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Case Report

Severe Cellular Immunodeficiency Triggered by the CDK4/6 Inhibitor Palbociclib

Zoé Guillaume,[1] Jacques Medioni,[1,2] Agnes Lillo-Lelouet,[3] Grégoire Marret,[1,2] Stéphane Oudard,[1,2] Audrey Simonaggio[1,2]

Clinical Practice Points

- Although it is a rare outcome, palbociclib can induce severe lymphopenia and severe cellular immunodeficiency, leading to life-threatening opportunistic infections.
- We strongly recommend a close monitoring of lymphocytes for patients receiving palbociclib and a primary pneumocystis prevention for those with a lymphopenia count less than 500/mm^3 and T4 lymphocytes less than 200/mm^3.

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Introduction

Breast cancer (BC) represents the most common malignancy and the second leading cause of cancer related-death worldwide. Almost two-thirds of BCs are estrogen receptor-positive (ER^+)/human epidermal growth factor receptor 2-negative ($HER2^-$). $ER^+/HER2^-$ BCs have been offered exciting advances with the development of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), leading to major shifts in the treatment landscape.

A combination of endocrine therapy and CDK4/6 inhibitor is now considered the mainstay treatment for pre- and postmenopausal patients with metastatic $ER^+/HER2^-$ BC. Neutropenia is the most common grade 3/4 adverse event observed in clinical trials involving CDK4/6 inhibitors, with a frequency of 66.5% and 62%, respectively, in PALOMA 2 and PALOMA 3.[1,2] Guidelines have been published to manage this adverse event with dose reduction.[3] In the case of isolated lymphopenia without any concomitant opportunistic infection, no specific monitoring or dose reduction is currently recommended.

Case Report

A 72-year-old female, receiving the CDK4/6 inhibitor palbociclib in combination with exemestane for a metastatic $ER^+/HER2^-$ breast cancer, was admitted to the emergency department because of acute dyspnea in the setting of severe cellular immunodeficiency.

Metastatic relapse had occurred in 2011. The patient received first-line chemotherapy with taxanes-chemotherapy in combination with bevacizumab, and then consecutive hormone therapies from February 2012 to January 2019. A symptomatic peritoneal tumor progression occurred in January 2019. Palbociclib 125 mg per day was then administered orally in 4-week cycles (3 weeks of treatment followed by 1 week off) concomitantly with exemestane 25 mg per day.

In May 2019, an intestinal obstruction occurred as a result of peritoneal disease. Both computed tomography (CT) scan and cancer antigen 15-3 were stable, with no argument for progressive disease. Corticosteroid therapy (prednisolone) was started in May 2019, as a result of the management of these intercurrent events. Grade 3 neutropenia was also reported. According to the palbociclib-induced neutropenia management guidelines, the dosage of palbociclib was adjusted from 125 mg to 100 mg per day, without disease progression on the July CT scan.

In August 2019, the patient was admitted to the emergency department for hypercalcemia, fever, and deterioration of general status. Patient was treated with intravenous bisphosphonates for hypercalcemia, and she was diagnosed with obstructive pyelonephritis as a result of double J-catheter impairment. Bacteriological investigation showed colonization with *Enterococcus faecalis* and *Klebsiella oxytoca*, leading to beta-lactam antibiotics (piperacilline/tazobactam) for 7 days, together with ureteral stents replacement.

The patient remained persistently febrile, with acute respiratory symptoms (coughing, phlegm, and dyspnea). Urine antigen tests for

[1]Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris, France
[2]University Paris Descartes Paris 5, Sorbonne Paris Cite, Paris, France
[3]Pharmacovigilance Department, Hôpital Européen Georges Pompidou, Paris, France

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Address for correspondence: Audrey Simonaggio, MD, Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris, France
E-mail contact: audrey.simonaggio@aphp.fr

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the diagnosis of respiratory infections (namely, legionellosis and pneumococcal pneumonia) were negative, as well as blood culture reports. Both chest x-ray and CT scan were performed, which showed acute diffuse interstitial pneumonia (Figure 1). On the basis of non-invasive bronchial wash cytology of lung lesions, bacterial and viral infections (including polymerase chain reaction [PCR] assays for influenza virus, coronavirus, rhinovirus, enterovirus, metapneumovirus, bocavirus, adenovirus, and parainfluenza virus) were excluded. Interestingly, the *pneumocystis*-specific PCR was positive, as well as detection of the fungal β-D-Glucan antigen. Another commonly encountered fungal agent *Aspergillus niger* was detected. Reactivation of multiple latent viruses was documented by PCR for herpes simplex virus, Epstein-Barr virus, and cytomegalovirus as well. Viral cytomegalovirus level was mildly elevated in bronchial washing fluid and plasma, respectively. Associated with those results, grade 3 lymphopenia was observed. After close observation, we found that decreased lymphocyte count over time was as follows: 1.3 G/L on January 16th, 1.2 G/L in February, 0.8 G/L in April, and less than 0.5 G/L in May (Figure 2). Immunophenotyping of peripheral T-lymphocytes recorded a reduction in absolute number of CD4+ T cells less than 200/mm^3, consistent with palbociclib-induced bone marrow suppression. Of note, the patient's human immunodeficiency virus test was negative.

The patient was started on high-dose sulfamethoxazole and trimethoprim (SMX-TMP) in an equivalent of TMP 15 to 20 mg/kg/day and SMX 75 to 100 mg/kg/day plus high-dose steroid therapy with prednisone 1 mg/kg equivalent per day with no improvement in the infection and further respiratory deterioration. Because of the treatment failure of pneumocystis pneumonia and the severe deterioration of her general status and after agreement of the patient, best supportive care was initiated until her death was recorded a few days later.

Pneumocystis pneumonia is a life-threatening opportunistic pulmonary fungal infection among immunocompromised patients. Some important factors, such as adjunctive steroids and immunomodulatory agents, in addition with the uncontrolled breast cancer, may underlie immunodeficiency disorders in non-human immunodeficiency virus-infected patients. As a result, treatment-related grade III lymphopenia (lymphocyte range between 0.45 and 0.20 G/L) was diagnosed in May 2019 with concomitant palbociclib and exemestane treatments. Prednisolone was initiated in May 2019 in doses of 40 mg/day and was given for 5 days and tapered in doses of 20 mg/day long-term.

In this case, causality assessment of *pneumocystis* pneumonia by palbociclib was supported by the temporality: progressive leucopenia associated with an unexpected lymphopenia, worsening during the palbociclib course, finally associated with an opportunistic infection. The patient had no risk factors for infectious complication, but co-prescription of corticosteroids could affect susceptibility to opportunistic infections.

Discussion

We report a case of fatal *pneumocystis* pneumonia involving a 72-year-old female with metastatic ER$^+$/HER2$^-$ BC and receiving palbociclib 125 mg per day concomitantly with exemestane 25 mg per day. This patient experienced a decreased lymphocyte count over time from 1.3 G/L in January 2019 (at the time of palbociclib-exemestane initiation) to less than 0.5 G/L in May 2019. The severe cellular immunodeficiency has led to the reactivation of multiple latent viruses and to the occurrence of *pneumocystis* pneumonia. We believe that grade 3 lymphopenia could have been triggered by the CDK4/6 inhibitor palbociclib.

Generation and analysis of cyclin D3-deficient mice showed that cyclin D3 −/− animals fail to undergo normal expansion of immature T lymphocytes. In the absence of cyclin D3, the normally assembled pre-TCR fails to drive expansion of immature thymocytes.[4,5] As a cofactor of cyclin D, CDK4/6 are required for this expansion. Thus, CDK4/6 inhibitors can impair it, leading to severe lymphopenia. This could be observed in the phase I and II PALOMA clinical trials, with, respectively, 36% and 30% of grade 3/4 lymphopenia.[6,7] Surprisingly, no grade 3/4 lymphopenia were documented in the phase III PALOMA clinical trial.[2,7-9]

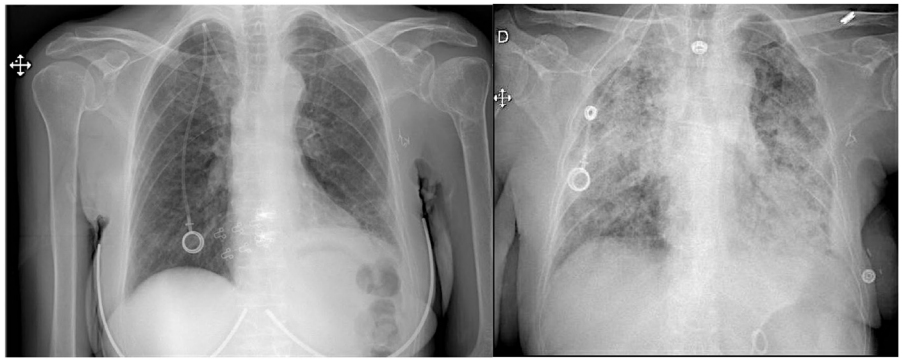
In our presentation, the patient experienced a severe and fatal immunodeficiency characterized by an extended grade 3 lymphopenia, according to the Common Terminology Criteria for Adverse Events v5.0, which was concomitant to the palbociclib and exemestane administration. This has led to the reactivation of viral infections: herpes simplex virus, varicella-zoster virus, Aleution disease virus, and Epstein-Barr virus, and to the occurrence of *pneumocystis* pneumonia.

According to our pharmacovigilance department, no similar case was found in their bibliographic sources (product information, Martindale, Pubmed); therefore, lymphopenia and opportunistic infection should be considered as an unexpected adverse effect of palbociclib. The pharmacovigilance unit run the VigiBase, the World Health Organization global database of individual case safety reports in September 2019. It contains reports from multiple sources, countries, and reporters, and the strength of causality is variable. Nevertheless, we found 30 cases of lymphopenia associated with palbociclib. Most (18/30) cases were part of an observational study, and no infection was associated. The remaining 12 cases were spontaneous reports from Europe (n = 8) and North America (n = 4). In 2 cases, the lymphopenia was associated with herpes zoster infection and in 1 case with influenza.

We have shown that lymphopenia could be owing to the CDK4/6 inhibitor palbociclib. In fact, we have no argument for a bone marrow involvement because leukocyte and platelet counts were normal. Grade 2 anemia was observed but was most probably induced by multifactorial causes including palbociclib toxicity, sepsis, vitamin deficiencies, and inflammation. Moreover, lymphopenia had occurred as soon as April 2019, long before the sepsis. It should be mentioned that exemestane can induce mild lymphopenia, but lymphocyte counts remained stable over time, and no grade 3/4 lymphopenia have been reported. Co-prescriptions included lansoprazole, prednisolone, nefopam, paracetamol, levothyroxine, and denosumab. None of these treatment is known to induce lymphopenia. Prednisolone in doses of 20 mg/day may have contributed to the opportunistic pulmonary fungal infection, through its immunosuppressive properties.

Although the management of palbociclib-induced neutropenia has been well-documented, the management of palbociclib-induced lymphopenia is more undefined. No close monitoring nor dose adaptation are required until opportunistic infection appears.

Figure 1 Chest x-ray Between August 3, 2019 and August 18, 2019

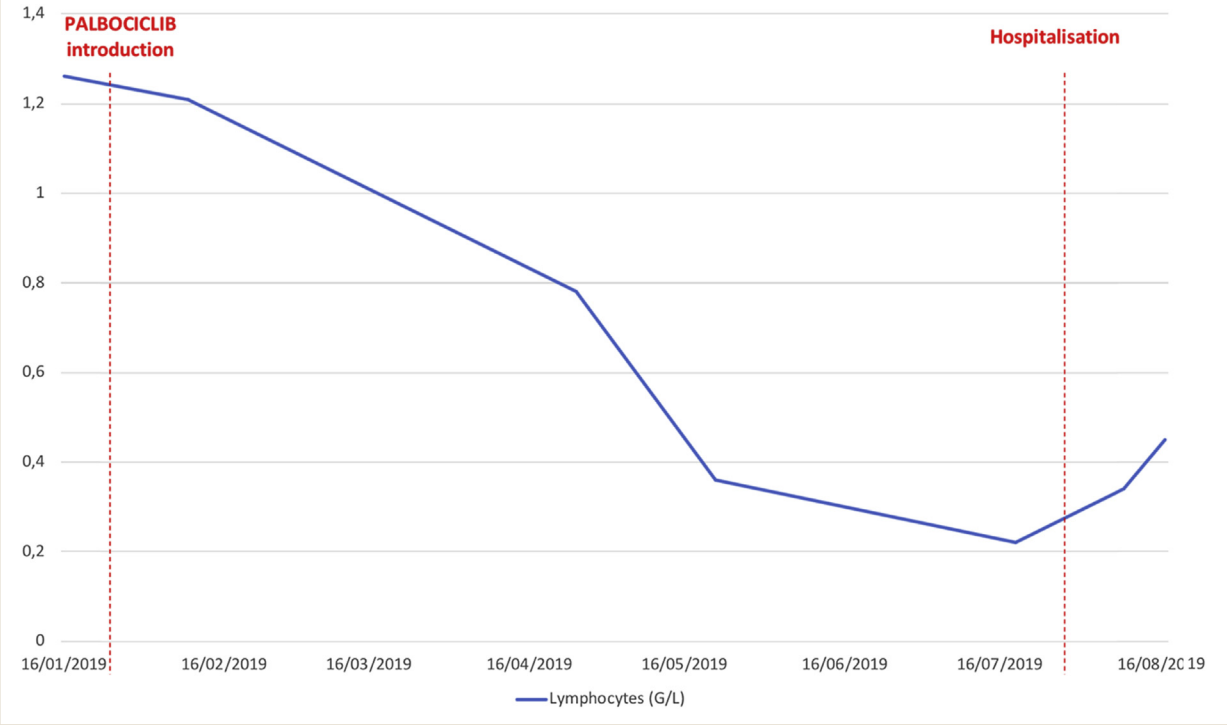


We have shown that lymphocyte counts should be carefully monitored and that severe lymphopenia (lymphocyte counts $< 500/mm^3 \pm$ T4 lymphocytes $< 200/mm^3$) could result in the prescription of a primary *pneumocystosis* prevention, like acquired immunodeficiency syndrome or organ-transplant patients' recommendations. Special attention should be given to patients receiving corticosteroids (prednisone, $\geq$ 20 mg equivalent for more than 1 month), which is a common situation in solid oncology to manage symptoms related to progressive disease (peritoneal carcinosis, pain, lymphangitis, etc). It should be mentioned that no drug interaction had been observed between SMX-TMP and palbociclib. Palbociclib is metabolized by CYP3A4 and SULT2A1, whereas SMX and TMP are selective inhibitors of CYP2C9, CYP2C8, and OCT2. Co-administration of these 2 drugs appears safe.[10]

Conclusion

As observed in the phase I and III PALOMA clinical trials, the CDK4/6 inhibitor palbociclib can induce severe lymphopenia and severe cellular immunodeficiency characterized by a low T4 lymphocyte count $< 200/mm^3$, leading to opportunistic infections. Primary *pneumocystis* pneumonia prevention should systematically be discussed for patients with a lymphopenia count

Figure 2 Lymphocyte Count During the Last 8 Months



less than 500/mm^3 and T4 lymphocytes less than 200/mm^3, and should be discussed for all patients receiving corticosteroids including prednisolone $\geq$ 20 mg equivalent for more than 1 month. We strongly recommend a close monitoring of lymphocytes for patients receiving palbociclib.

Disclosure

The authors have stated that they have no conflicts of interest.

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