Multidisciplinary Respiratory Medicine 2021; volume 16:731

ORIGINAL RESEARCH ARTICLE

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 Fujita[1]

[1]Department of Respiratory Medicine, Fukuoka University Hospital, Jonanku, Fukuoka
[2]Department of Respiratory Medicine, Fukuoka University Chikushi-Hospital, Chikushino
[3]Department 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.

Correspondence: Masaki Fujita, Department of Respiratory Medicine, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonanku, Fukuoka 814-0180, Japan. Tel. +81.92.801-1011 - Fax: +81.92.865-6220. E-mail: mfujita@fukuoka-u.ac.jp

Contributions: TI, YK, HI, and MF conceived the study, performed all of the experiments, and prepared the manuscript. AN, FI, and HK helped to accumulate the clinical data. YK and KN performed the pathological experiments. All authors read and approved the final manuscript.

Conflict of interest: The authors report no conflict of interest.

Funding: This study was not supported by any funding.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Fukuoka University (2017M157, 9 February 2018). Written informed consent was obtained from all patients.

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. Kuse *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 mm^2 (range 3.0-136.5 mm^2). 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 discussions by clinicians. Thirty-eight patients with diffuse lung disease were enrolled in this study until January 2020. We examined diagnostic rate of TBLC and the complications such as pneumothorax, bleeding, and atrial fibrillation. This study was approved by the Institutional Review Board of Fukuoka University (2017M157, 9 February 2018), and all participants or proxies gave written informed consent.

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 are 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)	0/4/42/1/45 (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/lower left lobe.

pattern was probable UIP pattern in 7 cases (18.4%), indeterminate for UIP pattern in 3 cases (7.9%), and an alternate diagnosis in 28 cases (73.6%). The histopathologic pattern was UIP in 0 cases (0.0%), probable UIP in 4 cases (10.5%), indeterminate for UIP in 8 cases (21.0%), and an alternate diagnosis in 22 cases (57.8%), unknown in 4 cases (10.5%) (Table 2). We could evaluate the samples which contain the subpleural or paraseptal regions in only 8/38 (21.0%). In TBLC, there were 2 cases of sample failure, and 36/38 (94.7%) were evaluable samples. The final diagnosis was IPF (n=3), idiopathic nonspecific interstitial pneumonia (n=2), cryptogenic organizing pneumonia (n=2), lymphoid interstitial pneumonia (n=1), unclassifiable IIP (n=6), drug-induced interstitial pneumonia (n=3), collagen vascular disease–ILD (n=7), immunoglobulin G4-related lung disease (n=2), hypersensitivity pneumonia (n=2), and sarcoidosis (n=3). Seven patients were not diagnosed. The diagnostic rate was 65.7% (25/38).

Regarding complications, grade ≥2 bleeding (requiring topical epinephrine or thrombin) was observed in six patients (15.8%) and mild pneumothorax and atrial fibrillation were observed in one patient (2.6%), respectively.

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 complication and mortality rates than SLB, as other researchers have reported [3]. Moreover, the diagnosis rate obtained by TBLC was also favorable.

The development of complications is a major issue in TBLC. In previous reports, complications of TBLB were pneumothorax in <5% of patients and bleeding in <5%. Conversely, these rates for TBLC were 10% and <5%, respectively [6,7]. In the present study, pneumothorax occurred in 2.6% of patients, but no patients developed severe bleeding. Although the balloon occlusion method effectively avoids severe bleeding, guiding the balloon blocker to the occlusion site is sometimes challenging and complicates the cryobiopsy procedure. We could evaluate the samples which contain the subpleural or paraseptal regions in only 8/38, most of which were airway and peri-airway specimens. This may be one of the reasons why we had less pneumothorax and more bleeding. The diagnostic rate of TBLC in the previous reports ranges from 51 to 91% [8,9]. In the present study, 65.7% of cases were diagnosed by TBLC. TBLC is considered to be a powerful tool to confirm several diagnoses, especially pulmonary diseases around the airway such as sarcoidosis and immunoglobulin G4-related pneumopathy. Yoshimura et *al*. reported two cases of anti-aminoacyl-tRNA synthetase syndrome diagnosed by TBLC [10].

For the diagnosis of IPF, obtaining specimens from the secondary lobules adjacent to the pleura is difficult using TBLC. Zaizen *et al*. [4] reported that six cases were diagnosed as UIP using both TBLC and SLB. One case was diagnosed as indeterminate for UIP by TBLC and as probable UIP by SLB. The etiological diagnoses were concordant between TBLC and SLB in two cases of IPF, but were discordant for other diagnoses. Based on these data, Zaizen *et al*. concluded that TBLC is useful for diagnosing UIP but no other ILDs. Using a multidisciplinary approach, a diagnosis of IPF may be determined by TBLC, whereas ILDs other than IPF may require SLB [4]. SLB for ILD can help clarify the diagnosis; however, while the in-hospital mortality rate after elective lung biopsy is as low as 1.7%, it significantly increases to 16.0% in nonelective, urgent, and emergency procedures [11]. Romagnoli *et al*. [12] reported that patients undergoing SLB underwent a preoperative cryobiopsy at the site of the biopsy, and diagnostic concordance was low. However, a similar direct comparison of SLB and cryobiopsy in the same patient recently showed high diagnostic agreement between the two techniques [13].

This study has some limitations. First, the number of cases was

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	4	**IPF**	**2**
		Unclassifiable IIP	2
Indeterminate for UIP	8	CVD–ILD	4
		IPF	1
		Unclassifiable IIP	**2**
		Drug-induced pneumonitis	1
Alternative diagnosis			
OP	4	Unclassifiable IIP	2
		COP	**2**
NSIP	5	**CVD–ILD**	**2**
		I-NSIP	**2**
		Drug-induced pneumonitis	**1**
LIP	1	**LIP**	**1**
Non-necrotizing granulomatous inflammation	5	**Sarcoidosis**	**3**
		Hypersensitivity pneumonitis	**2**
Focal interstitial change	3	Unknown	3
IgG4-related interstitial change	2	**IgG4-related pneumonitis**	**2**
OP + NSIP	1	**CVD–ILD**	**1**
OP + Non-necrotizing granulomatous inflammation	1	**Drug-induced pneumonitis**	**1**
Unknown	4	Unknown	4

TBLC, transbronchial lung cryobiopsy; IIP, 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.

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Received for publication: 20 October 2020. Accepted for publication:8 February 2021.

Multidisciplinary Respiratory Medicine 2021; 16:731
doi:10.4081/mrm.2021.731