

Perioperative nintedanib for lung resection in patients with idiopathic pulmonary fibrosis

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Abstract. Although nintedanib, an anti-fibrotic drug, relieves the chronological worsening of pulmonary function and prevents acute exacerbations of interstitial pneumonia, the perioperative safety and efficacy of nintedanib remains to be elucidated. The present study aimed to examine the safety and efficacy of nintedanib in patients with interstitial pneumonia. This study included 12 patients who underwent lung resection, including bilobectomy (n=2), lobectomy (n=7), segmentectomy (n=2) and wedge resection (n=1) between January 2020 and August 2023 at Juntendo University Nerima Hospital (Tokyo, Japan). Nintedanib was administered preoperatively to 10 male and two female patients with idiopathic pulmonary fibrosis and stage I to III lung cancer. The nintedanib dosing period ranged from 14 to 43 days. None of the patients canceled or postponed surgery because of side effects of nintedanib. Although prolonged air leak (n=3), surgical site infection (n=2), pyothorax (n=1), heart failure (n=1) and pleurisy (n=1) were observed postoperatively, the 30-day mortality rate was 0, with no acute exacerbation of interstitial pneumonia. These results encourage further investigation into the potential of nintedanib treatment in a larger patient cohort through prospective verification.

Introduction

Idiopathic pulmonary fibrosis (IPF), a major idiopathic interstitial lung disease, has an extremely poor prognosis (1). Moreover, patients with IPF have a higher incidence of lung cancer, more than seven times higher than that in the general population (2). A previous prospective cohort study revealed that 9% of patients with IPF were dead because of lung cancer (1,3). Additionally, IPF is detected in 3.7-8% of patients

with lung cancer (4-7), and the prognosis of lung cancer with IPF is poorer than that without IPF (4,5,8). Therefore, treatment strategies are crucial for patients with lung cancer and IPF. The postoperative acute exacerbation of interstitial pneumonia (IPAE) is a life-threatening complication. Several previous studies have shown that IPAE is associated with high mortality rates.

Research conducted by the Japanese Association for Chest Surgeons identified seven predictive risk factors for IPAE, with the study reporting a 43.9% mortality rate for this condition (9). Possible prophylactic measures against IPAE, such as steroids, sivelestat, or ulinastatin, have yet to be established (10). Recently, anti-fibrotic drugs such as pirfenidone and nintedanib have been identified to relieve the chronological worsening of pulmonary function or prevent IPAE (11-21). Although trials on the perioperative administration of pirfenidone have been reported (22), no reports exist on the perioperative safety and efficacy of nintedanib. This study aimed to examine the perioperative safety and efficacy of this medication in patients with acute exacerbation of interstitial pneumonia.

Materials and methods

This study focused on patients diagnosed with both lung cancer and IPF who underwent bilobectomy, lobectomy, segmentectomy, and wedge resection between January 2020 and August 2023 at Juntendo University School of Medicine, Nerima Hospital. Twelve patients with IPF and concomitant lung cancer who received perioperative nintedanib therapy after lung cancer surgery were retrospectively investigated. Clinical data were retrospectively obtained from the medical charts. Oral nintedanib (300 mg/day) was administered preoperatively, and patients were assessed for adverse events 1-2 weeks after the initiation of treatment. The oral dose was reduced to 200 mg/day in patients with liver dysfunction and those who developed side effects such as liver dysfunction and diarrhea. Nintedanib was withdrawn 5 days preoperatively and resumed postoperatively after chest tube removal.

This study was approved by the Institutional Review Board of our hospital (No. E23-0399). According to an International Working Group Report, IPAE is defined as the subjective worsening of dyspnea, new bilateral radiological opacities, and exclusion of causes of dyspnea such as cardiac failure

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or fluid overload (23). The assessment of postoperative IPAE was conducted within a specific time frame, and the study protocol defined the evaluation period as 30 days after surgery according to the PEOPLE study, which demonstrated the perioperative benefit of pirfenidone (22).

Results

Nintedanib was administered to 12 patients between January 2020 and August 2023. Ten patients did not receive any other medication for IPF during the perioperative period, including steroids, N-acetyl cysteine, erythromycin, or sivelestat sodium. Two patients received steroids, but no other agents were administered. Eleven patients were administered oral nintedanib (300 mg/day), and a decreased dose (200 mg/day) was administered to one patient with a hepatic comorbidity. Patients were assessed for adverse events 1-2 weeks after the initiation of treatment. In one of the 11 patients who developed liver dysfunction, the oral dose was reduced to 200 mg/day.

The patient characteristics are shown in Table I. The mean patient age was 75.1 ± 4.6 (64-81) years, and the body mass index ranged from 20.9 to 28.4 kg/m^2 (average, 25.0 kg/m^2). All the patients had a history of heavy smoking. Their past medical histories included heart disease in one case (8.3%), lung disease except for IPF in three cases (25%), diabetes in two patients (16.7%), stroke in one case (8.3%), and cancer affecting other organs in three cases (25%). None of the patients had autoimmune diseases. Clinically, ten cases (83.3%) were associated with the usual interstitial pneumonia pattern. In four cases, restrictive ventilatory failure was evident (33.3%). The percentages predicting vital capacity ranged from 82 to 123.1 (average, 101.5), the percentages predicting the diffusing capacity of the lungs for carbon monoxide ranged from 39 to 68.2 (average, 50.1), and the modified sex, age, and physiology score ranged from 2 to 7 (average, 4.9). The IPF markers in blood tests, such as Krebs von den Lungen-6 and surfactant protein-D, ranged from 349 to 1650 (average, 693.7) and 15 to 190 (average, 90.7), respectively. The pathological diagnosis of lung cancer included stage I in four cases (33.3%), stage II in five cases (41.7%), and stage III in three cases (25%) based on the Union for International Cancer Control, 8th edition (24). However, to date, no cases of stage 0 or IV disease have been reported. The histological types of lung cancer included adenocarcinoma in three cases (25%), squamous cell carcinoma in five cases (41.7%), small cell carcinoma in two cases (16.7%), and other histological subtypes in two cases (16.7%) (Table II). Most patients underwent lobectomy, while limited resections, including anatomical segmentectomies in two cases and wedge resection in one case, were performed in others. Two patients underwent bi-lobectomy. The length of surgery ranged from 167 to 365 min (average, 257.3 min), and blood loss ranged from 2 to 447 g (average, 164.6 g). The details of the surgical procedures are presented in Table III.

Table IV shows the complications observed during the study period, the mortality rates, and the nintedanib status. The dosing period of nintedanib before surgery ranged from 14 to 43 days (average, 27.1 days). None of the patients canceled or postponed surgery because of nintedanib-related side effects. The most frequent postoperative surgical complication was prolonged air leakage (three cases; 25%), followed by surgical

Table I. Patient characteristics.

Characteristic	Value
Number of patients	12
Age, years	75.1 ± 4.6
Sex	
Male	10
Female	2
BMI	25.0 ± 2.5
Smoking history, pack years ^a	54.7 ± 22.3
Medical history	
Heart disease	1
Lung disease (except IP)	3
Diabetes	2
Autoimmune disease	0
Stroke	1
Other organ cancer	3
ILD pattern	
UIP	10
Non-UIP	2
VC, %	101.5 ± 13.6
DLCO, %	50.1 ± 8.6
Modified GAP score	4.9 ± 1.4
KL-6	693.7 ± 392.8
SP-D	90.7 ± 60.6

^aA pack-year is defined as the equivalent of smoking one pack (20 cigarettes) of cigarettes a day for one year. Data are presented as mean $\pm$ SD, or N. ILD, interstitial lung disease; UIP, usual interstitial pneumonia; VC, vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; GAP, sex, age and physiology; KL-6, krebs von den lungen; SP-D, surfactant protein D; SD, standard deviation.

site infection (two cases; 16.7%). Pyothorax, heart failure, and pleurisy were observed in one case (8.3%). Three patients with prolonged air leakage did not receive post-operative nintedanib. However, during the entire follow-up period, IPAE was not identified, and the mortality rate in this study was 0%. The detailed clinical courses and patient characteristics are summarized in Table V.

Discussion

Nintedanib, an anti-fibrotic agent for IPF, inhibits multiple growth factors, such as vascular endothelial growth factor (VEGF)-2, platelet-derived growth factor, and fibroblast growth factor receptors (25,26). Inhibitors and antibodies targeting the VEGF receptor have gained recognition as effective anti-cancer treatments, particularly for patients with advanced-stage malignancies (27-29). Conversely, a previous report has revealed that VEGF is associated with the pathogenesis of IPAE and acute respiratory distress syndrome (30). Nintedanib suppresses the expression of VEGF receptors, which are believed to inhibit IPAE development. Data on the efficacy of nintedanib in patients with interstitial lung

Table II. Pathological diagnosis of lung cancer.

Classification	N
pT classification ^a	
T1	2
T2	9
T3	1
T4	0
pN classification ^a	
N0	8
N1	1
N2	3
pM classification ^a	
M0	12
M1	0
Cancer stage ^a	
I	4
II	5
III	3
IV	0
Pathology	
Adenocarcinoma	3
Squamous cell carcinoma	5
Small cell carcinoma	2
Other	2

^aBased on the Union for International Cancer Control, 8th edition (24).

Table III. Surgical procedure for lung cancer.

Procedure	Value
Operation	
Bi-lobectomy	2
Lobectomy	7
Segmentectomy	2
Wedge resection	1
Length of operation, min	257.3±58.8
Blood loss, g	164.6±170.0

Data are presented as either N or mean ± standard deviation.

diseases, except for IPF, were derived from two high-quality trials. In the SCENCIS trial for systemic sclerosis-induced interstitial lung disease and INBUILD trial for progressive fibrosing interstitial lung disease, nintedanib delayed the onset of the initial development of IPAE and the progression of lung function deterioration, especially forced vital capacity (13,14). In the TOMORROW phase II trial, the incidence of acute exacerbations was significantly lower in the nintedanib-treated group (15). Moreover, the INPULSIS cohort revealed the efficacy of nintedanib, with a particular focus on its effects on

Table IV. Perioperative complications and mortality rates.

Characteristics	Values
Dosing period of nintedanib before operation, days	27.1±9.1
Nintedanib resumed cases after operation	9
Time to nintedanib resumption, days	4.2±1.7
Perioperative complications	
IPAE	0 (0)
Bronchopleural fistula	0 (0)
Pyothorax	1 (9.1)
Prolonged air leak	3 (27.3)
Arrhythmia	0 (0)
Heart failure	1 (9.1)
Pleurisy	1 (9.1)
Renal complications	0 (0)
Surgical site infection	2 (18.2)
Mortality	
30 days	0 (0)

Data are presented as mean ± standard deviation, N or N (%). IPAE, acute exacerbation of interstitial pneumonia.

the Japanese patient population (16). Incidence of IPAE was 4% in patients who received nintedanib, while the incidence of IPAE was 12% in patients who received a placebo. Several complications in this study, such as persistent pulmonary fistulae, surgical site infections, and pyothorax, may have been influenced by the protracted wound healing effect due to the inhibition of multiple growth factors. However, none of the patients in this study experienced IPAE, suggesting that nintedanib has an inhibitory effect on IPAE, as previously reported.

However, there are no reports on the perioperative administration of nintedanib in patients with lung cancer or interstitial pneumonia. This is the first study on the perioperative administration of nintedanib to prevent acute exacerbation of interstitial pneumonia. However, studies on the perioperative administration of pirfenidone, such as the PEOPLE study, have been reported (22). A phase II PEOPLE study revealed the safety and efficacy of perioperative administration of pirfenidone, demonstrating an acute exacerbation rate of 5.1% and a mortality rate of 2.8% at 1 month after surgery. Furthermore, a Phase III PEOPLE study was conducted (22). Although the breakdown of anti-fibrotic drugs for the results is unclear, a retrospective study of 103 patients undergoing lung transplantation and receiving anti-fibrotic agents included 21 nintedanib recipients. This study found that anti-fibrotic drug therapy did not increase the incidence of post-operative complications related to the airway, bleeding, or wounds after lung transplantation. Furthermore, the study suggested a potential correlation between anti-fibrotic drug therapy and favorable outcomes in lung transplant patients, indicating a possible decrease in the incidence of primary graft dysfunction and a potential reduction in perioperative mortality rates (31). To the best of our knowledge, this study is the first to investigate the perioperative use of nintedanib to prevent IPAE in lung cancer.

Table V. Summary of patient characteristics and clinical course.

No.	Age, years	Sex	Purpose of surgery	Emphysema	IPF subtype	Medication	BI	Surgical procedure	Initial dose of nintedanib	Side effects	Resume dose	Perioperative complication	30 days outcome
1	81	M	Lung cancer	+	NSIP	Anticoagulant, antihypertensive agent, antiarrhythmic agent	600	Lobectomy	300	-	300	-	Alive
2	77	M	Lung cancer	-	UIP	Bronchodilator	1100	Bi-lobectomy	300	-	300	-	Alive
3	75	M	Lung cancer	+	UIP	Antihypertensive agent, hypoglycemic agent	960	Segmentectomy	300	-	300	-	Alive
4	72	M	Lung cancer	+	NSIP	Anticoagulant, antihypertensive agent, bronchodilator	1000	Lobectomy	200	-	200	-	Alive
5	73	M	Lung cancer	+	UIP	Antihypertensive agent, bronchodilator	1100	Wedge lobectomy	300	-	300	Surgical site infection, heart failure	Alive
6	80	M	Lung cancer	-	UIP	Bronchodilator	2400	Lobectomy	300	-	-	Prolonged air leak	Alive
7	70	M	Lung cancer	-	UIP	Thiamazole	900	Lobectomy	300	-	300	Surgical site infection, pleurisy	Alive
8	78	M	Lung cancer	+	UIP	Bronchodilator	1000	Lobectomy	300	Liver failure	200	-	Alive
9	77	F	Lung cancer	+	UIP	Antihypertensive x failure	800	Bi-lobectomy	300	-	-	Prolonged air leak	Alive
10	79	M	Lung cancer	-	UIP	Prednisolone, antihypertensive agent	750	Lobectomy	300	-	-	Prolonged air leak, pyothorax	Alive
11	75	M	Lung cancer	+	UIP	Bronchodilator, antihypertensive agent	1500	Segmentectomy	300	-	300	-	Alive
12	64	M	Lung cancer	+	UIP	Prednisolone, antihypertensive agent, hypoglycemic agent	1020	Lobectomy	300	-	300	-	Alive

IPF, idiopathic pulmonary fibrosis; BI, brinkman index; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

In this study, IPAE occurring within 1 month after surgery was not observed. Furthermore, after 30 days, the mortality rate was 0% in this study. This result was most likely related to the absence of cases of acute exacerbation of interstitial pneumonia. However, several complications, such as persistent pulmonary fistulae, surgical site infections, and pyothorax were observed in this study, which may have been influenced by the protracted wound-healing effect of nintedanib. However, establishing a causal relationship with nintedanib administration is challenging due to the occurrence of these common perioperative complications. Further prospective studies are required to elucidate the causal relationship between these complications. In addition, research should be conducted on the time required for drug discontinuation.

The various limitations of the present study prevented us from drawing conclusive inferences about the effectiveness of nintedanib in preventing postoperative IPAE. First, our investigation was confined to Japanese patients and utilized a relatively small sample size without statistical analysis, which potentially limits the generalizability of the results. The second limitation is the retrospective nature of the study. Finally, this was not a comparative study, and additional patients and randomized controlled trials are required to determine the statistical significance of the data.

IPF should be acknowledged as a crucial factor when planning lung cancer diagnosis and therapy. An established strategy for the accurate diagnosis of lung cancer using useful tools such as liquid biopsy (32) and reducing the occurrence of perioperative IPAE leads to more comprehensive and effective management of both the cancer and the underlying IPF, ultimately enhancing patient prognosis and quality of life.

In conclusion, this is the first study on the perioperative administration of nintedanib to prevent acute exacerbation of interstitial pneumonia. These results encourage further investigation into the potential of nintedanib treatment in a larger patient cohort through prospective verification.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RS and TB were responsible for study concept and design. RS was responsible for the acquisition, analysis and interpretation of data, and obtained funding. RS, HU, SH, TB and KS were responsible for clinical material support and analysis of clinicopathological data. RS and TB confirm the authenticity of all the raw data. RS and TB were responsible for drafting of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved (approval no. E23-0399) by the Institutional Review Board of the Juntendo University Nerima Hospital (Tokyo, Japan). The Institutional Review Board of Juntendo University Nerima Hospital (Tokyo, Japan) exempted this retrospective observational study from requiring written informed consent. Instead, informed consent was obtained in the form of an opt-out on a website. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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