



Idelalisib-related pneumonitis

To the Editor:

Idelalisib (Zydelig; Gilead Sciences Inc., Foster City, CA, USA) has recently been approved in combination with rituximab for the treatment of refractory chronic lymphocytic leukaemia (CLL) in patients who have received at least one prior therapy, as a first-line treatment in the presence of a 17p deletion or *TP53* mutation in patients unsuitable for chemoimmunotherapy, or as a monotherapy in follicular lymphoma refractory to two prior lines of treatment. Idelalisib specifically inhibits phosphatidylinositol 3-kinase δ (PI3K δ), which is part of the B-cell receptor signalling pathway, the activity of which is increased in B-cell malignancies, and which promotes cellular proliferation and survival [1–4]. Here, we report on five patients who were diagnosed with pneumonitis related to idelalisib treatment.

The patients were three men and two women with a median age of 72 years (interquartile range 68–79 years). None had a history of respiratory disease or environmental exposure and none was a current smoker (one had a 7- and another, a 10-pack-year history of smoking). The patients had received idelalisib for a mean time of 7.8 months (range 2–16 years). Four of them were being treated for refractory CLL whereas one had progressive lymphoplasmacytic lymphoma in the setting of Waldenström disease. All patients were receiving idelalisib at a dose of 150 mg twice daily, except for one patient who had been receiving 100 mg twice daily for 14 months (the initial dosing of 150 mg twice daily had to be decreased 2 months after introduction for severe hypertriglyceridaemia). The mean number of previous lines of therapy was 3.8 (range 1–5). For three patients with CLL, idelalisib was initially administered with ofatumumab. At the time of pneumonitis, ofatumumab had been stopped 4–12 months previously. The fourth patient with CLL was receiving rituximab in combination with idelalisib. The patient with Waldenström disease received idelalisib alone. At the time of pneumonitis, three patients had controlled haematological disease, whereas two patients had progressive disease.

All patients complained of cough, dyspnoea and fever. Four had progression of their clinical symptoms over 3–9 weeks, whereas one had progression over 5 days. Four patients had crackles on physical examination and one had a normal examination. One patient had a severe skin reaction attributed to idelalisib toxicity. One patient had diarrhoea.

A lung computed tomography (CT) scan showed diffuse ground-glass opacities (n=3), consolidations (n=2), diffuse micronodules (n=1) and pleural effusions (n=2) (figure 1).

All patients except one required oxygen supplementation and admission to an intensive care unit. Two of these patients required mechanical ventilation. Three of the patients had a bronchoalveolar lavage (BAL). The mean \pm SD total cell count was 583 \pm 380 per μ L. Lymphocytic alveolitis was found in two patients (mean lymphocyte proportion 71 \pm 5%), whereas one patient had neutrophilic alveolitis (77% neutrophils, 1% lymphocytes). An extensive search for pathogens, including respiratory viruses, bacteria and fungi, was negative in the BAL, except in one patient in whom *Stenotrophomonas maltophilia* was found to be associated with lymphocytic alveolitis (total cell count 980 per μ L; 66% lymphocytes, 1% neutrophils). The presence of *S. maltophilia* was considered a bronchial colonisation. Because of respiratory impairment, two patients could not have a BAL. They both had noninvasive microbiological investigations. Sputum examinations for bacteria and fungi, including *Pneumocystis jiroveci*, were negative. Nasal aspirates found rhinovirus in patients in whom the clinical picture could not be explained by this finding.

All patients received broad-spectrum antibiotics with no significant efficacy. Idelalisib was definitively stopped in all patients. Four received steroids (prednisone 1 mg \cdot kg $^{-1}$ of body weight per day for three, 0.5 mg \cdot kg $^{-1}$ for one), among whom two received three pulses of 500 mg methylprednisolone beforehand. The median time of the follow-up was 157 days (range 12–267 days). Among patients who received corticosteroids, three had a resolution of pneumonitis and one patient died 12 days after admission due to multiorgan failure. The patient with *S. maltophilia* did not receive any targeted antibiotics and had a favourable outcome with steroids. The patient who was not treated with steroids had a favourable outcome after the interruption of idelalisib.

Herein, we report for the first time the clinical features of idelalisib-related pneumonitis. The median age of our patients was 72 years, similarly to the median age of patients who are diagnosed with CLL [5]. Respiratory symptoms, including cough, dyspnoea and pneumonia, together with digestive symptoms, were the most frequent adverse events reported in previously conducted clinical trials evaluating the efficacy of idelalisib.

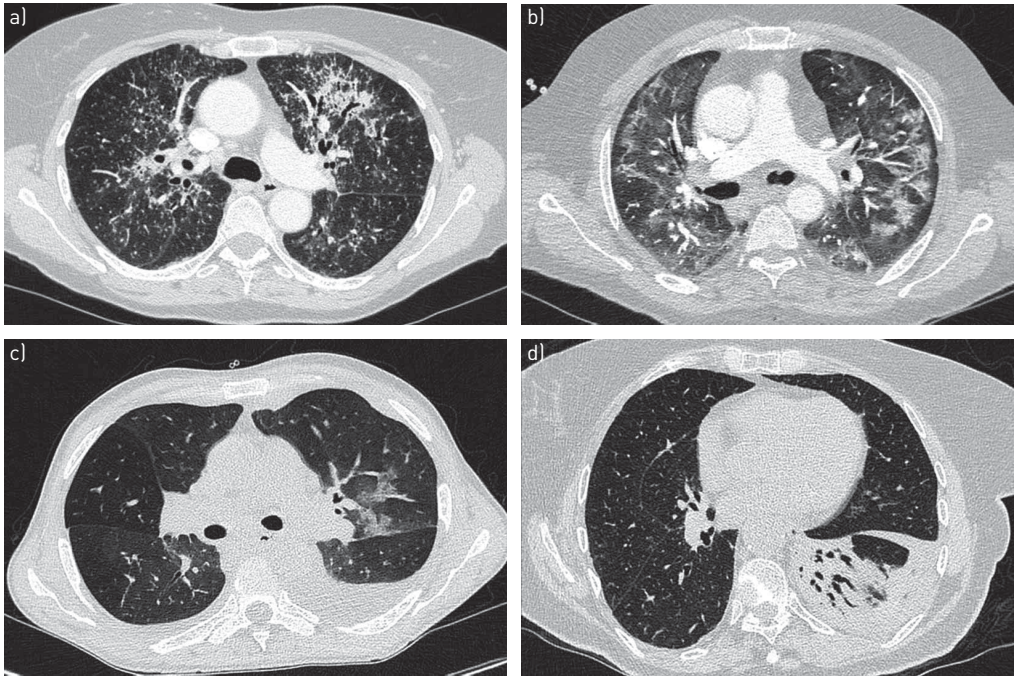


FIGURE 1 Lung CT scan patterns from patients with idelalisib-related pneumonitis showing ground-glass opacities a) with or b) without micronodules, associated with c) a pleural effusion or d) consolidation with a pleural effusion.

It is very difficult to accurately assess the prevalence of idelalisib-induced pneumonitis, especially because the drug was approved very recently. In phase 1–3 studies, cough was reported in 12–29% of patients and dyspnoea in 10–18%, whereas pneumonia was reported in 6–22% of patients [6–9]. Noninfectious pneumonitis was specifically diagnosed in 2–5% of patients treated with idelalisib, including fatal cases [7–10]. Among the five patients in our series, four patients (including two enrolled in a clinical trial) were treated in Hospital Saint Louis, Paris, France, which is mostly dedicated to onco-haematological patients. At the date of December 1, 2015, at this site, a total of 21 patients have been treated with idelalisib including those enrolled in clinical trials (*i.e.* 19% were diagnosed with an idelalisib-related pneumonitis). At the same time, seven cases of idelalisib-related pneumonitis were declared in the French pharmacovigilance database (four being concomitantly treated with rituximab). In parallel, approximately 1000 patients have been treated with idelalisib in France since this drug was approved (data obtained from Gilead Sciences Inc.), leading to an estimation of the prevalence of idelalisib-associated pneumonitis of 0.7%. However, these data should be taken with caution as they cannot be exhaustive and do not include patients treated in pre-licensing trials.

Although rarely, rituximab has also been associated with lung toxicity [11]. One could postulate that pneumonitis could be related to rituximab rather than idelalisib when both are administered. However, pneumonitis has also been reported in clinical trials evaluating idelalisib as a monotherapy [7, 9]. In our series, only one patient received rituximab together with idelalisib. Although this patient had previously been treated with rituximab 2 years before with no related adverse events, we cannot firmly exclude a pulmonary toxicity of rituximab.

Currently, there are no data on the mechanisms of idelalisib-related pneumonitis. No lung biopsies were available for our patients. Two patients had lymphocytic alveolitis in BAL whereas one had neutrophilic alveolitis. The significance of this BAL finding as regards the mechanisms for pulmonary reaction to drugs is as yet unclear, inasmuch as a given drug may produce varied BAL changes amongst patients. In the lung CT scan patterns of our series, ground-glass opacities are consistent with hypersensitivity pneumonitis, although the consolidation pattern is rather consistent with organising pneumonia. Interestingly, both hypersensitivity pneumonitis and organising pneumonia have been reported as adverse events of mammalian target of rapamycin (mTOR) inhibitors such as everolimus, temsirolimus or sirolimus [12–15]. By inhibiting PI3K δ , idelalisib also inhibits the mTOR pathway [10]. Thus, whether both idelalisib and mTOR inhibitor-related pneumonitis may share a similar pathophysiology remains to be explored [10].

Both lung physicians and haematologists should be aware of the possibility of drug-related lung manifestations in patients receiving idelalisib. Due to the potential severity of idelalisib-related pneumonitis, any respiratory symptom reported should be investigated. If pneumonia is suspected, the drug should be

promptly discontinued. Because patients treated with idelalisib are usually severely immunocompromised, particularly those with refractory CLL, antimicrobial treatments should be introduced, and an extensive search for pathogens should be conducted before prior to diagnosing a patient with idelalisib-related pneumonitis. After infectious pneumonia has been investigated and the severity of the pneumonitis has been determined, steroids should be discussed. We did not reintroduce idelalisib in any of our patients. Thus, we cannot conclude that it could be an option, even at a lower dose, in cases of the unavailability of an alternative treatment for a haematological disease. In this case, a combination of idelalisib with low-dose steroids could be discussed.



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Lung physicians and haematologists should be aware of the possibility of idelalisib-related lung manifestations <http://ow.ly/XmjGm>

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