around 5.3%; however, previous reports have shown trends of increasing incidence rates.[4] However, in our study we found a lower incidence (3.2%). Patients who developed NSCLC at a young age may have other unknown risk factors in addition to inherited risk.[3]

Adenocarcinoma was the most common histopathological type in this group, confirming previously published series.[1–5] The majority of patients presented with advanced stage disease at diagnosis, despite a good PS. Unfortunately, for most of the study period the patients were not screened for driver mutations so the *platinum-based doublet* was the most frequently used treatment scheme. There are conflicting data regarding prognosis in this group when comparing them with older adults.[1–5] In our study, despite the aggressive treatment, the prognosis was poor.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Dell'Amore A, Monteverde M, Martucci N, Davoli F, Caroli G, Pipitone E, et al. Surgery for non-small cell lung cancer in younger patients: what are the differences? Heart Lung Circ. 2015;24:62–8 [Epub 2014/08/19].
2. Rich AL, Khakwani A, Free CM, Tata LJ, Stanley RA, Peake MD, et al. Non-small cell lung cancer in young adults: presentation and survival in the English National Lung Cancer Audit. QJM. 2015:hcv052 [Epub 2015/03/01].
3. Subramanian J, Morgensztern D, Goodgame B, Baggstrom MQ, Gao F, Piccirillo J, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. J Thorac Oncol. 2010;5:23–8 [Epub 2009/11/26].
4. Zhang J, Chen SF, Zhen Y, Xiang J, Wu C, Bao P, et al. Multicenter analysis of lung cancer patients younger than 45 years in Shanghai. Cancer. 2010;116:3656–62 [Epub 2010/06/22].
5. Hsu CL, Chen KY, Shih JY, Ho CC, Yang CH, Yu CJ, et al. Advanced non-small cell lung cancer in patients aged 45 years or younger: outcomes and prognostic factors. BMC Cancer. 2012;12:241 [Epub 2012/06/15].

R. Gomes[a,b,*], H. Dabó[c], H. Queiroga[c,d], V. Hespanhol[c,d]

[a] *Pulmonology Department, Hospital Sousa Martins, Unidade Local de Saúde, Guarda, Portugal*
[b] *Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal*
[c] *Pulmonology Department, Centro Hospitalar de São João, Porto, Portugal*
[d] *Faculty of Medicine, University of Porto, Porto, Portugal*

* Corresponding author.
E-mail address: gomes.rita.dm@gmail.com (R. Gomes).

http://dx.doi.org/10.1016/j.rppnen.2015.10.001

Not yet known side effects of pirfenidone in the treatment of idiopathic pulmonary fibrosis?

To the Editor,

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing pneumonia of unknown cause, occurring primarily in older adults and limited to the lungs,[1,2] with a very poor prognosis.

There were no therapeutic options with proven efficacy until recent randomized controlled trials have shown the efficacy of pirfenidone and nintedanib in reducing the decline rate of forced vital capacity (FVC).[3,4]

Like any other recently introduced drug, the whole spectrum of the side effects of pirfenidone is still unknown. The most frequent side effects reported from the CAPACITY and ASCEND trials,[3,5] the follow-up extension study RECAP[6] and PASSPORT registry interim results,[7] are gastrointestinal (nausea, diarrhea, dyspepsia and vomiting), cutaneous (rash, photosensitivity), headache, dizziness and fatigue. Although cough, upper airway tract infection and worsening of IPF were also reported, these could be attributed to the pathophysiology of IPF *per se*.

We report the cases of 2 patients diagnosed with IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/ALAT consensus statement on IPF[1] and the 2013 ATS/ERS update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias statements,[2] who experienced probable toxicity induced by pirfenidone.

The first case reports a 62-year-old female non-smoker diagnosed with IPF (Possible UIP HRCT and UIP pattern in surgical lung biopsy) in 03-2011, being started on N-acetylcisteine 600 mg tid. The patient was started on pirfenidone in 05-2014; at that time a mild restriction was observed (FVC: 75%, 1760 mL, TLCO: 76.3%). From the time she was started on pirfenidone, she complained of dyspepsia, increasing dyspnea (modified Medical Research Council dyspnea scale [mMRC] 2–3), cough and wheezing. On physical examination, bilateral basilar crackles and expiratory wheezing were observed. Blood analysis was unremarkable and sputum microbiological exams were negative. Chest radiography was similar to the previous ones. Cardiac heart failure and pulmonary hypertension were pursued and excluded by echocardiogram, and NT pro-BNP was within normal range. After 4 months on pirfenidone the patient kept complaining of wheezing since the beginning of the drug and troublesome cough not alleviated by opioids; functional decline was observed (relative FVC drop of 10%, with maintained TLCO value). Pirfenidone was interrupted, with resolution of symptoms after one month and improvement of FVC back to basal values. Reintroduction of pirfenidone was attempted, but recurrence of symptoms led to its definitive suspension.

The second case reports a 66-year-old non-smoker woman diagnosed with IPF in 07-2014 (Possible UIP HRCT,

UIP pattern in surgical lung biopsy). She had mMRC 1 dyspnea and troublesome cough. At the time she started pirfenidone, FVC was 69.2% (1470 mL) and TLCO was 65%. In the six-minute walk test (6-MWT) walked 501 m with desaturation (from 96 to 86%). When pirfenidone was started there were complaints of astenia and mild anorexia. After two months on the drug the patient reported increasing fatigue, anorexia and increased dyspnea on exertion (mMRC 3). Physical examination showed a 5 kg weight loss and pulmonary auscultation revealed diffuse bilateral crackles. Blood panel was unremarkable, with normal leukocyte count and slightly increased C-reactive protein (1.02 g/dL). Chest HRCT revealed new diffuse ground glass attenuation, besides the fibrotic background already known. Pulmonary thromboembolism was excluded by angio-CT. A fiberoptic bronchoscopy was performed, which revealed no structural changes. Blood cultures were negative and no infectious agents were identified (bacteria, respiratory virus and *Pneumocystis jirovecii*) in bronchial lavage samples. FVC decreased to 55.2% (1140 mL) and TLCO to 55%. Pirfenidone was stopped, with marked improvement in the dyspnea and constitutional symptoms in 2 weeks; at that time no other measures were taken. After this time, since objective functional impairment was observed, the patient was treated for acute exacerbation with pulsed steroids (methylprednisolone 10 mg/kg/day 3 days followed by prednisolone 0.5 mg/kg/day with gradual reduction), which achieved clinical and functional stability.

New drugs that can change the ominous prognosis of IPF have recently become available. As with any recently introduced drug, one must bear in mind the possibility of unreported side effects like the ones the authors have described.

The first case describes an apparent causality between the use of pirfenidone and symptoms of wheezing and worsening dyspnea, a side effect not reported in CAPACITY and ASCEND trials.[3,5] In the second case, clinical and functional deterioration and new ground glass opacities in HRCT were observed and other frequent causes for rapid deterioration were excluded. The suspension of pirfenidone led to rapid clinical improvement, raising the possibility of pulmonary toxicity induced by this drug. Although the concomitant event of an acute exacerbation when the patient was started on this drug cannot be completely excluded, the clinical improvement when the drug was discontinued and the exclusion of other possible causes for rapid deterioration raises the suspicion of an exacerbation induced by pirfenidone. Taking into account there was no previous description of any case of lung toxicity induced by pirfenidone, the authors considered it would be better for the patient to treat this event as an acute exacerbation with high dose steroids.

To the best of the authors' knowledge the described side effects attributable to the use of pirfenidone have not yet been reported.

With the wider use of these new drugs, new side effects will certainly be increasingly described. The knowledge and awareness of the potential side effects induced by this new drug is of the greatest importance in order to identify potentially dangerous adverse events.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An Official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
2. Travis W, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An Official American Thoracic Society/European Respiratory Society Statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
3. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
4. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
5. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–9.
6. Costabel U, Albera C, Fagan E, Bradford WZ, King T, Noble P, et al. Long-term safety of pirfenidone in RECAP, an open-label extension study in patients with idiopathic pulmonary fibrosis, interim results. Eur Respir J. 2014;44 Suppl. 58:1903s.
7. Koschel D, Cottin V, Skold M, Tomassetti S, Azuma A, Giot C, et al. Pirfenidone post-authorisation safety registry (PASSPORT) – interim analysis of IPF treatment. Eur Respir J. 2014;44 Suppl. 58:1904.

S. Campainha[a,*], C. Nogueira[a], F. Costa[b], A. Sanches[c], S. Neves[a]

[a] *Centro Hospitalar de Vila Nova de Gaia/Espinho, Pulmonology Department, Portugal*
[b] *Centro Hospitalar de Vila Nova de Gaia/Espinho, Radiology Department, Portugal*
[c] *Centro Hospitalar de Vila Nova de Gaia/Espinho, Pathology Department, Portugal*

[*] Corresponding author.
E-mail address: sergio.fernandes@chvng.min-saude.pt (S. Campainha).

http://dx.doi.org/10.1016/j.rppnen.2015.10.002