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CD4+ LYMPHOCYTOPENIA AND PNEUMOCYSTIS JIROVECII PNEUMONIA IN A METASTATIC BREAST CANCER PATIENT TREATED WITH PALBOCICLIB AND CORTICOSTEROIDS

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ABSTRACT

Background: Palbociclib, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor used to treat metastatic breast cancer, is known to cause myelotoxicity and primarily neutropenia, but its potential to induce severe lymphopenia and opportunistic infections is less understood.

Case description: A 61-year-old woman with metastatic breast cancer treated with palbociclib and corticosteroids was admitted with fever and general weakness. Chest radiography and computed tomography showed bilateral consolidation. She was diagnosed with severe cellular immunodeficiency, very low CD4+ T cell count and several opportunistic infections including Pneumocystis jirovecii pneumonia (PCP).

Conclusion: This case underscores the need for monitoring lymphocyte counts in patients on CDK4/6 inhibitors, particularly those on concomitant corticosteroid therapy. and considering the risk for opportunistic infections in relevant patients.

KEYWORDS

Palbociclib, CDK4/6 inhibitor, immunosuppression, opportunistic infections, PCP

LEARNING POINTS

- Palbociclib, a CDK4/6 inhibitor, may be associated with severe immunosuppression and low CD4+ T cell count.
- There may a greater risk for patients with additional risk factors such as concomitant corticosteroid therapy.
- Significant opportunistic infections such as Pneumocystis jirovecii pneumonia should be considered in clinically relevant patients.
- Safety measures should be taken such as blood count monitoring and even consideration of an antibiotic prophylaxis in relevant patients.

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INTRODUCTION/BACKGROUND

Palbociclib is an oral small molecule inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that has been approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer in combination with endocrine therapies. This subtype represents the most prevalent form of metastatic breast cancer[1-4].

CDKs are a family of proteins crucial for the regulation of cell cycle progression, with the cyclin D-CDK4/6-retinoblastoma (Rb) pathway being particularly significant. Dysregulation of this pathway is implicated in various malignancies, including metastatic breast cancer[4]. Palbociclib in conjunction with endocrine therapy (either letrozole or fulvestrant) was evaluated in the PALOMA-1, PALOMA-2 and PALOMA-3 clinical trials[1,2,5] showed longer progression-free survival compared to endocrine therapy alone, although myelotoxicity was higher. Other CDK4/6 inhibitors currently available include abemaciclib and ribociclib[4,6].

Frequently observed adverse events associated with palbociclib include neutropenia, leukopenia, nausea, fatigue, stomatitis and diarrhoea[3,4]. Pulmonary toxicity is uncommon, however interstitial lung disease has been recognised as a rare but severe adverse event associated with CDK4/6 inhibitors, with an incidence of all-grade toxicity of 1.6%[7,8]. While complete blood count monitoring is recommended during treatment, lymphopenia and opportunistic infections are not typically associated with CDK4/6 inhibitors.

CASE DESCRIPTION

A 61-year-old woman was admitted to the internal medicine department following three days of generalised weakness, confusion and diarrhoea from her ileostomy. Her past medical history included heart failure with reduced ejection fraction, chronic kidney disease, diabetes mellitus and a prior total colectomy due to pseudo-obstruction. Her regular medications included aspirin, clopidogrel, candesartan, dapagliflozin, metformin, ezetimibe, rosuvastatin and insulin (both long- and short-acting).

Her oncologic history included mucinous luminal right-sided breast cancer ER 100% PR 2–3% HER2 0, diagnosed in 2000, for which she underwent neoadjuvant chemotherapy followed by mastectomy, axillary lymph node dissection, post-mastectomy radiation therapy and adjuvant endocrine therapy (tamoxifen). In 2017 she was diagnosed with a luminal left-sided breast cancer, for which she underwent left lumpectomy and intraoperative radiotherapy, and completed five years of adjuvant endocrine therapy (letrozole). In 2024, two months prior to hospitalisation, she experienced a metastatic recurrence of her disease with painful osteolytic spinal metastases associated with impending dorsal spinal cord compression. She underwent urgent palliative radiation therapy to D5–D6 (30 Gray in 10 fractions) and received corticosteroids (dexamethasone 10 mg once daily for one month, then tapering over another month).

One month after the diagnosis of recurrence, she initiated treatment with palbociclib and letrozole. She received the standard dose of palbociclib (125 mg once a day for three weeks followed by a week off treatment).

Following her first course of therapy, the patient was hospitalised; she finished steroid therapy a week before she was hospitalised. Upon admission she was afebrile, vital signs were BP 104/60, pulse 104 BPM and O_2 saturation was 94% in room air. A physical examination revealed no significant findings. Laboratory results revealed elevated C-reactive protein (CRP) levels (105 mg/l), leukopenia (1.74 $\times 10^3$/µl) with lymphopenia (0.38 $\times 10^3$/µl) and mild neutropenia (1.16 $\times 10^3$/µl), acute-on-chronic kidney disease and elevated lactate dehydrogenase levels. Blood and stool cultures, polymerase chain reaction (PCR) for respiratory viruses and for West Nile virus, performed due to a concurrent outbreak in Israel)[9], were negative. Chest X-ray showed bilateral consolidations, predominantly in the right lung. Palbociclib was withheld and letrozole was continued. One day into her hospitalisation, her fever rose to 39.4°C. Due to the radiological and clinical findings, we initially treated her empirically for community-acquired pneumonia with ceftriaxone (1 g daily for five days) and azithromycin (500 mg daily for three days), alongside intravenous fluids due to pre-renal azotaemia. Despite antibiotic therapy, she remained febrile and dependent on nasal oxygen supplementation with persistently elevated CRP levels (up to 230 mg/l). A repeat physical examination revealed bilateral pulmonary crackles (with a little right predominance), oral thrush and a new herpetic lesion that had developed over her naso-labial fold during hospitalisation.

Further investigations for opportunistic infections included additional blood (aerobic, anaerobic, fungal) and stool cultures, urinary Legionella pneumophila antigen and serum galactomannan, all of which were negative. Serum cytomegalovirus (CMV) PCR was borderline positive (1,000 copies), and serum herpes simplex viruses PCR was negative. Given the very low level of CMV viraemia – and the low likelihood that this was the cause of the symptoms – in consultation with an infectious diseases specialist, we did not administer anti-viral therapy. A chest-abdomen-pelvis CT scan revealed bilateral ground-glass opacities, with no additional findings outside the lungs *(Fig. 1)*.

Given the patient's iodine allergy, she received pre-medication with prednisone (three doses of 40 mg) prior to the CT scan. In the subsequent days, clinical improvement was noted and the patient became afebrile. This raised the suspicion of interstitial or inflammatory pneumonitis, rather than an infectious aetiology. Due to the patient's history, we suspected a lung disease related to palbociclib[6,7,10], although such an adverse effect typically occurs later in treatment. Given her response to steroids, we continued the prednisone regimen of 40 mg once daily.

However, following an additional two days of prednisone 40 mg, the patient experienced a recurrence of fever and worsening dyspnoea. Due to the unique pulmonary findings

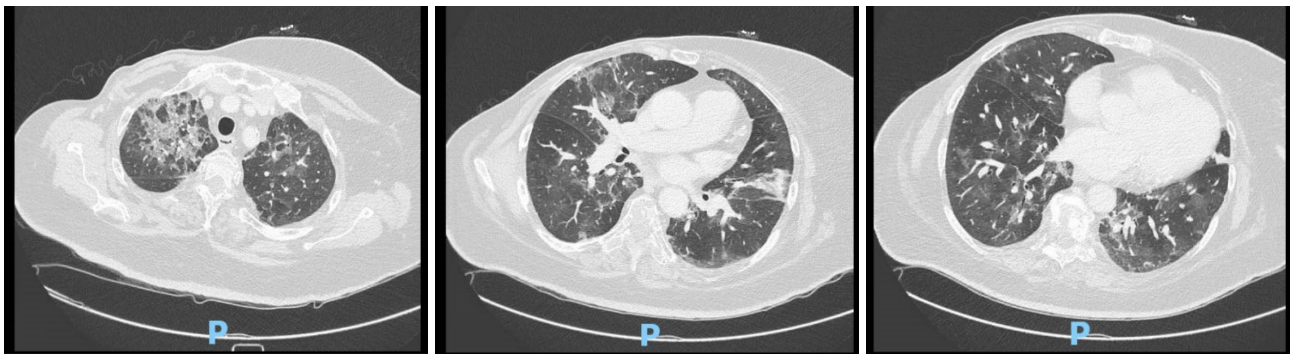


Figure 1. Axial chest CT scan at different planes showing diffuse bilateral consolidations. Abbreviations: P, posterior.

and her immunosuppressed state, a bronchoscopy with bronchoalveolar lavage was performed. Bronchoalveolar cultures and PCR for respiratory viruses, galactomannan, mycobacteria and PCR for Pneumocystis jirovecii pneumonia (PCP) were conducted. Initial results showed herpes simplex viruses 1 positivity; however, a more clinically significant result revealed a positive PCR test for PCP (cycle threshold value 28.6).

The diagnosis of PCP was established based on the patient's cellular immunodeficiency, inflammatory markers, increased lactate dehydrogenase levels, bilateral ground-glass consolidations on imaging and microbiological confirmation. Because of her significant cellular immunodeficiency, lymphopenia and multiple opportunistic infections – including PCP, CMV viremia, a naso-labial herpetic infection and oral thrush – we performed a lymphocytic immunophenotyping, revealing severe decrease in CD4+ T cells (53 cell/mm^3). Testing for the human immunodeficiency virus (HIV) was negative.

The patient was diagnosed with severe cellular immunodeficiency, most probably secondary to palbociclib combined with steroid therapy. We initiated treatment with trimethoprim-sulfamethoxazole at a therapeutic dose (trimethoprim 160 mg and sulfamethoxazole 800 mg, two pills, three times daily) for three weeks, and then at a preventive dose (trimethoprim 160 mg and sulfamethoxazole 800 mg, one pill, three times a week). Concomitantly, she received prednisone over three weeks (followed by tapering), resulting in clinical improvement. She was discharged in a stable condition, the weakness and dyspnoea improved, she was haemodynamically stable and afebrile, and required only minimal nasal oxygen supplementation.

At a follow-up visit in the oncology clinic 40 days post-discharge, the patient reported significant clinical improvement and a reduced need for oxygen supplementation.

Figure 2 demonstrates lymphocyte count trends over time, correlated with important clinical events. The patient presented with a low-normal lymphocyte count upon the diagnosis of metastatic breast cancer. Her lymphocyte count dropped after initiation of systemic steroid therapy and further decreased following the initiation of palbociclib. During the hospitalisation and after palbociclib was withheld, lymphocyte levels were still low with nadir several days after admission. A few days later, we diagnosed the opportunistic infections and started antibiotics and also started to witness recovery with continue of recovery post-discharge. A CD4+ T cell count three months after discharge was higher (256 cell/mm^3).

DISCUSSION

We present a case of severe cellular immunodeficiency, a markedly low CD4+ T cells count and PCP with multiple additional concomitant opportunistic infections in a patient with metastatic breast cancer treated with palbociclib.

Pneumocystis jirovecii is an opportunistic fungal pathogen responsible for aggressive and potentially life-threatening pneumonia, generally affecting

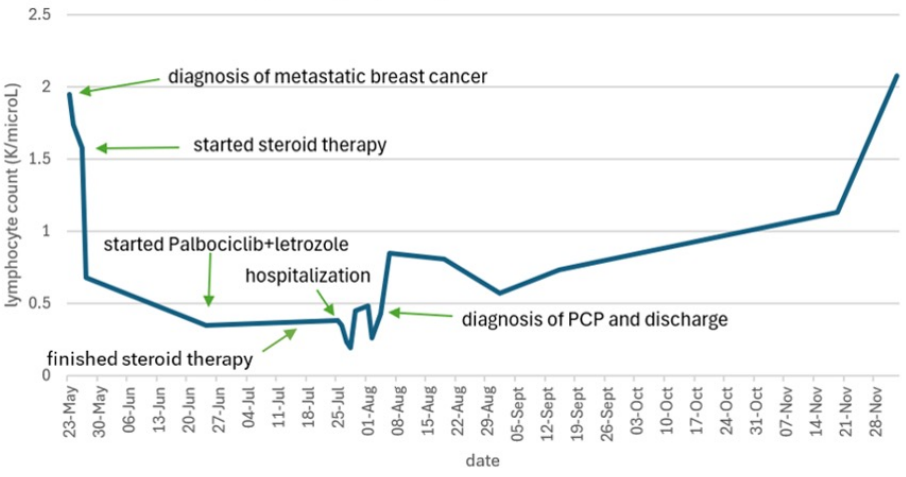


Figure 2. Lymphocyte count trend over time, correlated with important clinical events.

immunocompromised patients, such as those living with HIV, post organ transplantation or malignancies, or receiving immunosuppressive therapies, including corticosteroids[11].

There are several guidelines regarding the recommended antibiotic prophylaxis against *Pneumocystis jirovecii* pneumonia in immunocompromised patients. In patients living with HIV, prophylaxis is recommended based on CD4+ T cell count (below 200/µl). In non-HIV patients, prophylaxis is recommended by the Infectious Diseases Society of America (IDSA) and the European Alliance of Associations for Rheumatology (EULAR) for immunocompromised patients. These include patients with haematologic malignancies, recipients of solid organ or haematopoietic stem cell transplants, and those receiving prolonged high-dose corticosteroids (≥20 mg prednisone equivalent daily for ≥1 month), especially when there is additional cause for immunodeficiency such as underlying malignancy for additional immunosuppressive therapy[12-14]. Trimethoprim-sulfamethoxazole is recommended as the first-line prophylactic therapy. Alternatives are atovaquone, dapsone or aerosolised pentamidine. Duration of prophylaxis varies based on the duration of the immunosuppressive state and the different indication for prophylaxis.

In our case, PCP may have been triggered by lymphopenia (and specifically the low CD4+ T cell count) promoted by palbociclib and corticosteroid therapies. The patient's susceptibility to opportunistic infections may have been exacerbated by prolonged steroid therapy prior to her admission, known to induce immunosuppression (including lymphopenia), and is well known as a major risk factor for PCP. We note that the lymphocyte count decreased when the patient was on steroid therapy alone – before the administration of palbociclib – and continued to drop afterwards. Other risk factors that may have contributed to the patient's status are her metastatic disease and recent radiotherapy. Guillaume et al. reported a similar case in France in 2020[15], and while neutropenia is a frequently reported adverse event associated with palbociclib, typically occurring during the initial cycles of treatment[1,2,4], lymphopenia is less mentioned and there are no clear guidelines or consensus regarding the recommended monitoring.

Other haematologic adverse events include anaemia and thrombocytopenia. Non-haematologic adverse effects are primarily gastrointestinal (e.g. nausea, vomiting, diarrhoea, constipation) and general symptoms (e.g. fatigue, headache). Notably, our patient exhibited malaise and watery diarrhoea prior to the onset of respiratory symptoms, potentially attributable to palbociclib.

It is also important to note that this immunosuppression state occurred within the patient's first cycle of palbociclib. Although prior CD4+ T cell counts were unavailable, a review of the patient's medical records revealed a normal to low lymphocyte count, which decreased to a nadir of 0.19 $\times 10^3$/µl during hospitalisation and subsequently increased following discharge.

This case highlights the importance of lymphocyte count monitoring in addition to neutrophil counts in patients on CDK4/6 inhibitor therapy. Patients with additional risk factors (such as concomitant corticosteroid therapy) may have greater risk for opportunistic infections and CD4+ T cell count monitoring may also be appropriate. There may be appropriate to consider prophylactic antimicrobial treatment (e.g. trimethoprim-sulfamethoxazole for PCP) in patients with severe lymphopenia and those undergoing steroid therapy. However, further data is needed to substantiate this recommendation.

As this is a rare incidence, there is no data regarding the long-term prognosis for patients who develop immunodeficiency as a result of the treatment. Additionally, it is unclear if this should be considered a class-related toxicity, and specifically whether alternative CDK4/6 inhibitors, such as abemaciclib – associated with relatively less myelotoxicity – would cause similar lymphopenia in these patients. Future research should address these gaps.

Ongoing studies are exploring novel CDK inhibitors and expanding their use to treat various types of breast cancer and other malignancies[4]. As the use of CDK inhibitors becomes more prevalent, including in the adjuvant setting, it is crucial to maintain vigilance regarding potential severe adverse effects, including immunodeficiency and opportunistic infections.

CONCLUSION

Palbociclib, a CDK4/6 inhibitor, may be associated with severe cellular immunosuppression with low CD4+ T cell counts, increasing the risk for opportunistic infections such as Pneumocystis jirovecii pneumonia (PCP). Corticosteroid treatment can further increase this risk. Clinicians should consider these risks in patients presenting with opportunistic infections while on CDK4/6 inhibitors. Furthermore, concomitant long-term corticosteroid treatment should be avoided as much as possible and complete blood count monitoring (especially for lymphopenia and CD4+ T cells depletion) may be advised for high-risk patients.

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