Accuracy of transbronchial biopsy as a rebiopsy method for patients with relapse of advanced non-small-cell lung cancer after systemic chemotherapy

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of death worldwide due to cancer.1 Transbronchial biopsy (TBB) using a flexible bronchoscope has been commonly used for establishing a diagnosis of lung cancer, having a more favourable safety profile than transthoracic needle aspiration or surgical procedures.2–4 Although the diagnostic yield of TBB has not been satisfactory, especially for small peripheral lesions, recent technical advances have improved its diagnostic accuracy.4

Therapeutic strategies for NSCLC over the past few decades have focused on overcoming resistance to molecular targeted therapies and development of immunotherapies.5–14 It has been suggested that expression of programmed cell death-ligand 1 (PD-L1) in tumours may predict a favourable response to immune checkpoint inhibitors.13 14 In order to evaluate the mechanisms of resistance to molecular targeted therapies, immunostaining for PD-L1 is necessary using tumour samples obtained after disease progression. Rebiopsy is performed for this purpose, and TBB seems to be the safest method for doing so, except for cases of skin, muscle or superficial lymph node metastasis. However, the utility of TBB as a rebiopsy method and the impact of

KEY MESSAGES

▸ Therapeutic strategies for non-small-cell lung cancer (NSCLC) have focused on next-generation EGFR-TKIs and immunotherapies.
▸ Rebiopsy is required to evaluate the T790M mutation or programmed cell death-ligand 1 expression.
▸ The aim of this study was to assess the feasibility and safety of transbronchial biopsy (TBB) in patients with NSCLC relapse.
▸ We demonstrated that TBB for rebiopsy has a high diagnostic yield without severe complications.
▸ The diagnostic yield was not associated with patient background and treatment history.
previous treatment on its diagnostic yield are unknown. Here, we retrospectively evaluated the accuracy and safety of TBB as a rebiopsy method in patients with advanced NSCLC that had relapsed after systemic chemotherapy, and the factors influencing its diagnostic yield.

MATERIALS AND METHODS

Patients

We retrospectively screened 2126 consecutive patients who underwent bronchoscopy at Kurume University Hospital between January 2012 and June 2016. Among these patients, 109 with advanced NSCLC who underwent TBB for rebiopsy after developing resistance to systemic chemotherapy were enrolled. These patients underwent TBB for enrolment in clinical trials that required rebiopsy, further investigation of tumour mutations, or assessment of whether TKI treatment should be continued. In patients who underwent multiple rebiopsies, the result of the initial rebiopsy was selected. The clinical characteristics of the patients, including age, sex, smoking status, histology, mutational status, tumour size, previous treatment and efficacy of the previous treatment, were recorded. Tumour response was examined by CT and evaluated using the Response Evaluation Criteria for Solid Tumors V.1.0 (RESIST V.1.0). 

The present study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University Hospital (IRB No. 12029). Informed consent was obtained from the patients.

Procedure of TBB

For TBB, a conventional flexible bronchoscope (BF-260, P260F, P290 or 1T240 Bronchovideoscope, Olympus, Tokyo, Japan) was used after spraying the pharynx with 2% xylocaine. Procedures were performed under conscious sedation with midazolam. TBB was performed under guidance with a radial ultrasound probe (UM-S20-17S, Olympus, Tokyo, Japan) and a guide sheath kit (K-201, Olympus, Tokyo, Japan) was used after spraying the pharynx with 2% xylocaine. Procedures were performed under conscious sedation with midazolam.

Statistical analysis

Correlations between patient characteristics and the success of rebiopsy were analysed using Fisher’s exact test for categorical variables. All tests were two-sided, and differences were considered statistically significant at p<0.05. All of the statistical analyses were conducted using JMP V.10 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient characteristics

The clinical characteristics of the 109 patients are shown in table 1. The median age of the patients at the time of rebiopsy was 67 years (range 35–85 years), and 50 of the patients were men. One hundred and one patients had adenocarcinoma, and 59 patients had no smoking history. Sixty-two of the patients had epidermal growth factor receptor (EGFR) mutation, five had anaplastic lymphoma kinase (ALK) rearrangement, and 42 were negative for both EGFR and ALK anomaly. Rebiopsy was performed after first-line treatment in 61 patients, after second-line treatment in 24, and after third-line or further treatment in 24. The mean diameter of the target lesions for rebiopsy was 34.6 mm (range 10–89 mm). Ten patients had lung metastasis that was targeted for rebiopsy. Tumour or bronchial mucosal infiltration was visible on bronchoscopy in 25 patients, and invisible in 84 patients who had only peripheral lung lesions. The overall rate of response to the previous treatment before rebiopsy was 55.0%.

Results of rebiopsy and postprocedural complications

Adequate tumour samples were obtained from 88 patients, giving an overall diagnostic yield of 80.7% (figure 1A). Among these patients with positive diagnostic results, 64 were analysed by predesigned mutational testing and 24 by immunohistochemistry. In 21 patients, the tumour samples collected were inadequate. Although the pathological features of the specimens

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Number</th>
<th>Per cent</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>33–85</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>45.9</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
<td>54.1</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>59</td>
<td>45.1</td>
</tr>
<tr>
<td>Former/current</td>
<td>50</td>
<td>45.9</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>101</td>
<td>92.7</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Mutational status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>62</td>
<td>56.9</td>
</tr>
<tr>
<td>ALK</td>
<td>5</td>
<td>4.6</td>
</tr>
<tr>
<td>Wild</td>
<td>42</td>
<td>38.5</td>
</tr>
<tr>
<td><strong>Pretreatment line</strong></td>
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<td></td>
</tr>
<tr>
<td>First</td>
<td>61</td>
<td>56.0</td>
</tr>
<tr>
<td>Second</td>
<td>24</td>
<td>22.0</td>
</tr>
<tr>
<td>Third or further</td>
<td>24</td>
<td>22.0</td>
</tr>
<tr>
<td><strong>Tumour size (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>10–89</td>
<td></td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor.
suggested possible malignancy in four patients, these samples were inadequate for mutational analysis or immunostaining because of fragmentation or low numbers of cells. Furthermore, one patient had only a necrotic tissue without viable tumour cells (figure 1B). The specimen from the remaining patients showed normal lung tissue and fibrosis in 13 and 3 patients, respectively (figure 1C).

Postprocedural complications were observed in 12 cases. Four patients developed transient fever, and haemorrhage during the biopsy, requiring haemostasis, occurred in eight patients. However, none of these events required inpatient hospitalisation or prolongation of existing hospitalisation. There were no cases of pneumothorax or massive haemoptysis.

**Association between diagnostic yield and clinicopathological features**

The factors affecting the diagnostic yield of TBB for rebiopsy are shown in table 2. The diagnostic yield of TBB for mass lesions was significantly higher than that for nodular lesions (≥30 mm: 59 of 65 lesions; 90.1% vs <30 mm: 29 of 44 lesions; 65.9%, p<0.01). There was no significant correlation between diagnostic yield and other clinicopathological features including tumour mutational status, previous treatment and efficacy of the previous treatment before rebiopsy.

**DISCUSSION**

With the development of new therapeutic strategies for NSCLC, including next-generation EGFR-TKIs or blockade of immune checkpoints with monoclonal antibodies, the importance of rebiopsy has increased.\(^\text{11-14}\) Any method for tissue collection in this setting should be reliable and safe. In the present study, we investigated TBB as a method for rebiopsy in patients with advanced NSCLC that had relapsed after systemic chemotherapy. We found that TBB had a high diagnostic yield of 80.7% and was not associated with severe complications. As far as we are aware, no previous study has investigated the utility of TBB for rebiopsy in NSCLC patients, or the factors influencing its diagnostic yield. Some previous studies have investigated the feasibility of rebiopsy in NSCLC patients. Chouaid et al\(^\text{16}\) and Bosc et al\(^\text{17}\) reported that an adequate tissue sample was obtained in 74.4% (61/82) and 89.7% (35/39) of cases, the proportions of patients undergoing TBB for rebiopsy being 52% (43/
the diagnostic yield for small peripheral pulmonary lesions, as long as the tumour was detectable by EBUS-GS (figure 2). Furthermore, there were no severe complications such as pneumothorax or serious haemorrhage. In comparison with core needle biopsy or surgical biopsy, which have higher accuracy for rebiopsy but are more invasive, TBB is a safer method with equivalent diagnostic ability.

We initially hypothesised that a dramatic reduction of tumour volume resulting from previous treatment might have a negative impact on the diagnostic yield of TBB. Use of the antiangiogenic agent bevacizumab for nonsquamous cell NSCLC and molecular targeting inhibitors for EGFR/ALK-positive NSCLC has yielded relatively high response rates in comparison with conventional systemic chemotherapies. We investigated the association between diagnostic yield and several factors, including the previous treatment regimen or response to the previous treatment before rebiopsy. However, the success of tissue collection by TBB was not associated with tumour mutational status, previous treatment or efficacy of the previous treatment before rebiopsy. Our results suggest that TBB is one of the safest and most accurate procedures for rebiopsy, and can yield information useful for decision-making about possible next-line treatment.

This study had several limitations. First, the number of patients included was relatively small. Second, the information was collected retrospectively. Third, the indication of TBB for rebiopsy was determined by individual attending physicians. Also, as TBB was performed for pulmonary lesions considered to have sufficient tissue for biopsy based on CT findings, this may have resulted in selection bias.

In conclusion, we have demonstrated that TBB for rebiopsy of NSCLC that has relapsed after chemotherapy is not associated with severe complications and has a high diagnostic yield, regardless of tumour mutational status, previous treatment or efficacy of the previous treatment before rebiopsy. Our results suggest that TBB is one of the safest and most accurate procedures for rebiopsy, and can yield information useful for decision-making about possible next-line treatment.

Figure 2  Successful tissue collection in patients with relapse of EGFR-positive adenocarcinoma after EGFR-TKI treatment. (A) Chest CT demonstrates a nodular lesion 12 mm in diameter in S10 of the left lung. (B) EBUS image shows a hypoechoic nodule with an irregular margin. (C) Transbronchial biopsy of the lesion detected by EBUS. EBUS, endobronchial ultrasound; EGFR, epidermal growth factor receptor.


