

Suspected accelerated disease progression after discontinuation of nintedanib in patients with idiopathic pulmonary fibrosis

Two case reports

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Abstract

Rational: The efficacy of nintedanib, a multitarget receptor tyrosine kinase inhibitor, has been demonstrated in recent randomized controlled trials involving patients with idiopathic pulmonary fibrosis (IPF). However, accelerated disease progression after nintedanib discontinuation has never been reported.

Patient concerns: We report 2 cases involving patients with a history of IPF who presented with respiratory deterioration at 3 weeks after the discontinuation of nintedanib therapy for IPF. Neither patient fulfilled the definition of “acute exacerbation of IPF” on unilateral computed tomography.

Diagnoses: Accelerated disease progression after the discontinuation of nintedanib therapy for IPF.

Interventions: One patient received steroid therapy. The other patient refused to undergo steroid therapy.

Outcomes: The first patient showed that the affected lobe exhibited volume loss with traction bronchiectasis after receiving steroid therapy, and succumbed to pneumothorax after 3 months. The other patient was transferred to another hospital because of a decline in his general condition.

Lessons: To our knowledge, this report is the first to document accelerated disease progression after the discontinuation of nintedanib therapy for IPF. Although the accurate mechanism remains unclear, the effects of nintedanib against vascular endothelial growth factor and platelet-derived growth factor receptor may play a role. Our findings suggest that physicians should carefully monitor patients with IPF after nintedanib discontinuation.

Abbreviations: AE-IPF = acute exacerbation of idiopathic pulmonary fibrosis, CT = computed tomography, DOE = dyspnea on exertion, FVC = forced vital capacity, GGOs = ground glass opacities, IPF = idiopathic pulmonary fibrosis, PDGF = platelet-derived growth factor, TKI = tyrosine kinase inhibitor, VEGF = vascular endothelial growth factor.

Keywords: accelerated disease progression, acute exacerbation, idiopathic pulmonary fibrosis, nintedanib, tyrosine kinase inhibitor

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive pulmonary disorder with an unknown etiology, a poor prognosis, and an increasing prevalence.^[1] Nintedanib, a multitarget receptor tyrosine kinase inhibitor (TKI), has been shown to be efficacious in

recent randomized controlled trials involving patients with IPF.^[2] In addition, nintedanib was found to suppress the acute exacerbation of IPF (AE-IPF),^[3] which is associated with high mortality.^[4] However, accelerated disease progression after nintedanib discontinuation has never been reported. Here, we report 2 cases of accelerated disease progression 3 weeks after the discontinuation of nintedanib administered for IPF.

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Written informed consent was obtained from the patient or the family of the patient.

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2. Case reports

2.1. Case 1

A 71-year-old man with a history of pulmonary tuberculosis presented to our hospital with progressive dyspnea on exertion (DOE). Two years before admission, he had been diagnosed with IPF based on clinical, radiological, and pathological assessments. He was prescribed the antifibrotic agent pirfenidone, which was replaced by nintedanib (300 mg/d) 8 months before admission because of worsening of his DOE and forced vital capacity. Three weeks before admission, he developed diarrhea, forcing discontinuation of nintedanib. Shortly thereafter, his DOE worsened. He did not change his medicine or living environment, and was not exposed to inhaled antigens. On admission, he exhibited tachypnea, respiratory failure, and bilateral fine crackles over the



Figure 1. Chest computed tomography (CT) findings for a 71-year-old man with idiopathic pulmonary fibrosis who presented with accelerated disease progression after nintedanib discontinuation. Chest CT findings at 8 months before admission (A), at the time of admission (B), and after treatment with methylprednisolone pulse therapy (1 g/d for 3 days) and prednisolone (C). Note the new ground glass opacities (GGOs) in the left lower lobe on images obtained at the time of admission (B, black arrow). After treatment, the GGOs were alleviated; however, the affected lobe exhibited volume loss with traction bronchiectasis (C, white arrow).

lung. Other vital signs and physical examination findings were unremarkable. Chest computed tomography (CT) showed new ground glass opacities (GGOs) in the left lower lobe (Fig. 1A and B) that were unrelated to the bronchial distribution, and were atypical for pulmonary infection. Empiric antibiotic treatment with piperacillin/tazobactam resulted in no clinical improvement. We administered methylprednisolone pulse therapy (1 g/d for 3 days) followed by prednisolone (1 mg/kg per d). Although the respiratory failure symptoms and GGOs were alleviated, the affected lobe exhibited volume loss with traction bronchiectasis

(Fig. 1C). Three months later, he developed secondary spontaneous pneumothorax due to IPF. He refused mechanical ventilation and died soon thereafter.

2.2. Case 2

An 86-year-old man presented at our hospital with appetite loss for the past week. Six years before admission, he was diagnosed with IPF based on a definite usual interstitial pneumonia pattern on high-resolution CT. The disease progressed gradually during the follow-up period; nintedanib (300 mg/d) was initiated 3 weeks before admission. He had no diarrhea, nausea, or abdominal pain. He had previously received medications for diabetes mellitus, including insulin. On admission, his oxygen saturation was 98% while breathing 2 L/min of oxygen via a nasal cannula. There were no remarkable findings other than bilateral fine crackles over the lungs. Chest CT showed reticular abnormalities and a honeycomb pattern with traction bronchiectasis (Fig. 2A). After the clinical and radiological confirmation of IPF stability, his continued loss of appetite forced the discontinuation of nintedanib. However, his respiratory condition gradually deteriorated over the next 3 weeks, necessitating administration of 5 L/min of oxygen via a nasal cannula at rest. Chest CT revealed a newly developed GGO with traction bronchiectasis in the left upper lobe (Fig. 2B). Although

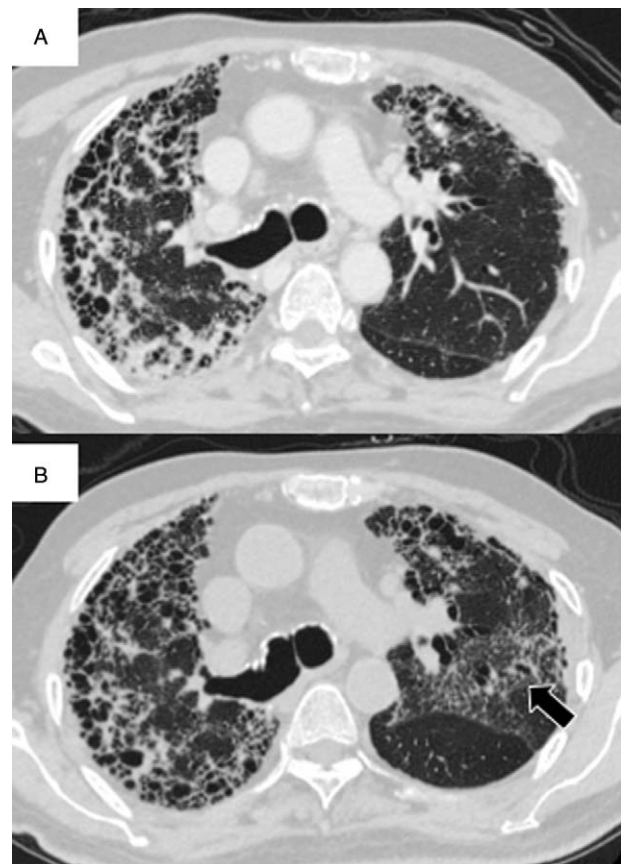


Figure 2. Chest computed tomography (CT) findings for an 86-year-old man with idiopathic pulmonary fibrosis who presented with accelerated disease progression after nintedanib discontinuation. Chest CT findings at the time of nintedanib discontinuation (A) and at 3 weeks after discontinuation (B). Note the new ground glass opacities with traction bronchiectasis in the left upper lobe after discontinuation of nintedanib (B, arrow).

levofloxacin (500 mg/d) was administered as an empiric antibiotic treatment, his condition showed no improvement. He did not consent to steroid therapy because of the associated risks, such as infection and worsening of diabetes mellitus. He was transferred to a hospital near his home.

3. Discussion

We described 2 cases of IPF with deteriorated respiratory condition at 3 weeks after nintedanib discontinuation. We believe that these deteriorations were consistent with accelerated disease progression for 2 reasons. First, other possible causes that exacerbate the respiratory condition were unlikely, such as infection, drug toxicity, inhaled antigens, and congestive heart failure. Indeed, we saw no signs of any of the above potential causes in either patient. Second, the new GGOs in high-resolution CT images were accompanied by traction bronchiectasis, which reflects the fibrotic change in the lung.^[5] Although their presentations did not fulfill the definition of AE-IPF due to the unilateral CT findings,^[4] 1 patient died after 3 months, while the other had deteriorated significantly prior to being transferred to another hospital because of his overall declining health.

Nintedanib is an oral triple TKI targeting vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor receptors, which play critical roles in the pathogenesis of pulmonary fibrosis and several cancers.^[2,6,7] In our cases, IPF progressed over 3 weeks after nintedanib discontinuation. Studies on TKI therapy for various cancers such as gastrointestinal stromal tumor, lung cancer, and renal cell carcinoma have reported disease flare after TKI discontinuation.^[8–10] However, the exact mechanism underlying this effect has not been elucidated. A study on epidermal growth factor receptor TKIs for epidermal growth factor receptor-driven lung cancers considered the rapid growth of sensitive clones following TKI discontinuation to be 1 possible mechanism.^[10] On the other hand, other studies on renal cell carcinoma showed disease flare due to rapid angiogenesis after the discontinuation of TKIs targeting VEGF and PDGF receptors.^[11,12] Furthermore, multiple protein tyrosine kinases have been implicated in the development and progression of fibrosis.^[13] Notably, VEGF and PDGF have been shown to stimulate lung fibroblast proliferation^[14] and may play an important role in human studies regarding AE-IPF.^[15] Although the role of angiogenesis in IPF remains unclear,^[16] we believe that reactivation of several different receptor tyrosine kinases after TKI discontinuation, including VEGF and PDGF receptors, can result in accelerated disease progression.

To our knowledge, this is the first report documenting accelerated disease progression after nintedanib discontinuation in patients with IPF. In one case, although steroid therapy

resulted in respiratory improvement, the affected lung remained impaired. Our findings suggest that physicians should carefully monitor patients with IPF after nintedanib discontinuation to prevent accelerated disease progression, which has an invariably poor prognosis. Further investigation is required to clarify the mechanism underlying accelerated disease progression after nintedanib discontinuation in patients with IPF.

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