

# New Drugs, Old Toxicities: Pneumonitis Related to Palbociclib – A Case Report

Eudald Felip<sup>a, b, h</sup> Laia Llobera<sup>b</sup> Clara Perez-Mañá<sup>c, d</sup> David Quintela<sup>e</sup> Ignacio Guasch<sup>f</sup>  
Mireia Margelí<sup>a, b</sup> Iris Teruel<sup>a, b</sup> Beatriz Cirauqui<sup>a, b</sup> Carmen Centeno<sup>g</sup> Margarita Romeo<sup>a, b</sup>  
Ester Ballana<sup>h</sup> Vanesa Quiroga<sup>a</sup>

<sup>a</sup>Badalona Applied Research Group in Oncology (B-ARGO Group), Oncology Department, Catalan Institute of Oncology, Badalona, Spain; <sup>b</sup>Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; <sup>c</sup>Clinical Pharmacology Unit, Hospital Germans Trias i Pujol, Badalona, Spain, Badalona, Spain; <sup>d</sup>Department of Pharmacology, Therapeutics and Toxicology, Autonomous University of Barcelona, Cerdanyola del Vallès, Spain; <sup>e</sup>Department of Clinical Hematology, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; <sup>f</sup>Radiology Department, Hospital Germans Trias i Pujol, Badalona, Spain; <sup>g</sup>Pulmonology Department, Hospital Germans Trias i Pujol, Badalona, Spain; <sup>h</sup>AIDS Research Institute-IrsiCaixa and Health Research Institute Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, Badalona, Spain

## Established Facts

- Cyclin-dependent kinase 4/6 inhibitors such as palbociclib have already been approved in metastatic breast cancer patients.
- The median progression-free survival is about 24 months in the first-line treatment in metastatic breast cancer patients.
- Neutropenia G3 was seen in about 80% of the patients, mostly asymptomatic without any infection symptomatology.
- Lung toxicity such as drug-related pneumonitis has been described in other cancer drugs in metastatic breast cancer patients.
- Pivotal trials and drug information of palbociclib do not inform about pneumonitis related to palbociclib.

## Novel Insights

- Pneumonitis is an acute, life-threatening toxicity.
- Pneumonitis related to palbociclib is not well documented in the literature and may lead to underdiagnosis.
- Other possible causes, such as infection, pulmonary thromboembolism, and cardiac dysfunction, have to be discarded before the diagnosis.
- The mechanism of toxicity is still not known, but it is reversible by stopping CDK 4/6 inhibitor treatment and initiate corticotherapy.
- Multidisciplinary approach is needed to conclude the final diagnosis.

## Keywords

Case report · Palbociclib · Pneumonitis · Drug-related pneumonitis · Lung toxicity

## Abstract

**Background:** Palbociclib is a specific inhibitor of cyclin-dependent kinases 4 and 6 that is approved for the treatment of advanced or metastatic breast cancer patients. Despite a good toxicity profile in pivotal trials, where asymptomatic

neutropenia was the main adverse effect, its wider use in clinical practice may show less prevalent but serious toxicities. **Case Presentation:** Here, we describe a case of pneumonitis due to palbociclib. A 57-year-old female with breast cancer with bone metastasis presented dyspnea at rest 3 months after beginning treatment with palbociclib and letrozole. Palbociclib-induced pneumonitis was considered the most probable cause after ruling out all alternatives, and the patient was successfully treated with steroids and showed complete remission. **Conclusions:** In summary, we present a well-documented case report of pneumonitis related to palbociclib. However, the mechanism of toxicity is still unknown, and there are as yet no reliable biomarkers to predict toxicity with cyclin-dependent kinase 4/6 inhibitors. In this case report, we alert physicians about new drugs that can provoke old toxicities.

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## Background

Palbociclib is a highly specific inhibitor of cyclin-dependent kinases (CDK) 4 and 6. CDK are a large family of serine-threonine kinases involved in the regulation of cell-cycle progression [1]. Cyclin D binds both CDK4 and CDK6 and induces hyperphosphorylation of the retinoblastoma protein, causing progression of tumor cells by promoting the transcription factor E2F that regulates progression from the G1 to the S phase. Both CDK4 and CDK6 are thus key regulators of cell division, and their inhibition controls cell growth and suppresses tumor activity [2]. Palbociclib has been approved for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (*HER2*)-negative, advanced, or metastatic breast cancer in combination with either an aromatase inhibitor as initial hormonal therapy in postmenopausal women or fulvestrant in women with disease progression following hormonal therapy [3].

Two pivotal phase III randomized trials [4, 5] have shown a benefit in progression-free survival (PFS) for palbociclib plus hormonal therapy. The PALOMA-2 randomized patients in a 2:1 ratio to receive either palbociclib-letrozole or placebo-letrozole. The median PFS was 24.8 months in the palbociclib-letrozole arm, compared to 14.5 months in the placebo-letrozole arm ( $p < 0.001$ ) [4]. The PALOMA-3 trial [5], comparing palbociclib-fulvestrant and placebo-fulvestrant in patients who had progressed on previous endocrine therapy, also showed a benefit in PFS for palbociclib (9.5 vs. 4.6 months;  $p < 0.001$ ).

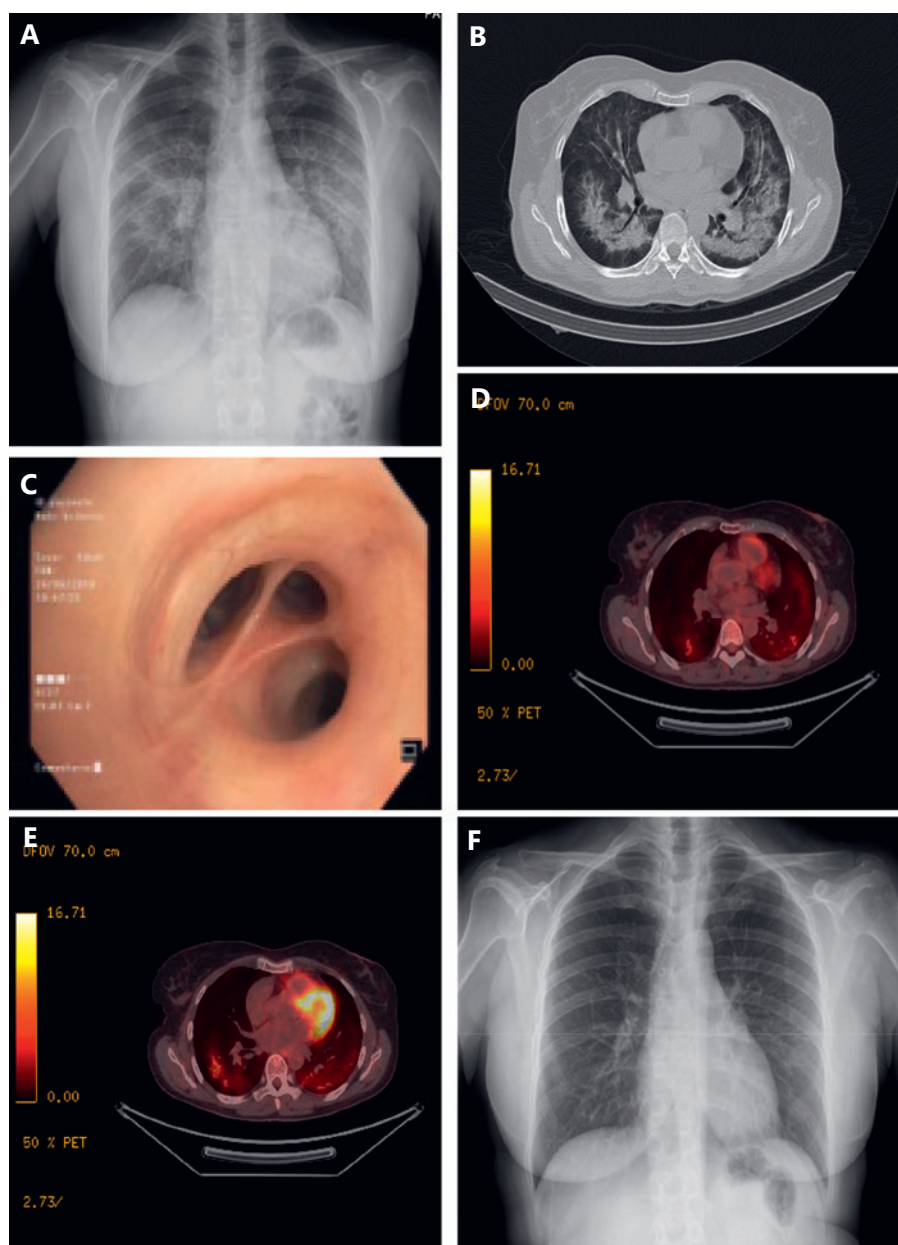
Other CDK 4/6 inhibitors have also been approved in combination with hormonal therapy in breast cancer, including ribociclib [6–8] and abemaciclib [9, 10].

In clinical trials, CKD 4/6 inhibitors have shown good tolerability. The most common adverse reaction to palbociclib in the PALOMA trials [4, 5] was neutropenia. Other common toxicities included leukopenia, anemia, thrombocytopenia, stomatitis, alopecia, rash, and fatigue. However, it is not reported any lung toxicity in palbociclib information sheet. The MONARCH 2 trial of abemaciclib reported two deaths due to pneumonitis [10], and the palbociclib risk management plan includes pneumonitis as a potential risk [11]. However, pneumonitis was not observed in either of the PALOMA trials, although clinical trials include only a limited number of patients, usually without comorbidities. Long-term safety is unknown and less prevalent adverse effects can only be identified when the drug has been used in clinical practice.

In fact, only a few cases of palbociclib-related pneumonitis have been reported. A meta-analysis [12] of 8,906 patients with different cancers enrolled in 470 phase I trials found that only 6 patients with pneumonitis had received CDK 4/6 inhibitors. In a single-center study of 100 patients, one case of pneumonitis was observed in a 72-year-old female [13]. A single case report described a 52-year-old woman receiving palbociclib who developed pneumonitis [14]. These cases of pneumonitis may have been palbociclib-related, but no diagnosis of exclusion was performed to rule out alternatives. Here, we present a case of pneumonitis in a patient receiving palbociclib where a diagnosis of exclusion based on the Spanish Pharmacovigilance System Algorithm [15], a modification of the Karch and Lasagna algorithm [16], indicated that the pneumonitis was treatment related.

## Case Presentation

A 57-year-old, Caucasian, female ex-smoker with no prior history of pulmonary disease was diagnosed with high-grade infiltrating ductal carcinoma (estrogen receptors, 99%; progesterone receptors 5%; *HER2*-negative; Ki67 index 30%, stage IV due to confirmed bone involvement). She received palbociclib 125 mg/day in 4-week cycles (3 weeks on, 1 week off) plus letrozole 2.5 mg/day continuously and zoledronic acid 4 mg/every 28 days, with no other concomitant treatments. After 3 months of treatment, she came to the emergency department of our hospital with a 1-week history of progressive shortness of breath accompanied by nonproductive cough and fever (maximum 37.7 °C). On physical examination, the patient was afebrile and eupnoeic; pulmonary auscultation showed no remarkable findings. Pulse oximetry was normal but dropped below 90% with minimum effort. Blood analysis showed an elevation of acute-phase reactants, without leukocytosis or neutropenia. A chest X-ray showed bilateral pulmonary infiltrates (Fig. 1A). Empirical antibiotic therapy with ceftriaxone and levofloxacin was initiated without clinical improvement. Blood culture and urine antigen test of *L. pneumophila* and *S. pneumoniae* were negative. A computed tomography (CT) of the chest revealed extensive ground glass opacities throughout both lungs (Fig. 1B) but no signs of pulmonary embolism. The CT pat-



**Fig. 1.** Radiological and pulmonological tests performed on our patient. **A** X-ray performed when the patient was admitted to the Emergency Department, showing a diffuse bilateral consolidation pattern. **B** CT performed during hospital admission, showing dense infiltrates in both lungs and areas with ground-glass attenuation. **C** Bronchoscopy showing no morphological alterations. **D, E** Positron-emission tomography-CT revealing a bilateral inflammatory pattern. **F** X-ray performed after 6 weeks with corticoid therapy showing complete resolution of the pulmonary infiltrations.

tern suggested a differential diagnosis between infectious causes and drug-induced toxicity, and the patient was hospitalized for further study. She underwent a positron emission tomography-CT with a bilateral inflammatory pattern and a bronchoscopy (Fig. 1C) where the bronchoalveolar lavage (BAL) showed lymphocytosis (55%) with a CD4/CD8 ratio of 0.18. Cultures for bacteria, fungus, mycobacteria, and virus in BAL and bronchial aspirates were negative. Cytology showed no malignancies, and a 2D echocardiogram showed no cardiac dysfunction.

The patient's clinical presentation and the negative cultures argued against an infectious cause, while the radiological findings and the predominance of CD8 in the BAL suggested that drug-induced pulmonary toxicity was likely. We confirmed this in accordance with the Spanish Pharmacovigilance System Algorithm [15], which assesses the causality of an adverse reaction by assigning points to different factors (Table 1). The total number of points obtained in our patient was six, indicating a probable drug-related toxicity. Therefore, palbociclib was stopped, and she was treated

with prednisolone (2 mg/kg/day), showing clinical improvement within 72 h. Six weeks later, the patient presented a normal clinical exploration without any symptomatology, with a complete radiologic resolution. Corticoid therapy was slowly reduced, and the symptomatology did not recur. Due to pulmonary toxicity grade 4 attributed to palbociclib, treatment was not restarted. The patient has been treated with letrozol in monotherapy for 6 months without disease progression or associated toxicity.

## Conclusions

In summary, while palbociclib-related pneumonitis remains a rare event, with an unknown mechanism of action, it is crucial for physicians to be alert to this risk in spite of the good toxicity profile reported in clinical trials.

**Table 1.** Diagnosis of exclusion of other causes of pneumonitis in our patient, based on the Spanish Pharmacovigilance System Algorithm (SPSA) [15]

| SPSA factor   | Our patient                                  | Points assigned |
|---|--|-----------------|
| <i>Chronology</i><br>Did the adverse event occur after drug exposure?   | Yes  | 2               |
| <i>Criteria from the literature</i><br>Have other cases been reported?  | Yes<br>Two cases [13, 14]                    | 1               |
| <i>Outcome of the adverse reaction after drug discontinuation</i><br>Did the patient improve when the drug was stopped? | Yes<br>Dyspnea disappeared within 4 days     | 2               |
| <i>Rechallenge</i><br>Was treatment resumed after improvement?  | No   | 0               |
| <i>Other possible causes</i><br>Were other causes ruled out?  | Yes<br>Negative cultures showed no infection | 1               |
| <i>Contributory factors</i><br>Are there other factors favoring a causal relationship?                                  | No   | 0               |
| <i>Investigations</i><br>Is there any evidence of drug concentration in a biological fluid or biopsy?                   | No<br>No analyses were performed             | 0               |
| Total number of points  | 6  |                 |

The association between pulmonary disease and anti-neoplastic drugs is well known, although its pathogenesis is complex, multifactorial, and dependent on different mechanisms [17, 18]. Although 14 metabolites have been identified in palbociclib, none have toxicity potential [19]. With no biomarkers currently available to predict toxicity, the identification of palbociclib-induced toxicity must rely on a diagnosis of exclusion to rule out pulmonary infections, lymphangitis carcinomatosa, and cardiogenic pulmonary edema. Algorithms [15, 16, 20] for assessing the causality of an adverse event can help unify the varying clinical impressions of different observers and lead to a final empirical diagnosis. The role of the clinical pharmacologist is critical to the correct implementation of these algorithms when determining the cause of suspected drug reactions in clinical practice.

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### Statement of Ethics

The patient gave consent to publish the manuscript and signed a consent form.

### Disclosure Statement

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### Author Contributions

E.F., L.L., C.P.-M., D.Q., I.G., M.M., I.T., B.C., C.C., M.R., E.B., and V.Q. contributed to writing and designing the study and gave final approval to publish the manuscript.

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