Pulmonary Hypertension Exacerbated by Nintedanib Administration for Idiopathic Pulmonary Fibrosis

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Abstract:
The patient was a 71-year-old man with severe idiopathic pulmonary fibrosis (IPF) and who demonstrated a slow deterioration of his respiratory condition. After nintedanib administration, his forced vital capacity and chest high-resolution computed tomography (HRCT) findings were stable, but his dyspnea on exertion were worsened. He was diagnosed with pulmonary hypertension (PH) by right heart catheterization (mean pulmonary arterial pressure: 30 mmHg). In this case, we suspected that nintedanib caused his PH, as his IPF had not progressed.

Key words: idiopathic pulmonary fibrosis, pulmonary hypertension, nintedanib

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Introduction

Idiopathic pulmonary fibrosis (IPF), a chronic, slowly progressing fatal lung disease, is a form of idiopathic interstitial pneumonia; the prognosis is very poor with a life expectancy of 3-5 years from the diagnosis (1). Although the relationship is not fully understood, pulmonary hypertension (PH) is commonly present in patients with IPF, where it is classified as group III PH by the World Health Organization (WHO). IPF patients complicated with PH have a worse prognosis than those without PH (2).

Nintedanib, a multi-target receptor tyrosine kinase, has recently been recognized as an acceptable treatment modality (3). In a clinical trial, cardiac adverse events occurred in 9.7-10.3% of patients during nintedanib administration, and 0.3-0.6% of them were fatal (4). However, there have been no reports describing the involvement of nintedanib in PH.

We herein report the first case of exacerbation of PH following nintedanib administration without interstitial worsening.

Case Report

A 71-year-old man presented to our hospital with worsening dyspnea in June 2011. On a physical examination, the patient had dorsobasal Velcro crackles on auscultation, with no other noticeable physical findings. The laboratory tests showed an elevation of the serum Krebs von den Lungen-6 (KL-6) level, and a pulmonary function test showed restrictive impairment. High-resolution computed tomography (HRCT) of the chest showed reticulation and a honeycomb appearance; thus, according to the statement of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT), he was diagnosed with IPF (KL-6 level, and a pulmonary function test showed restrictive impairment. High-resolution computed tomography (HRCT) of the chest showed reticulation and a honeycomb appearance; thus, according to the statement of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT), he was diagnosed with IPF (Fig. 1, 2). He had a history of appendicitis, cholelithiasis, and diabetes mellitus. He had a smoking history of 54 pack-years and no other related family history.

During his follow up, we prescribed N-acetylcysteine (NAC) inhalation from December 2013 and long-term oxygen therapy for 2 L/min oxygen during exercise from May 2015, but his dyspnea worsened, and the CT appearance and forced vital capacity (FVC) on a pulmonary function test gradually deteriorated. Nintedanib was therefore adminis-
Nintedanib was safely continued without severe side effects, and after the initiation of nintedanib administration, his CT findings and FVC stabilized, and the serum KL-6 level declined; however, his dyspnea on exertion worsened [modified medical research council (mMRC) dyspnea scale 3 → 4] (Fig. 3).

One year after initiating nintedanib, his blood gas analysis revealed a dose of 300 mg/day with a combination of long-term oxygen therapy. The tricuspid regurgitation pressure gradient (TRPG) was 44 mmHg, and the ejection fraction (EF) was 68% as measured by echocardiography. His 6-minute walk test showed severe desaturation (230 m, percutaneous oxygen saturation (SpO2) 95 → 75%, 3 L/min oxygen), and he was found to be experiencing severe hypoxia. Nintedanib was safely continued without severe side effects, and after the initiation of nintedanib administration, his CT findings and FVC stabilized, and the serum KL-6 level declined; however, his dyspnea on exertion worsened [modified medical research council (mMRC) dyspnea scale 3 → 4] (Fig. 3).

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on 2 L/min supplemental oxygen at rest revealed the following: partial pressure of arterial oxygen (PaO₂) 59.9 Torr; partial pressure of carbon dioxide in arterial blood (PaCO₂) 34.2 Torr; and pH, 7.475. Laboratory findings showed an elevation of the brain natriuretic peptide (BNP) level (19 to 105 pg/mL), negative for D-dimer, and a decline in the KL-6 level (4,184 to 2,493 U/mL). Echocardiography did not indicate the presence of tricuspid stenosis or pulmonary artery stenosis. It showed a TRPG of 72 mmHg, mean pulmonary artery pressure (mPAP) 41.8 mmHg, EF 80.5%, tricuspid annular plane systolic excursion (TAPSE) 20.7 mm, tissue Doppler tricuspid annular peak systolic velocity, TRPG: Tricuspid regurgitation pressure gradient

Discussion

To our knowledge, this is the first report of a patient with severe IPF whose PH was worsened secondarily to nintedanib administration. Although his HRCT findings and FVC were stable, and the KL-6 level was improving with the administration of nintedanib, his pulmonary artery pressure worsened after starting nintedanib, suggesting that the worsening of his PH was not due to the progression of IPF but rather due to nintedanib administration.

Patients with IPF progress slowly and have a poor prog-
nosis; however, there are few therapeutic modalities available (1). Recently, a large-scale randomized phase III study (INPULSIS 1, INPULSIS 2) revealed that nintedanib inhibited the progression of IPF (4). Nintedanib is a multi-target receptor tyrosine kinase inhibitor that works on key angiogenesis pathways including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) (5-7). In our case, IPF progression was controlled after nintedanib administration. Given that VEGF is required for normal endothelial cell maintenance, its function, and signaling, blockade of the VEGF function deregulates the angiogenesis in the vascular lumen of arterioles.

It was reported that nintedanib did not influence right ventricular pressure adaptation in rats (8). However, it has been shown that VEGF blockade combined with chronic hypoxia induces endothelial cell dysfunction and cell death and causes PH (9, 10). Through its inhibitory action against the VEGF receptor, nintedanib might be associated with the development of PH under conditions of chronic hypoxia. There are also reports that treatment with imatinib, a well-known BCR-ABL tyrosine kinase inhibitor, also inhibits platelet derived growth factor receptor (PDGFR) tyrosine kinase, as add-on therapy in pulmonary arterial hypertension (PAH) patients is associated with improvement in echocardiographic measures of the RV function; however, dasatinib, another multi-target-receptor kinase that is more potent than imatinib on BCR-ABL and PDGFR, causes pulmonary vascular damage and aggravates PH under conditions of chronic hypoxia (11, 12). The development of PH is considered to be caused by the combination of exposure to hypoxia and the use of tyrosine kinase inhibitors. In the present case, his oxygen saturation level on the 6-minute walk test declined during follow-up, suggesting that he had been exposed to severe hypoxia.

While the general consensus regarding the development of PH in IPF is that it is due to the progression of lung fibrosis (13), it may be difficult to determine whether PH is associated with IPF progression or the use of nintedanib in patients with severe IPF. A high prevalence of PH has been reported in patients with IPF; in their primary stages, almost 10% of these patients had PH (14), and the incidence was noted to increase in accordance with the severity of IPF (15). Since the progression of IPF was controlled by nintedanib administration in this case, we considered his PH to have developed due to the combination of severe hypoxia and the use of nintedanib.

We encountered a patient with severe IPF who experienced worsening of PH after the administration of nintedanib. Further investigations to identify the relationship between PH and IPF are needed; the use of nintedanib in patients with severe IPF should be carefully considered.

The authors state that they have no Conflict of Interest (COI).

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