Pirfenidone treatment in idiopathic pulmonary fibrosis: too much of a great expectation?

To the Editors:

Idiopathic pulmonary fibrosis (IPF) is a dreadful, chronic and irreversibly progressive fibrosing disease lacking any effective treatment and leading to death in all affected patients [1, 2]. The scientific community is becoming aware that corticosteroids and immunosuppressors have failed to prove any efficacy concerning both mortality and the prevention of devastating complications, such as IPF acute exacerbations [1, 3]. Not only has this approach proven ineffective, but also harmful. Recently, the National Heart, Lung, and Blood Institute (Bethesda, MD, USA) aborted the continuation of treatment of combined prednisone, azathioprine and *N*-acetylcysteine (one arm of the three-arm multicentre PANTHER-IPF clinical trial) due to safety concerns [4]. The results of the interim analyses revealed that patients with IPF receiving the conventionally used triple-drug therapy consisting of prednisone, azathioprine and *N*-acetylcysteine had worse outcomes than those who received matched placebos. Thus, the need for an effective and safe treatment for IPF is still being pursued in several clinical trials.

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone), a novel compound with anti-inflammatory, antifibrogenic and antioxidant properties, appears promising in IPF patients [1, 2]. Besides the first phase II study, which was stopped early because an interim analysis showed favourable clinical efficacy regarding one of the secondary end-points of the study, the acute exacerbations [5], the data of the following three phase III trials exploring the effectiveness of pirfenidone in IPF were rather disappointing and unconvincing [6, 7]. While the primary and one of the secondary end-points were met in the subsequent phase III trial [6], the significant difference in acute exacerbations in favour of the treated arm observed in the phase II study [5] was not verified. In addition, the primary end-point of the study was changed during the study period. Among the CAPACITY studies, only CAPACITY 1 succeeded to confirm its primary end-point whereas CAPACITY 2 failed although it was very similarly designed [7]. The clinical significance of such ''positive'' results needs further consideration, so we wish to focus on the clinical significance of minor lung function decline, presented as the proof of the effectiveness of pirfenidone in IPF [5–7] and on the need of validated and clinically meaningful end-points in IPF trials.

Given the fatal prognosis of IPF within 3 to 5 yrs in the majority of patients, we believe that the most appropriate and clinically meaningful end-point for assessing drug efficacy in IPF should be the overall survival, and possibly the progression-free survival time [2]. Due to the relatively low prevalence of IPF [1] and the requirement of long-term follow-up in pirfenidone trials, as well as in other IPF trials, the change in 6-min walk distance and related oxygen desaturation, and the change in forced vital capacity (FVC) have been used as surrogates for mortality [2, 5–7].

It is widely accepted that FVC change is strongly associated with IPF mortality [8]. In the CAPACITY 1 trial the decline of FVC % predicted after 72 weeks of treatment was 8% and 12.4% in the high-dose pirfenidone arm and the placebo arm, respectively, which was statistically significant [7]. The FVC % pred mean decline in the pirfenidone high-dose arm of the CAPACITY 1 and 2 studies was 8% and 9%, respectively, and the treatment effect of FVC 4.4% pred in the CAPACITY 1 trial raises the following concerns on the potential clinical significance of these findings. 1) All values are less than the 10% threshold in FVC which is considered an accepted negatively predicting change in IPF at present [1, 8]. More precisely, a decline of FVC $\geqslant$10% in 24 weeks is associated with a nearly five-fold increase in the mortality risk over the subsequent year [9]. 2) Moreover, emerging data show that the minimal clinically important difference for the decline in FVC % pred is 2–6% and even a marginal decline in FVC is associated with poor outcome in IPF [9]. As a consequence, changes in FVC % pred that were previously considered as evidence of stable disease are clinically significant. Additionally, although in the CAPACITY studies the results for progression-free survival time were either statistically significant or numerically favourable, they were mainly related to the criterion of 10% decline in FVC % pred. Had the cut-off point of 5% decline in FVC % pred been used, then even the secondary end-points of the CAPACITY trials regarding the progression-free survival time and the categorical change in FVC would not have been met.

Based on these observations, it is our opinion that the statistically significant results in IPF trials should be examined under the prism of minimal clinically important difference [10, 11]. Furthermore the lack of validated thresholds for the markers used as end-points in pirfenidone clinical trials for IPF has a major impact on the interpretation of the clinical significance of their results. One would expect that if a treatment were to show true benefit for IPF patients then it should certainly have an effect on survival or disease worsening as well.

While the highly anticipated data of approved administration of pirfenidone in IPF patients in Japan since 2008 are still unavailable, it is our belief that pirfenidone should not be considered a proven therapy for IPF. The ''great expectations'' of reduced mortality and disease progression benefit have not been met so far and the decelerated decline in respiratory function could, under the light of minimal clinically important difference, prove more of a ''false hope''.

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Primary pulmonary extranodal natural killer/T-cell lymphoma: nasal type with multiple nodules

To the Editors:

Primary pulmonary lymphoma (PPL) is an uncommon disease representing only 3–4% of extranodal non-Hodgkin's lymphoma (NHL), and <1% of NHL [1]. The true incidence of PPL other than NHL is unknown, while primary pulmonary T-cell lymphoma is extremely rare. Natural killer (NK)/T-cell lymphoma usually shows an extranodal presentation. Nasal NK/T-cell lymphomas occur in the nose and the upper aerodigestive tract. Extranasal NK/T-cell lymphomas represent the counterpart of nasal NK/T-cell lymphomas and can involve every other part of the body. Primary sites of involvement are mainly the skin, soft tissue, gastrointestinal tract and testis [2]. Although some cases of primary pulmonary T-cell lymphoma have been reported, there are only two reports written in English to date [3, 4]. Here, we describe a case of primary pulmonary NK/T-cell lymphoma with multiple nodules in both lung fields.

The patient was a 50-yr-old Japanese male with an abnormal shadow on chest radiography in a health examination (fig. 1a). He was an office worker with no history of dust inhalation or asbestos exposure and was a current smoker (50 pack-yrs). He had a history of hypertension and gallstones. He had a high fever of over 39°C for 10 days before the health examination, and had appetite loss and general fatigue. A chest computed tomography (CT) on admission revealed multiple nodules, measuring a maximum of 40 mm in size, were in both lung fields (fig. 1b–d). Administration of broad-spectrum antibiotics did not resolve his symptoms. Bronchoscopic examination and CT-guided needle biopsy did not give a definite diagnosis. Laboratory data showed elevation of lactate dehydrogenase, transaminases, hepatobiliary enzymes and an inflammatory reaction without cytopenia. Two sets of blood cultures were both negative and no tumour markers were elevated. Anti-neutrophil cytoplasmic antibodies were negative and soluble interleukin (IL)-2 receptor was elevated to 5,060 $U \cdot mL^{-1}$. Although we first planned a surgical biopsy to make a definitive diagnosis, it was not performed due to the rapid deterioration in his performance status. The final needle aspiration showed lymphocytes of various morphologies invading the blood vessels.

At this point, we suspected pulmonary lymphoma, such as lymphomatoid granulomatosis. The Otolaryngologists investigation of the upper respiratory tracts showed no specific findings. Lung nodules increased and grew larger, and hypoxia progressed. His clinical condition deteriorated so rapidly that we had to start treatment without a definitive diagnosis. He was treated with methylprednisolone (mPSL) pulse therapy (1,000 mg per day for 3 days) twice followed by cyclophosphamide pulse therapy (500 mg per day) as a salvage therapy. Progressive hypoxia was temporarily improved; however, his respiratory condition immediately worsened. Direct haemoperfusion using a polymyxin B immobilised fibre column was also performed;