Feasibility, utility, and safety of transbronchial cryobiopsy for interstitial lung diseases in Japan

Takato Ikeda,1,2 Akira Nakao,1 Fumiyasu Igata,1 Yoshiaki Kinoshita,2,3 Hisako Kushima,2 Takemasa Matsumoto,1 Hiroshi Ishii,2 Kazuki Nabeshima,3 Masaki Fujita1

1Department of Respiratory Medicine, Fukuoka University Hospital, Jonanku, Fukuoka
2Department of Respiratory Medicine, Fukuoka University Chikushi-Hospital, Chikushino
3Department of Pathology, Fukuoka University Hospital, Jonanku, Fukuoka, Japan

ABSTRACT

Background: Transbronchial lung cryobiopsy (TBLC) is a new technique that enables larger tissue collection than can be obtained by conventional transbronchial lung biopsy. TBLC is becoming popular worldwide and is performed for diffuse lung disease and lung cancer. However, only a few reports of TBLC have been published in Japan. This study was performed to evaluate the efficacy and safety of TBLC at our hospital and compare these findings with past reports.

Methods: From April 2018 to January 2020, 38 patients who underwent TBLC for diffuse lung disease at our hospital were evaluated with respect to age, sex, biopsy site, biopsy size, diagnostic disease, and complications.

Results: The patients who underwent TBLC were 20 men and 18 women with an average age of 63.7 years. The average sample size was 5.7 mm, and the diagnostic rate was 65.7% (25/38). Grade ≥2 complications included bleeding (15.8%), pneumothorax (2.6%), and atrial fibrillation (2.6%).

Conclusions: TBLC was considered to be useful for the diagnosis of diffuse lung disease and could be safely performed.

Key words: Transbronchial lung cryobiopsy; transbronchial lung biopsy; interstitial lung disease; idiopathic pulmonary fibrosis.
Introduction

Lung biopsy is often useful for diagnosing interstitial pneumonia [1]. Although transbronchial lung biopsy (TBLB) is the most commonly used diagnostic biopsy technique, the specimens are often too small and contain artifacts that make evaluation of interstitial lung disease (ILD) difficult. Open lung biopsy or video-assisted thoracoscopic lung biopsy increase the burden on patients. Transbronchial lung cryobiopsy (TBLC) was recently introduced. In an official clinical practice guideline from the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) [2], conditional recommendations were made for performing bronchoalveolar lavage and surgical lung biopsy (SLB) in patients with newly detected ILD who have a high-resolution computed tomography (HRCT) pattern of probable usual interstitial pneumonia (UIP), indeterminate for UIP, or an alternative diagnosis. Because of lack of evidence, however, no recommendation was made for or against performing TBLB or TBLC [2].

TBLC is a useful technique that can be performed using a flexible bronchoscope. However, pneumothorax and bleeding can reportedly occur [3]. In Japan, several institutes have begun using TBLC. Kise et al. [1] reported that the median maximal diameter of the cryobiopsy specimens was 5.3 mm (range 2.0–23.0 mm) and that the median area of the cryobiopsy specimens was 15.5 mm² (range 3.0–136.5 mm²). The rate of obtaining adequate specimens was 91%, and the pathological diagnostic yield was 76%. No complications were observed except for one case of pneumonia. Conversely, Zaizen et al. [4] reported that TBLC is useful for the diagnosis of UIP but not for other ILDs. With a multidisciplinary approach, a diagnosis of idiopathic pulmonary fibrosis (IPF) may be determined by TBLC, whereas diagnosis of ILDs other than IPF may require SLB. The use of TBLC to obtain a diagnosis of ILD remains controversial. In this study, we examined the feasibility, utility, and safety of TBLC in Japan.

Methods

Patient enrollment

In our department, cryobiopsy was introduced in April 2018. Considering the official ATS/ERS/JRS/ALAT clinical practice guidelines with reference to the 2018 IPF international guidelines (2), we basically performed TBLC for patients whose HRCT scan indicated an alternate diagnosis, or had an indeterminate UIP pattern or probable The indication of TBLC was determined by TBLC, whereas diagnosis of ILDs other than IPF may require SLB. The use of TBLC to obtain a diagnosis of ILD remains controversial. In this study, we examined the feasibility, utility, and safety of TBLC in Japan.

TBLC technique

The patients were sedated with midazolam and fentanyl and underwent tracheal intubation before TBLC. After intubation, a Fogarty catheter was placed through the tracheal tube, in advance where to perform TBLC. A cryoprobe was then inserted through the bronchoscope under fluoroscopy, and TBLC was performed at a location 1 cm away from the chest wall. After TBLC, the bronchoscope and cryoprobe were simultaneously removed, and the balloon of the Fogarty catheter was immediately inflated with saline to stop any bleeding. The TBLC specimens were stored in saline. The bronchoscope was reinserted to check for hemostasis. We defined bleeding complications as moderate bleeding, which was defined as grade ≥2 bleeding (requiring topical epinephrine or thrombin).

Determining the diagnosis

We made the final diagnosis according to a post-procedure multidisciplinary discussion (MDD) [2]. Diagnostic rates were determined according to histological findings that contributed to a final diagnosis, or histological findings consistent with the final diagnosis. Diagnostic rates were calculated using the final diagnoses, excluding unclassifiable idiopathic interstitial pneumonia (IIP) and unknown diagnoses.

We diagnosed IPF according to the 2018 IPF international diagnostic guidelines for HRCT and an IPF diagnosis based on histopathologic patterns [2]. In the guidelines, IPF (likely) is confirmed as IPF in the presence of extensive reticular shadows (>30%) on HRCT and patient age >70 years, or bronchoalveolar lavage without increased lymphocyte numbers. We defined unclassifiable IIP as multiple patterns in HRCT and/or pathological patterns, new diseases not characterized by the current ATS/ERS classification, or special cases not usually recognized (e.g., organizing pneumonia with fibrosis) [5]. For fibrosis that could not be attributed to any specific type of interstitial lung diseases according to a MDD discussion, the condition was defined as unclassifiable IIP [1]. Unknown was defined as sample failure or no significant findings. When we could not determine the specific diagnosis based on the MDD, we classified the patients as unknown diagnosis. Sample failure was defined as cases where the collected sample included only the airway.

Statistical analysis

Clinical data were expressed as mean, percentage, or median. Data were recorded and analyzed using StatMate V (GraphPad Software, San Diego, CA, USA).

Results

Results of TBLC

The patient characteristics of 38 patients who underwent TBLC are summarized in Table 1. The patients were 20 men and 18 women with an average age of 63.7 years. TBLC was performed safely in all cases, and tissue was obtained for evaluation. The average number of biopsies was 2.4. Zero, 4, 42, 1, and 45 biopsies were taken from the right upper lobe, right middle lobe, right lower lobe, upper left lobe, and lower left lobe, respectively. The average specimen size was 5.7 mm. We found that the HRCT

| Table 1. Characteristics of patients who underwent TBLC. |
|---------------------------------|------------------|
| **Factor**                      | **n=38**         |
| Age (average)                   | 64±13            |
| Sex (male/female)               | 20/18            |
| Biopsy number (average)         | 2                |
| Frozen time                     | 6 sec            |
| Biopsy area (RUL/RML/RLL/LUL/LLL)| 0/4/2/1/5 (total: 92) |
| Sample size                     | 5.7 ± 1.4 mm     |

TBLC, transbronchial lung cryobiopsy; RUL/RML/RLL/LUL/LLL, right upper lobe/right middle lobe/right lower lobe/left upper lobe/left lower lobe.
Discussion

In this study, we examined the feasibility, utility, and safety of TBLC for ILD. Lung specimens with an average diameter of 5 mm were obtained. We observed no serious complications such as pneumothorax or bleeding. In the present study, the diagnostic rate was 65.7%. TBLC seems to be a safe procedure with lower complications and mortality rates than SLB, as other researchers have reported [3]. Moreover, the diagnostic rate obtained by TBLC was also favorable.

The development of complications is a major issue in TBLC. In previous reports, complications of TBLC were pneumothorax and atrial fibrillation were observed in one patient (2.6%), respectively.

Table 2. Diagnoses in patients who underwent TBLC. Cases in which the histological and MDD diagnoses are consistent are listed in bold.

| Histopathologic diagnosis                  | Multidisciplinary diagnosis |
|--------------------------------------------|-----------------------------|
| Probable UIP                                | IPF                         |
|                                            | Unclassifiable IIP          |
| Indeterminate for UIP                       | CVD–ILD                     |
|                                            | IPF                         |
|                                            | Unclassifiable IIP          |
|                                            | Drug-induced pneumonitis    |
| Alternative diagnosis                       |                            |
| OP                                         | Unclassifiable IIP          |
| NSIP                                       | COP                         |
| LIP                                        | CVD–ILD                     |
| Non-necrotizing granulomatous inflammation | I-NSIP                      |
| Focal interstitial change                   | Drug-induced pneumonitis    |
| IgG4-related interstitial change            | LIP                         |
| OP + NSIP                                  | Sarcoïdosis                 |
| OP + Non-necrotizing granulomatous         | Hypersensitivity pneumonitis|
| Unknown                                    |                            |

TBLC, transbronchial lung biopsy; UIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; I-NSIP, idiopathic nonspecific interstitial pneumonia; OP, organizing pneumonia; COP, cryptogenic organizing pneumonia; LIP, lymphoid interstitial pneumonia; CVD–ILD, collagen vascular disease–interstitial lung disease; IgG4, immunoglobulin G4.
small. Second, this study was performed at a single center, increasing the possibility of bias. To build on our findings, multicenter prospective studies will be needed to clarify the role of TBLC in patients with ILD.

Conclusion

The feasibility, utility, and safety of TBLC for the diagnosis of ILD were evaluated in this study. TBLC was effective for the diagnosis of ILD. TBLC did not induce serious bleeding or pneumothorax.

Acknowledgments

We thank Angela Morben, DVM, ELS, and Jane Charbonneau, DVM, from Edanz Group (https://en-author-services.edanzgroup.com), for editing a draft of this manuscript.

Abbreviations

TBLC transbronchial lung cryobiopsy;
TBLB transbronchial lung biopsy;
SLB surgical lung biopsy;
UIP usual interstitial pneumonia;
ILD interstitial lung disease;
IPF idiopathic pulmonary fibrosis;
HRCT high-resolution computed tomography;
ATS American Thoracic Society;
ERS European Respiratory Society;
JRS Japanese Respiratory Society;
ALAT Latin American Thoracic Society;
MDD Multidisciplinary Discussion;
IIP idiopathic interstitial pneumonia.

References

1. Kuse N, Inomata M, Awano N, Yoshimura H, Jo T, Tone M, et al. Management and utility of transbronchial lung cryobiopsy in Japan. Respir Investig 2019;57:245-51.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-68.
3. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Picciucci S, et al. Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: A comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. Respiration 2016;91:215-27.
4. Zaizen Y, Kohashi Y, Kuroda K, Tabata K, Kitamura Y, Hebisawa A, et al. Concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in patients with diffuse interstitial lung disease. Diagn Pathol 2019;14:131.
5. Travis WD, 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.
6. Colella S, Haentschel M, Shah P, Poletti V, Hetzel J. Transbronchial lung cryobiopsy in interstitial lung diseases: Best practice. Respiration 2018;95:383-91.
7. Stather DR, MacEachern P, Chee A, Dumoulin E, Tremblay A. Trainee impact on procedural complications: an analysis of 967 consecutive flexible bronchoscopy procedures in an interventional pulmonology practice. Respiration 2013;85:422-8.
8. Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: Retrospective analysis of 74 cases. Chest 2017;151:400-8.
9. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, et al. Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2016;193:745-52.
10. Yoshimura H, Awano N, Inomata M, Kuse N, Tone M, Jo T, et al. Diagnostic utility of transbronchial lung cryobiopsy: Two cases of anti-aminocycl-tRNA synthetase syndrome with respiratory failure. Respir Investig 2019;57:399-403.
11. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States, 2000 to 2011. Am J Respir Crit Care Med 2016;193:1161-7.
12. Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, et al. Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. Am J Respir Crit Care Med 2019;199:1249-56.
13. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung