Feasibility of Rebiopsy in Non-Small Cell Lung Cancer Treated with Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors

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Abstract

Objective Analyses of tumor biopsy samples from non-small cell lung cancer patients with acquired epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) resistance are expected to reveal the molecular mechanisms of resistance. However, due to limited tissue availability, performing such analyses can be challenging. We herein investigated the feasibility of tumor rebiopsy in this patient population.

Methods From April 2004 to March 2013, 53 consecutive patients were treated with EGFR-TKIs at our department. A retrospective medical chart review was conducted among patients with progressive disease (PD) assessed radiographically. Sites of progression were evaluated at the time of PD.

Results Forty patients experienced PD at the following sites: isolated central nervous system (CNS) in 10 patients; isolated bone in five patients; isolated lymph nodes in two patients; the primary lesion in 10 patients; and systemic disease in 11 patients. Concerning the site of progression, 20 of the 40 patients had a lesion that could be accessed using endobronchial, transbronchial or percutaneous biopsy procedures. Among the 19 patients with oligoprogressive disease or CNS failure, the median overall survival was 24.1 months in eight patients who had received continuing treatment with EGFR-TKIs following radiotherapy and 16.8 months in 11 patients who received other therapies after PD.

Conclusion In this study, few patients had a site of progression capable of being accessed using relatively noninvasive biopsy procedures. Further investigations are warranted to develop more optimal treatment strategies after PD in patients with oligoprogressive disease or CNS failure.

Key words: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, oligoprogressive disease, rebiopsy

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Introduction

Somatic mutations of the epidermal growth factor receptor (EGFR) gene are found in approximately 25-40% of Japanese patients with non-small cell lung cancer (NSCLC) (1, 2). Approximately 60-80% of EGFR mutation-sensitive NSCLC patients initially show a good clinical response to EGFR-tyrosine kinase inhibitors (TKIs) (3-5). EGFR-TKI treatment also has a survival benefit in EGFR-mutant NSCLC patients (6). However, disease recurrence frequently occurs in patients exhibiting a previous response to EGFR-TKI therapy; this phenomenon is referred to as acquired EGFR-TKI resistance (7). Analyses of tumor biopsy samples from patients with acquired EGFR-TKI resistance have indicated the molecular mechanisms of resistance, including the presence of secondary T790M mutations in the EGFR, as well as MET or HER2 gene amplification (8, 9).

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Table. Patients’ Characteristics (40 Patients That Experienced PD).

| Characteristics                     | n=40 | Percent |
|-------------------------------------|------|---------|
| Median age (range), years           | 66   | (43–83) |
| Sex                                 |      |         |
| Male                                | 13   | 32.5    |
| Female                              | 27   | 67.5    |
| Stage                               |      |         |
| IIIB                                | 3    | 7.5     |
| IV                                  | 27   | 67.5    |
| Recurrence                          | 10   | 25.0    |
| Histology                           |      |         |
| Adenocarcinoma                      | 39   | 97.5    |
| Unknown                             | 1    | 2.5     |
| Type of EGFR mutation               |      |         |
| Exon 18 (G719X)                     | 2    | 5.0     |
| Exon 19 (deletion)                  | 15   | 37.5    |
| Exon 21 (L858R)                     | 13   | 32.5    |
| Exon 18 (G719X) + Exon 19 (deletion)| 1   | 2.5     |
| Unknown                             | 9    | 22.5    |
| Line of EGFR-TKI                    |      |         |
| First                               | 22   | 55.0    |
| Second or later                     | 18   | 45.0    |
| EGFR-TKI                            |      |         |
| Gefitinib                           | 33   | 82.5    |
| Erlotinib                           | 7    | 17.5    |
| Response to EGFR-TKI                |      |         |
| CR/PR                               | 19   | 47.5    |
| SD                                  | 21   | 52.5    |

PD: Progressive disease, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, CR: complete response, PR: partial response, SD: stable disease

Several clinical trials aimed at stratifying the molecular mechanisms of acquired resistance to EGFR-TKI treatment are ongoing; however, due to the locations of sites of tumor progression, tumor biopsies are often invasive in patients with acquired EGFR-TKI resistance. It is therefore necessary to investigate the number of patients able to undergo rebiopsies. In this report, we sought to determine the feasibility of performing tumor rebiopsy in these patients.

Materials and Methods

Patient selection

The cases of 53 consecutive patients treated with EGFR-TKIs at the Department of Respiratory Medicine and Medical Oncology, Gifu Municipal Hospital between April 2004 and March 2013 were reviewed. The criteria for the use of the patients’ data were as follows: general consent; a diagnosis of Stage IIIB or IV disease; and recurrent NSCLC showing a clinical benefit from initial EGFR-TKI treatment. A clinical benefit derived from EGFR-TKI treatment was defined based on either a documented partial or complete response or a significant and durable (≥6 months) clinical benefit after the initiation of EGFR-TKI treatment (7). This study was approved by the institutional review board of Gifu Municipal Hospital, and informed consent regarding the EGFR mutational analyses was obtained from all patients.

Evaluation

The tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1. Progression-free survival (PFS1) was measured from the initiation of EGFR-TKI treatment to the date of disease progression or death from any cause or withdrawal of treatment. Subsequent PFS (PFS2) was measured from the time of the first instance of disease progression to the date of the second instance of disease progression and/or death from any cause or withdrawal of treatment in patients with oligoprogressive disease. Overall survival (OS) was measured from the time of initiation of EGFR-TKI treatment to the date of death or the last visit in patients whose death could not confirmed.

Definition of difficulty in rebiopsy

The sites of progression were evaluated at the time of diagnosis of progressive disease (PD). As assessed based on the radiological findings, cases in which there were no sites of progression capable of being accessed using endobronchial, transbronchial or percutaneous biopsy procedures were defined as being difficult for rebiopsy.

Definition of oligoprogressive disease

Oligoprogressive disease was defined as either or both of the following at the time of PD: non-leptomeningeal central nervous system (CNS) disease or four or fewer sites of extra-CNS progression (10).

Definition of CNS failure

CNS failure was defined as CNS progression only, without systemic deterioration, at the time of PD.

Statistical analysis

The PFS1, PFS2 and OS rates were estimated using the Kaplan-Meier method. All statistical analyses were performed using the SPSS v.21.0 software program (IBM, Armonk, USA).

Results

Patient characteristics

From April 2004 to March 2013, 45 patients exhibiting a clinical benefit from EGFR-TKI treatment were identified. The median PFS was 13.3 months [95% confidence interval (CI), 10.2–16.3], and the median OS was 39.9 months (95% CI, 23.4–56.3). Forty of the patients who had experienced PD were further analyzed. The characteristics of these patients are shown in Table. Of these patients, 28 (70.0%) had a major type of EGFR mutation (exon 19 deletion or exon 21L858R) and nine (22.5%) were of unknown EGFR status.

Progression patterns at the time of PD

At the time of PD, 10 patients showed isolated CNS me-
tastasis, 19 had solitary lesions and 11 displayed multiple lesions. As assessed according to the radiological findings, 20 patients (50%) showed sites of progression defined as being difficult for rebiopsy. Sites found to be noninvasive for rebiopsy were as follows: bone (n=1); lymph nodes (n=1); liver (n=1); primary lesion (n=1) and pleural effusion (n=2). A total of five procedures, including thoracentesis in two cases and transbronchial biopsy in three cases, were conducted for rebiopsy (one patient had a secondary T790M mutation). PD: progressive disease, EGFR: epidermal growth factor receptor, CNS: central nervous system, TKI: continuation of EGFR-TKI only, RT: radiotherapy as local therapy, Chemo: cytotoxic chemotherapy, BSC: best supportive care.

Discussion

NSCLC patients with EGFR mutations exhibit a high response rate (RR) and long PFS when treated with EGFR-TKIs. Previous studies have reported that these patients display a poorer prognosis when treated with chemotherapy alone than with EGFR-TKIs (11, 12). Therefore, EGFR-TKIs are key drugs for the treatment of NSCLC associated with EGFR mutations. In addition, there is a lack of standardized timing for the termination of EGFR-TKI treatment, and careful decision making is required regarding whether to continue EGFR-TKI therapy, switch to chemotherapy or apply the EGFR-TKI drugs with other therapies. The development of therapeutic agents in accordance with the molecular mechanisms of resistance, including the presence of secondary T790M mutations in EGFR, is underway. In order to provide these treatments in appropriate cases, it is necessary to investigate the mechanisms underlying the onset of resistance. Importantly, various mechanisms of acquired resistance to EGFR-TKI treatment have been reported, and different sites of progression show different mechanisms of resistance.

Performing a rebiopsy at the time of acquired resistance may inform treatment decisions, and understanding the mechanisms that underlie acquired resistance is essential for developing treatment strategies. A previous report by Yu et
al. evaluated the mechanisms of acquired resistance to EGFR-TKI treatment; however, in that study, a total of 162 procedures, including invasive procedures, such as brain resection in 10 cases, lung resection in four cases, adrenalectomy in three cases and lymph node excision in five cases, were conducted to obtain samples for the analysis (8). In addition, not all biopsy samples provided sufficient material for a molecular analysis. In the current study, half of the sites of progression required the use of an invasive procedure for rebiopsy. Identifying EGFR-TKI-resistance mechanisms in individual patients may be difficult in many cases. Therefore, the creation of a noninvasive method for identifying resistance mechanisms is required, and overcoming this issue is important for developing future targeted therapies for lung cancer.

Furthermore, oligoprogressive disease often requires invasive procedures for biopsy. In the present study, only three such patients (15.7%) had sites of progression found to be feasible for rebiopsy. Moreover, not all biopsy samples provide sufficient material for molecular analyses, and rebiopsy procedures should be carried out using minimally invasive procedures. At the time of onset of acquired resistance, oncogene-addicted NSCLC with oligoprogressive disease being treated with relevant targeted therapies often appears to be suitable for local ablative therapy and the continued administration of the targeted agent, and these treatments are well tolerated in such cases (10, 13). Therefore, in cases of oligoprogressive disease in which invasive procedures are required for rebiopsy, the rebiopsy may not be necessary.

The present study is associated with several limitations. First, this study was retrospective. Second, the interval between the evaluations was variable, as was the line of EGFR-TKI therapy; these variations represent bias in the PFS assessments. Furthermore, although our data set was small, it was similar to the size of data sets in previous reports of the progression patterns of PD (14, 15). It is therefore reasonable to consider that half of sites of progression are difficult for rebiopsy.

**Conclusion**

In conclusion, few patients have sites of progression that can be accessed using relatively noninvasive biopsy procedures. Therefore, additional noninvasive methods for identifying resistance mechanisms are required, and further evaluations of effective therapies after treatment failure with EGFR-TKIs are needed to develop more optimal therapeutic strategies.

The authors state that they have no Conflict of Interest (COI).

**References**

1. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97: 339-346, 2005.
2. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer Res 64: 8919-8923, 2004.
3. Mitsudomi T, Morita S, Yatabe Y, et al. West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomized phase 3 trial. Lancet Oncol 11: 121-128, 2010.
4. Zhou C, Wu YI, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12: 735-742, 2012.
5. Rosell R, Cancereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13: 239-246, 2012.
6. Takano T, Fukui T, Ohe Y, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: A historical comparison of patients treated before and after gefitinib approval in Japan. J Clin Oncol 26: 5589-5595, 2008.
7. Jackman D, Pao W, Riedly GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 28: 357-360, 2010.
8. Yu HA, Arcilla ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 19: 240-246, 2013.
9. Uramoto H, Yamada T, Yano S, et al. Prognostic value of acquired resistance-related molecules in Japanese patients with NSCLC treated with an EGFR-TKI. Anticancer Res 32: 3785-3790, 2012.
10. Weichhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in onco-gene-addicted non-small-cell lung cancer. J Thorac Oncol 7: 1807-1814, 2012.
11. Inoue A, Kobayashi K, Maemondo M, et al. Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations [abstract]. J Clin Oncol 29: 7519, 2011.
12. Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 30: 7520, 2012.
13. Yu HA, Shima CS, Huang J, et al. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. J Thorac Oncol 8: 346-351, 2013.
14. Yoshida T, Yoh K, Goto K, et al. Progression patterns at RECIST PD during EGFR-TKIs in advanced NSCLC patients harboring EGFR mutation [abstract]. J Clin Oncol 31: 8078, 2013.
15. Chen MJ, Zhong W, Zhang L, et al. Recurrence patterns of advanced non-small cell lung cancer treated with gefitinib. Chin Med J 126: 2235-2241, 2013.