Efficacy of Ceritinib After Alectinib for ALK-positive Non-small Cell Lung Cancer

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Abstract. Background: Alectinib is a new standard treatment for treatment-naïve anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC); however, resistance ultimately develops in almost all patients, and data regarding the efficiency of ceritinib for such patients are insufficient. Patients and Methods: Patients with ALK-positive NSCLC treated at the Kyoto University Hospital from January 2012 to March 2017 were reviewed. Patients who were treated with ceritinib after alectinib were identified, and the efficacy of ceritinib after alectinib was retrospectively evaluated. Results: There were 35 patients with ALK-positive NSCLC, nine of whom received ceritinib after alectinib. The overall response rate to ceritinib was 44%. It was 16% in patients who received ceritinib immediately after alectinib, and 100% in patients who received chemotherapy before ceritinib. The median progression-free survival for patients treated with ceritinib was 4.4 months (95% confidence interval (CI)=1.1-6.5 months). Conclusion: Ceritinib demonstrated a modest clinical benefit after failure of alectinib. Ceritinib may be a reasonable treatment option in this setting.

Anaplastic lymphoma kinase (ALK) rearrangement is an established driver oncogene in non-small cell lung cancer (NSCLC) (1), and ALK inhibitors are the standard treatment for ALK-positive NSCLC. Crizotinib is a first-generation ALK inhibitor (2, 3), and current second-generation ALK inhibitors, such as alectinib and ceritinib, are also available in Japan. Previous studies have demonstrated the efficacy of alectinib in patients with crizotinib-resistant (4-6) or crizotinib-naïve ALK-positive NSCLC (7). Furthermore, two randomized phase III studies independently found that alectinib was significantly superior to crizotinib in progression-free survival (PFS), response rate, and toxicity (8, 9). Based on the results of the phase III studies, alectinib is considered to be a new standard treatment for treatment-naïve ALK-positive NSCLC; however, almost all patients acquire resistance to alectinib, leaving only two treatment options: cytotoxic chemotherapy and another second-generation ALK inhibitor, ceritinib. Preclinical data have suggested the efficacy of ceritinib after alectinib (10), but clinical data are limited. Here, we investigated the clinical efficacy of ceritinib after failure of alectinib for ALK-positive NSCLC.

Patients and Methods

Patients with ALK-positive NSCLC treated at the Kyoto University Hospital from January 2012 to March 2017 were reviewed. Patients who were treated with ceritinib after alectinib were identified, and the efficacy of ceritinib after alectinib was retrospectively evaluated. Patients were diagnosed as having ALK-positive NSCLC when the tumor sample was double-positive by both immunohistochemistry and fluorescence in situ hybridization. The objective tumor response was evaluated according to the Response Evaluation Criteria for Solid Tumors, version 1.1 (11). PFS was measured from the date of initiation of ceritinib to the date of disease progression or death. All analyses were performed with JMP 10 software (SAS Institute, Cary, NC, USA). The cutoff date for data collection was December 28, 2017. This study was approved by the Institutional Review Board (approval number #G0799).

Results

Patient characteristics. There were 35 patients with ALK-positive NSCLC, nine of whom received ceritinib after alectinib. The clinical characteristics of the nine patients are...
Efficacy of ceritinib after alectinib for ALK-positive NSCLC. Ceritinib treatment and its efficacy is summarized in Table I. The starting dose of ceritinib was 750 mg in six patients, five of whom required dose reduction. Of the nine patients, four had a partial response, two had stable disease, and three had progressive disease. The overall response rate (ORR) and disease control rate were 44% and 67%, respectively. The ORR was 16% in six patients who received ceritinib immediately after alectinib, and 100% in three patients who received chemotherapy before ceritinib. The median PFS was 4.4 months (95% confidence interval=1.1-6.5 months) (Figure 1). At the time of data cut-off, three patients were still receiving ceritinib (median duration of follow-up was 8.5 months).

summarized in Table I. The median age at the time of ceritinib initiation was 57 (range=27-93) years. Four patients were male, and three patients had an Eastern Cooperative Oncology Group Performance Status of 2. All but one patient with large-cell neuroendocrine carcinoma demonstrated adenocarcinoma histology. Four patients received both crizotinib and alectinib before ceritinib, and six patients received ceritinib immediately after failure of alectinib. Eight patients had achieved partial response with alectinib, and the median duration of alectinib treatment was 10.5 (range=6.5-29.9) months. The reasons for alectinib termination were progressive disease in eight patients and toxicity (interstitial lung disease) in one.

| Case | Age (years) | Gender | PS | Histology | Treatment sequence | ALC treatment | CER treatment |
|------|-------------|--------|----|-----------|--------------------|---------------|---------------|
| 1    | 33          | M      | 1  | Ad        | Cis/PEM → Ch/PAC/BEV → NIVO → ALC → CER | PD             | 750 Yes PR 1.5 |
| 2    | 93          | F      | 2  | Ad        | ALC → CER         | PR 8.0 PD 1   | 150 No PR 2.7* |
| 3    | 27          | F      | 1  | Ad        | ALC → CER         | PR 8.4 PD 344 | 750 No PR 4.4  |
| 4    | 66          | F      | 2  | LCNEC     | Cb/PAC/BEV → ERL/BEV → PEM → DOC → CPT → CRZ → ALC → GEM → S-1/BEV → CER | PR 22.8 PD 1  | 450 No PD 2.8  |
| 5    | 57          | F      | 0  | Ad        | Cb/PAC/BEV → CRZ → DOC → ALC → CER | PR 6.5 ILD 441| 750 Yes PR 4.0*|
| 6    | 44          | M      | 0  | Ad        | Cb/PAC/BEV → CRZ → DOC → ALC → CER | PR 29.9 PD 1  | 750 Yes SD 6.5 |
| 7    | 70          | F      | 1  | Ad        | Cb/PAC/BEV → PEM → S-1 → GEM → CPT → DOC → ALC → CER | PR 10.5 PD 7  | 750 Yes PD 1.1  |
| 8    | 65          | M      | 1  | Ad        | Cb/PAC/BEV → CRZ → ALC → Cb/PAC/BEV → NIVO → DOC → CER | PR 12.8 PD 287| 600 No PR 3.5  |
| 9    | 41          | M      | 2  | Ad        | CRZ → ALC → CER  | PR 24.5 PD 1  | 750 Yes SD 5.8*|

M, Male; F, female; PS, Eastern Cooperative Oncology Group Performance Status; Ad, adenocarcinoma; LCNEC, large-cell neuroendocrine carcinoma; CRZ, crizotinib; Cis, cisplatin; PEM, pemetrexed; Ch, carboplatin; PAC, paclitaxel, BEV, bevacizumab; NIVO, nivolumab; ERL, erlotinib; DOC, docetaxel; CPT, irinotecan; GEM, gemcitabine; S-1, tegafur/gimeracil/oteracil; PR, partial response; SD, stable disease; PD, progressive disease; ILD, interstitial lung disease. *Censored.
that the I1171T mutation confers resistance to alectinib but remains sensitive to ceritinib, using a cell line derived from the patient who subsequently responded to ceritinib (19). In contrast, ceritinib is ineffective against the ALKG1202R secondary mutation, which is sensitive to third-generation ALK inhibitors (10, 18). These results strongly suggest that examining resistance mechanisms, especially resistance-associated mutations, is essential for selecting drugs for patients with ALK-positive NSCLC resistant to alectinib.

In conclusion, we evaluated the efficacy of ceritinib after alectinib in nine patients with ALK-positive NSCLC. Ceritinib demonstrated a modest clinical benefit after failure of alectinib. Although the sample size was small and it was a retrospective study, our results suggest that ceritinib may be a reasonable treatment option in this setting.

Conflicts of Interest

The Authors declare no conflicts of interest.

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