Study on Perioperative Administration of a Neutrophil Elastase Inhibitor for Interstitial Pneumonias

Mariko Fukui, PhD, Kazuya Takamochi, PhD, Shiaki Oh, PhD, Takeshi Matsunaga, PhD, Kazuhiro Suzuki, PhD, Katsutoshi Ando, PhD, and Kenji Suzuki, PhD

Departments of General Thoracic Surgery, Radiology, and Respiratory Medicine, Juntendo University School of Medicine, Tokyo, Japan

Background. **Although acute exacerbation of idiopathic interstitial pneumonias (IIPs) is a lethal complication after pulmonary resection for lung cancer with IIPs, there are no established methods to prevent its occurrence. This prospective randomized study was conducted to evaluate whether perioperative administration of the neutrophil elastase inhibitor sivelestat prevents acute exacerbation after surgery.**

Methods. **The IIP patients with suspected lung cancers were randomly assigned to two groups before surgery: in group A (n = 65), sivelestat was perioperatively administered for 5 days; in group B (n = 65), no medications were administered. The primary endpoint was the frequency of acute exacerbation of IIPs. The secondary endpoints were perioperative changes in the lactate dehydrogenase, C-reactive protein, sialylated carbohydrate antigen, surfactant protein D and surfactant protein A values, and the safety of preoperative administration of sivelestat. Multivariate analyses were performed using a logistic regression model to identify the factors that predicted acute exacerbation.**

Results. **Acute exacerbation developed in 2 patients in group A and 1 patient in group B ($p = 0.559$). Administration of sivelestat did not contribute to decreasing the acute exacerbation as well as short- and long-term mortality. The differences were not statistically significant in perioperative lactate dehydrogenase, C-reactive protein, sialylated carbohydrate antigen, and surfactant protein D and A levels. No subjective adverse events were observed. A preoperative partial pressure oxygen level of less than 70 mm Hg was the only predictive factor identified in the logistic analysis ($p = 0.019$, hazard ratio 19.2).**

Conclusions. **Perioperative administration of neutrophil elastase inhibitor appeared to be safe; however, it could not prevent the development of acute exacerbation after surgery in lung cancer patients with IIPs.**

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Idiopathic interstitial pneumonias (IIPs) are well-known lung conditions that are frequently associated with lung cancer [1]. Surgery is a mainstay treatment for early stage lung cancer, and the postoperative mortality rate is generally quite low (30-day mortality 0.6% to 4.1%) [2, 3]. Idiopathic interstitial pneumonias are the main risk factors for high surgical mortality after pulmonary resection (30-day mortality 2.6% to 17%) [4, 5], because lung cancer surgery has the potential to cause acute exacerbation of IIPs. Once acute exacerbation of IIPs develops, it is difficult to manage. Some factors have been reported to predict the occurrence of acute exacerbation after surgery [4, 6, 7]; however, there is no consensus on the effectiveness of prophylactic treatments against acute exacerbation of IIPs after surgery.

Sivelestat, a neutrophil elastase inhibitor, has been approved for the treatment of patients with acute lung injury (ALI) associated with systemic inflammatory response syndrome [8]. Some Japanese reports [9, 10] indicate that sivelestat sodium is effective in preventing the development of acute exacerbation of IIPs. However, no extensive research has been done to evaluate whether the perioperative administration of neutrophil elastase inhibitors prevent acute exacerbation of IIPs. We therefore conducted a prospective randomized study to evaluate whether perioperative administration of a neutrophil elastase inhibitor prevents acute exacerbation of IIPs.

Material and Methods

Patient Selection

The present study included IIP patients with clinically suspected lung cancer. All of the patients underwent preoperative thoracic computed tomography (CT) to evaluate the primary tumor and mediastinal nodes. The CT scans were performed with a slice thickness of 2 mm or less using mediastinal window settings (level 40 HU, width 400 HU) and lung window settings (level 600 HU, width 1,600 HU). A diagnosis of IIPs was made at a surgical conference based on the reported criteria [11]. In the present study, all the CT findings of IIP were re-reviewed by the authors (K.S., K.A., M.F., K.T.). The IIPs were

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Address correspondence to Dr Kenji Suzuki, Department of General Thoracic Surgery, Juntendo University School of Medicine, 1-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113-8431, Japan; email: kjsuzuki@juntendo.ac.jp.

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Abbreviations and Acronyms

ALI = acute lung injury
CRP = C-reactive protein
CT = computed tomography
IIPs = idiopathic interstitial pneumonias
KL-6 = sialylated carbohydrate antigen
LDH = lactate dehydrogenase
SP = surfactant protein
UIP = usual interstitial pneumonia

diagnosed based on reported criteria [11–13] and classified into three groups: usual interstitial pneumonia (UIP) pattern; possible UIP pattern; and inconsistent with the UIP pattern based on the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement [11]. Patients with reticular shadows, which may represent displacement of the lungs by osteophytes or self-weight consolidation, were excluded from the study. The preoperative workup of the surgical candidates consisted of a complete history, a physical examination, laboratory findings, an arterial blood gas analysis, a plain chest roentgenogram, thoracic CT (enhanced if possible), brain magnetic resonance imaging, positron emission tomography, respiratory function test, an electrocardiogram, and an echocardiogram (in cases with abnormal electrocardiogram findings or a history of heart disorders).

Study Design

Patients who met the eligibility criteria were randomly allocated to one of two groups: in group A, sivelestat sodium hydrate (0.2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) was administered from after the induction of anesthesia to postoperative day 5; in group B, no medications were administered. The patients were randomly assigned to the two groups using a random numbers list.

The primary endpoint was the frequency of acute exacerbation of IIPs. The secondary endpoints were perioperative changes in lactate dehydrogenase (LDH), C-reactive protein (CRP), sialylated carbohydrate antigen (KL-6), surfactant protein D (SP-D) and surfactant protein A (SP-A) levels, and safety of preoperative administration of sivelestat sodium hydrate.

An acute exacerbation of IIPs was defined as follows: an unexplained worsening or the development of dyspnea within 30 days of surgery; high-resolution CT with new ground-glass abnormalities or consolidation superimposed on a reticular background or a honeycombing pattern consistent with a UIP; a decrease in arterial oxygen tension of more than 10 mm Hg under similar conditions; no evidence of pulmonary infection by endotracheal aspiration; and the exclusion of alternative causes, including left heart failure, pulmonary embolism, or an identified cause of acute lung injury [14]. All patients in whom acute exacerbation of IIPs was suspected immediately underwent thoracic CT, which included a high-resolution view. The diagnosis of acute exacerbation was made clinically without a histologic biopsy by thoracic surgeons and doctors of pulmonary medicine.

The levels of LDH, CRP, KL-6, SP-D, and SP-A were checked preoperatively. The blood examinations for LDH and CRP were performed on postoperative days 1, 3, and 5; the levels of KL-6, SP-D, and SP-A were measured on postoperative days 1 and 5.

This study was approved by the Ethics Committee of our institute (UMIN000008862). All patients agreed to treatment with written consent.

Perioperative Management

In the present study, the same surgical team performed all the surgeries and coordinated the perioperative management of all the patients. Details of our management have been reported previously [7].

Statistical Analysis

The clinicopathologic features of groups A and B were investigated. Continuous variables were compared using Student's *t* test and Welch's *t* test, and categoric variables were compared using the χ^2 test. The predictors of acute exacerbation of IIPs were determined by univariate and multivariate analyses using a logistic regression model. Differences in LDH, CRP, KL-6, SP-D, and SP-A values were compared using the Mann-Whitney *U* test. Survival rates were calculated by the Kaplan-Meier estimation method using the log rank test. All statistical analyses were performed using the IBM SPSS Statistics 24.0 (IBM Corporation,, Armonk, NY) software program. All *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Among the patients selected as candidates for this trial, 1 patient was excluded as an inoperable case due to pleural dissemination of the lungs (Fig 1). Therefore, 130 patients were randomly assigned to two groups. The study began in October 2009 and ended in April 2015.

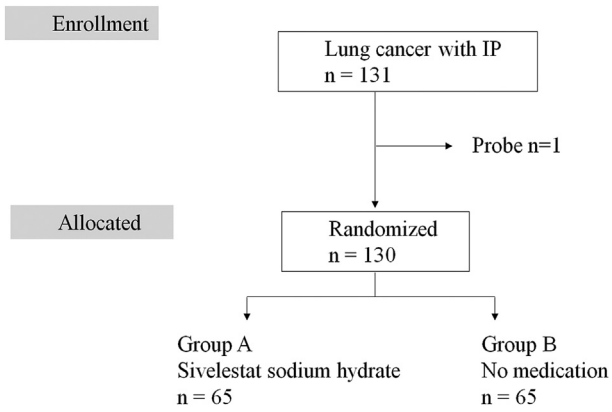

Fig 1. Disposition of the patients in the present study. (IP = interstitial pneumonia.)