and completed on 12/05/2024 but did not demonstrate clear tumor progression. Tumor biomarker testing via CA15-3 and CEA had also remained normal on 11/20/24. The results from her next generation sequencing (NGS) taken from her previous left iliac bone biopsy showed microsatellite stable disease, a low tumor burden (0 Muts/Mb), and mutations in PIK3CA (E545K), IDH2 (R140Q-subclonal), CDH1 (L343fs*6), & DNMT3A (G543C – subclonal). Due to the pathogenic mutation found in the PIK3CA gene, she was switched to capivasertib and fulvestrant on 12/06/2024 while still continuing with denosumab therapy. On 12/20/2024, her CBC with manual differentiation showed 55% blasts (1.65 K/uL absolute) and was therefore directly admitted to the acute leukemia service for additional work up and all therapy was held. Figure 1 shows a chronological mapping of our patient's CBC levels in relation to CDK4/6i therapy initiation. A bone marrow biopsy of her right posterior superior iliac crest was done on 12/23/2024 and an official diagnosis of acute myeloid leukemia was made at this time with a myeloid blast population of 63.2% and expression of CD13+, CD33+, CD117+, MPO+, and CD123+. Cytogenetic testing was normal and additional sequencing tests revealed a pathogenic IDH2 mutation (p.R140Q (c.419G>A), with negative FLT3 and IDH1 testing. Testing for PML-RARA fusion transcripts was also negative. Goals of care were discussed and given the unlikelihood of a favorable outcome with aggressive therapy, the patient opted for comfort care via home hospice. She passed away on 12/27/2024 as a result of her leukemia.

Figure 1A

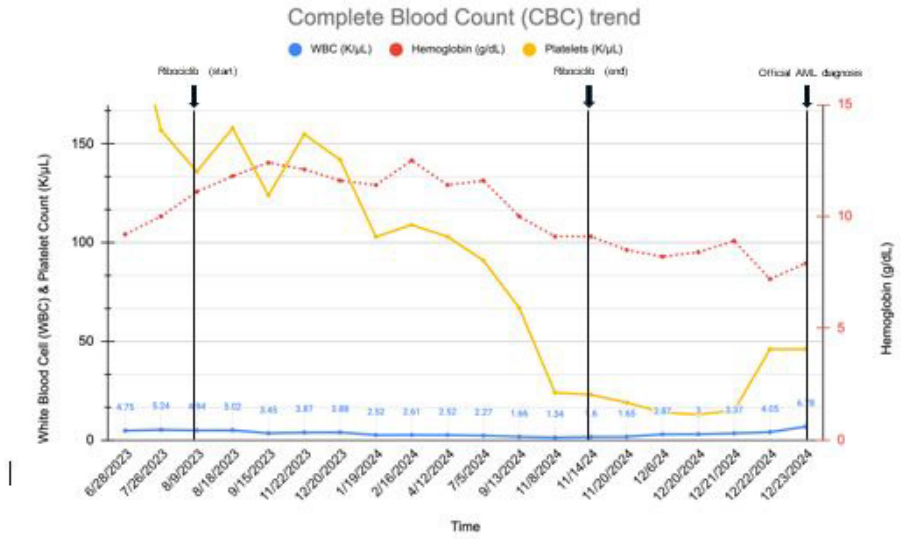

Figure 1B

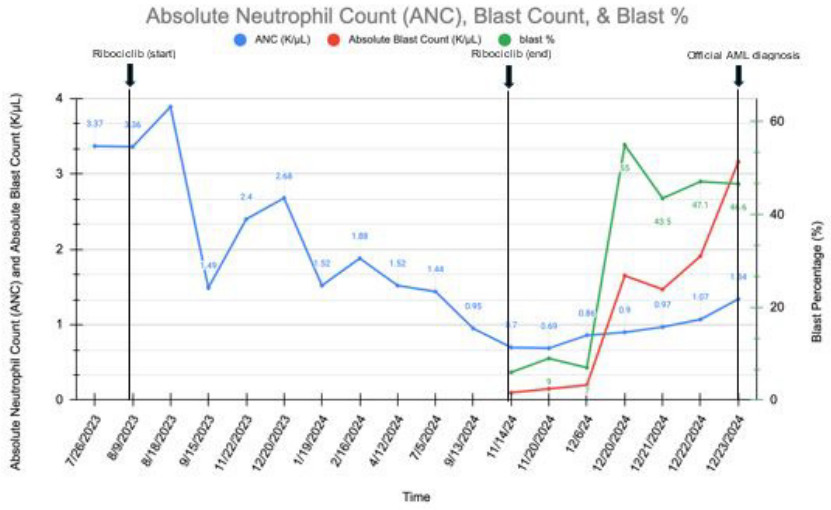

Figure 1: Complete Blood Count (CBC) trend (A) and Absolute Neutrophil Count (ANC), Blast Count, and Blast % (B) following ribociclib. The timing of initiating (8/04/2023) and stopping (11/08/2024) ribociclib as well as the diagnosis of AML (12/23/2024) are denoted by the vertical lines.

Discussion

Multiple phase 3 and phase 4 trials investigating the efficacy and safety profile of CDK4/6i therapy have been conducted. Notably, the results from the monarchE phase 3 trial in 2023 that studied the effectiveness of abemaciclib + endocrine therapy (ET) in HR+, HER2- early breast cancer and reported all treatment emergent adverse events (TEAEs) in both cohorts of patients who received abemaciclib + ET (n = 2791) and patients who received ET alone (n = 2800). The adverse events from the study with a focus on hematologic malignancies is summarized in Table 1.

Among the Grade 1/2 toxicities in the abemaciclib + ET group, there was 1 incidence of myelodysplastic syndrome along with 1 incidence of a Grade 1/2 toxicity reported in the ET group. For Grade 3 toxicities there were 2 cases of MDS reported in the

abemaciclib + ET group compared with 0 cases for Grade 3 toxicities in the ET group alone. For AML occurrences, only 1 case was reported as a Grade 3 toxicity in the abemaciclib + ET group. The study also tracked adverse events leading to death that occurred > 30 days from the study treatment discontinuation where 1 instance of MDS as such an event was noted [9]. Anand et al. reported a case of AML with eosinophilia (AML-M4Eo) occurring in a normal human subject without known cancer shortly after the initiation of a single dose of ribociclib followed by GCSF for the subsequent neutropenia [10]. While just a solitary case report, investigators took a closer look into the etiology of this AML developed due to concerns present that this CDK4/6 inhibitor accelerated leukemic transformation in a patient with otherwise no known malignancy risk but likely undiagnosed pre-existing clonal hematopoiesis of indeterminate potential (CHIP). Investigators performed Next Generation Sequencing which revealed STAG2 mutations in the cohesion complex and inversion 16 (p13.1q22). Cohesin is a tripartite ring that exists in humans as 2 paralogs of STAG2 and STAG1. These molecules are integral for chromosomal cohesion and regulate movement through the G1/S phase transition, as such, mutations in these cohesin complex genes were found in 10% of patients with primary AML and 20% in patients with secondary AML [11]. Researchers subsequently tried replicating these parameters in a mouse model in an attempt to validate a causal relationship between the initiation of ribociclib and development of AML. However, their mouse model with 1 mutation in the cohesin gene did not develop any leukemic transformations, though the sample size for both the control and intervention groups were small. Of note, researchers noticed a higher frequency of immature "blast" cells in the peripheral blood of the mice with the heterozygous mutation in the cohesin gene immediately following the CDK4/6i treatment, but these findings were not statistically significant. They ultimately hypothesized that the patient likely had a pre-existing CHIP due to this cohesin gene complex mutation and a "second hit" genetic event, likely inversion 16 (p13.1q22), resulted in leukemogenesis for this patient.

The above case ties directly to our own case report as our patient underwent Next Generation Sequencing prior to the initiation of ribociclib therapy through the use of a bone tumor specimen, which identified a sub-clonal IDH2 mutation (R140Q; 419G>A) and DNMT3A mutation (G543C; 1627G>T) – both frequently seen in CHIP [12] [13]. At the time of her AML diagnosis, a subsequent bone marrow biopsy revealed this same IDH2 mutation via pyrosequencing (R140Q; 419G>A). The presence of these mutations prior to CDK4/6i exposure is temporally aligned with CDK4/6i exposure, but whether the drug influenced clonal dynamics cannot be determined from a single case in the context of pre-existing CHIP. Alternative explanations warrant further consideration. For instance, in an older patient with documented CHIP (IDH2/DNMT3A) and baseline cytopenias, leukemic transformation could reflect age-related AML, CHIP-driven evolution independent of CDK4/6i therapy, or therapy-related AML (including previous radiation exposure) [14] [15] [16]. These pathways are well-described in older adults with CHIP and prior exposures, but a temporal association with CDK4/6i in our case does not establish causation. These findings highlight possible potential that pre-treatment molecular screening may have in allowing providers to screen for those at higher risk of CHIP-related progression to AML.

In contrast to their use in breast cancer, CDK4/6i have been investigated for their use as therapeutic agents in several genetically defined subtypes of AML. For instance, the t(8; 21) translocation is the most common cytogenic variant of AML and is associated with the mutation and resultant overexpression of CCND2, a gene that encodes cyclin D2. Cyclin D2 belongs to a family of D-type cyclins which form complexes with CDK4/6 to induce progression from G1 to S phase as previously described [17]. A preclinical trial conducted in 2021 examined the effect of CDK4/6 inhibition on t(8; 21) AML cells. Nakatani et al. found that the use of palbociclib and abemaciclib in combination with autophagy inhibitors such as chloroquine (CQ) or LY294002 significantly increased the rates of apoptosis of AML cells compared with treatment of abemaciclib alone (abemaciclib vs abemaciclib + CQ: $p = 0.0001$). It was demonstrated that CDK4/6i therapy in combination with autophagy inhibitors led to increased autophagosome formation, which strongly demonstrates a synergistic effect in inducing apoptosis for these cell lines in vitro [17].

FMS-like tyrosine kinase 3 (FTL3) is another overexpressed protein frequently found in AML. FLT3 is a type III receptor tyrosine kinase that has an important role in the regulation of HSC proliferation. Increased activity in CDK4/6 results in FTL3-acti-

vated proliferation, and upon treatment with palbociclib, human FLT3-internal tandem duplications (FTL3-ITD+) AML cell lines demonstrated sustained cell-cycle block. However, only a transient block was observed in the wild-type variant (FLT3) AML cells in vitro [18].

While CDK4 is often co-targeted with CDK6, the cellular mechanisms behind CDK6 alone have been studied extensively and its inhibition may serve as a new therapeutic target for specific subtypes of AML. As previously discussed, CDK4/6 inhibitors are traditionally used in HR+ metastatic breast cancer due to their ability to induce cell cycle arrest, however, the therapeutic relevance of CDK6 inhibition in AML extends beyond this antiproliferative effect. CDK6 has been shown to directly regulate the transcription of several oncogenic and HSC survival-promoting genes such as FLT3, MYC, BCL2, and VEGFA. This effect on oncogenes was particularly pronounced in several genetically defined subtypes of AML which included FLT3-ITD+ and mixed-lineage leukemia (MLL)-rearranged leukemias now renamed to Lysine-specific methyltransferase 2A (KMT2A) located on chromosome 11q23 [19].

Despite these promising findings, CDK6 is crucial for maintaining HSC quiescence, and its inhibition may lead to bone marrow suppression. This limits the therapeutic window of CDK6 inhibitors necessitating context-specific targeting to avoid bone marrow injury.

Importantly, the same transcriptional activity that makes CDK6 an attractive target may paradoxically increase the leukemogenic risk. CDK6 overexpression has been associated with transcriptional activation of FLT3 and MYC genes, both of which are implicated in the development of AML [7]. Theoretically, if CDK6 is inhibited, this could potentially disrupt regulatory feedback eliminating suppressive HSC populations and cause a compensatory expansion of pre-leukemic clonal cells. While there is no direct evidence of leukemogenic transformation due to CDK6 inhibition, there remains a delicate balance of CDK6's role in hematopoiesis due to its multifaceted role in numerous transcription and cell cycle pathways.

Conclusions

This case report and review of literature highlight the potential risk of secondary hematologic malignancy development following CDK4/6 inhibition, particularly among patients receiving therapy for breast cancer and for patients with underlying clonal hematopoiesis of indeterminate potential (CHIP). Given the increased utilization of CDK4/6i for the management of older breast cancer patients, further studies are needed to assess for the development of AML and other hematologic malignancies.

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