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Clinical Efficacy of Alectinib in Patients with *ALK*-Rearranged Non-small Cell Lung Cancer After Ceritinib Failure

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Abstract. *Several second-generation inhibitors of anaplastic lymphoma kinase (ALK) have demonstrated potent activity in ALK rearrangement-positive non-small cell lung cancer (NSCLC). Two of these agents, ceritinib, and alectinib, recently received approval for the treatment of ALK-rearranged NSCLC in Japan. The efficacy of treatment with a second-generation ALK inhibitor after failure with a different second-generation ALK inhibitor remains unclear. We present a series of eight patients with ALK-rearranged NSCLC treated with alectinib who experienced disease progression after ceritinib. Both crizotinib and ceritinib were administered to six patients, with four (29%) patients receiving crizotinib followed by ceritinib. Among the eight study patients, two (25%) had partial response, one (12%) stable disease, and five (63%) had progressive disease. The median progression-free survival was 3.6 months (95% confidence interval=0-7.1 months). The results of this study suggest that the second-generation ALK inhibitor alectinib has limited efficacy after initial treatment with the second-generation ALK inhibitor ceritinib.*

Rearrangements of anaplastic lymphoma kinase (*ALK*) gene are present in 3-5% of cases of non-small-cell lung cancer (NSCLC). ALK tyrosine kinase inhibitors have demonstrated promising clinical activity for the treatment of NSCLC cases that harbor an *ALK* rearrangement. Crizotinib was the first ALK inhibitor approved for such NSCLC cases, demonstrating significant improvements in objective response rates and progression-free survival compared with cytotoxic chemotherapy in randomized phase III studies (PROFILE 1007 and 1014 trials) (1, 2). Recently, several second-generation ALK inhibitors were demonstrated to have potent activity in cases of *ALK* rearrangement-positive NSCLC (3-7). Two of these agents, ceritinib and alectinib, recently received approval for the treatment of *ALK* rearrangement-positive NSCLC in Japan. However, despite the significant clinical responses to these inhibitors, almost all patients treated with ALK inhibitors developed resistance. The mechanism of acquired resistance has been identified, and it includes *ALK* gene alterations, such as *ALK* point mutations and copy-number gains (8, 9), as well as the activation of bypass signaling *via* the activation of other oncogenes (10, 11). There have been few reports on the efficacy of second-generation ALK inhibitors after the failure of a different second-generation ALK inhibitor in NSCLC cases with an *ALK* rearrangement (12). Herein, we present a series of eight patients with *ALK* rearrangement-positive NSCLC treated with alectinib who experienced disease progression after initial treatment with ceritinib.

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Key Words: Alectinib, non-small cell lung cancer, ALK-rearrangement, ceritinib, anaplastic lymphoma.

Patients and Methods

Patients. Between January 2007 and October 2016, four patients with advanced *ALK* rearrangement-positive NSCLC were treated with ceritinib as the first ALK inhibitor, and eight patients with it as second ALK inhibitor after crizotinib failure. Among these 12 patients, we retrospectively reviewed eight patients who were treated with alectinib after ceritinib failure. All eight patients were treated with ceritinib as part of a clinical trial. The *ALK* gene rearrangement status was assessed by fluorescent *in situ* hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), or immunohistochemistry (IHC), as previously reported(13). We considered that a tumor was ALK rearrangement-positive when at least two of the tests (FISH, RT-PCR, or IHC) yielded positive results. ALK inhibitor resistance-associated mutations were assessed by direct sequencing of PCR products from fresh samples. These eight patients were retrospectively evaluated based on patient characteristics and clinical outcomes after alectinib treatment. The disease progression date was based on routine surveillance imaging. This study was approved by the Institutional Review Board of the Aichi Cancer Center (2015-1-192).

Table I. *Details of anaplastic lymphoma kinase (ALK) rearrangement-positive patients treated with alectinib after ceritinib failure.*

Patient no.	Age (years)	Gender	Stage	ALK inhibitor treatment sequence	PFS on Ce (months)	Response to Ce	Duration between Ce and Al (months)	Treatment before Al	Lesion description	Response after Al	Resistance mutation in *ALK*
1.	68	M	IV	Ce	22.4	PR	0	Ce	Pleural effusion, and dissemination	PD	-
2.	55	F	IIIB	Cr→Ce	11.9	PR	0	Ce	Pulmonary	PD	Negative
3.	71	M	IV	Ce→Cri	9.4	PR	5.8	Cr	CNS, liver, Pleural effusion, and dissemination	PD	-
4.	29	M	IV	Cr→Ce→Cr	3.0	SD	0	Ce	Mediastinal LN and pleural effusion	PD	G1269A
5.	37	M	IV	Cr→Ce	4.1	PR	0	Ce	Liver	PR	-
6.	51	M	Rec	Ce→Cr	1.7	PD	21.2	Cr	CNS, Bone	PR	-
7.	39	M	IV	Cr→Ce→Cr	7.1	PR	0	Ce	Pulmonary and pleural effusion	PD	-
8.	63	M	IV	Ce	7.5	PR	11.9	Pem	Pulmonary	SD	Negative

M, Male; F, female; Ce, ceritinib; Cr, crizotinib; Al, alectinib; PFS, progression-free survival; PR, partial response; SD, stable disease; PD, progressive disease; Rec, postoperative recurrence, Pem, pemetrexed; LN, lymph nodes; CNS, central nervous system.

Evaluation of alectinib efficacy. Alectinib was initially administered orally at a dose of 300 mg twice daily until progressive disease (PD) or unacceptable toxicity. In cases of toxicity, the patients underwent dose reduction or treatment interruption. The objective tumor response was evaluated according to a radiographic assessment using RECIST version 1.1(14). The objective response rate (ORR) was calculated as the total percentage of patients with a complete (CR) or partial (PR) response. The disease control rate was calculated as the total percentage of patients with CR, PR, and stable disease (SD). The objective response rate (ORR) was calculated as the total percentage of patients with a complete (CR) or partial (PR) response. The disease control rate was calculated as the total percentage of patients with CR, PR, and stable disease (SD).

Statistical analysis. All statistical analyses were performed using the statistical software package JMP for Windows version 9 (SAS Institute, Cary, NC, USA). PFS was measured from the start of alectinib treatment until the date of PD. We regularly monitored brain metastases by routine follow-up imaging, but the frequency and monitoring methods varied. The survival probabilities were estimated using the Kaplan–Meier method.

Results

Patient characteristics are listed in Table I. The median age was 53 years (range=29-71 years), and six of the patients (75%) were male. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Histological examination revealed adenocarcinoma in seven patients and squamous cell carcinoma in one patient. Both crizotinib and ceritinib were administered to six patients, with four (29%) patients receiving crizotinib followed by ceritinib for advanced or recurrent disease. Prior to treatment with alectinib, three patients had primary or metastatic pulmonary lesions, two patients had pleural effusion and dissemination, one patient had liver metastasis, and one patient had bone metastasis and central nervous system (CNS) parenchymal lesion. Additionally, before switching the treatment regimen to alectinib, four patients were receiving ceritinib, three were receiving crizotinib, and one was receiving pemetrexed. The clinical outcomes after alectinib treatment of patients after ceritinib failure are shown in Table I. Among the eight study patients, two (25%) had PR, one (12%) had SD, and five (63%) had PD. The median PFS was 3.6 months (95% confidence interval=0-7.1 months).

Discussion

In the present study, we evaluated the clinical efficacy of alectinib therapy after ceritinib failure; ORR and PFS were 25% and 3.6 months, respectively. The results of this study might suggest that the second-generation ALK inhibitor alectinib has limited efficacy after treatment with the second-generation ALK inhibitor ceritinib, compared with the setting of ALK inhibitor-naïve or crizotinib failure.

Alectinib has been reported to have potent efficacy in patients with *ALK* rearrangement-positive NSCLC, including those harboring mutations that confer resistance to crizotinib. In addition, two phase III studies (J-ALEX and ALEX), which directly compared alectinib and crizotinib therapies in patients with crizotinib-naïve, *ALK* rearrangement-positive disease, showed that alectinib had significantly better

efficacy than crizotinib (15, 16). Ceritinib also showed efficacy in patients with ALK rearrangement-positive, crizotinib-naïve, and crizotinib-refractory disease, although no trials compared ceritinib and other ALK inhibitors (5, 7, 17-19). On the other hand, few reports have examined the efficacy of second-generation ALK inhibitor use after initial failure of second-generation ALK inhibitor (12). Gainor *et al*. showed that alectinib was active in ALK rearrangement-positive patients with leptomeningeal metastases despite prior exposure to both crizotinib and ceritinib, suggesting that alectinib has greater CNS activity (20). Treatment with alectinib after crizotinib or ceritinib failure might be a reasonable treatment strategy in cases of NSCLC with an *ALK* rearrangement with CNS progression. However, to our knowledge there are no data about the clinical activity of alectinib against lesions outside the CNS after ceritinib failure. Indeed, in the present study, one patient (patient 6) with CNS progression responded to alectinib. In contrast, only one patient out of seven with systemic progression after ceritinib treatment experienced response to alectinib. In addition, in five patients treated with alectinib immediately after ceritinib failure, four patients experienced PD. Therefore, establishing a treatment strategy after systemic progression in patients treated with ceritinib will be a challenge for the future.

Recently, Gainor *et al*. published the largest study to date that evaluated the mechanism of resistance to ALK inhibitors in patients with *ALK* rearrangement-positive NSCLC (21). Detection of a mutation conferring ALK resistance was more common after treatment with second-generation ALK inhibitors than after treatment with crizotinib. Although *ALK* G1202R, which confers resistance to all second-generation ALK inhibitors, is the most common resistance-associated mutation in patients after either ceritinib or alectinib treatment failure, the spectrum of other resistance-associated mutations differs across second-generation ALK inhibitors. Although *ALK* F1174L/C, which confers sensitivity to alectinib, is the second-most common ALK inhibitor resistance-associated mutation in patients after ceritinib failure, *ALK* I1171T/N/S, which confers sensitivity to ceritinib, is the second-most common in patients after alectinib failure. In this study, biopsy specimens of three patients provided an evaluation of ALK inhibitor resistance-associated mutations after alectinib failure. Among these patients, one patient, who experienced PD during alectinib treatment, had *ALK* G1269A mutation (patient 4). The G1269A mutation is reported to confer resistance to crizotinib while conferring sensitivity to alectinib and ceritinib; in this case, treatment with crizotinib before ceritinib treatment might affect G1269A mutation expression. The other two patients had no ALK inhibitor resistance-associated mutations after alectinib failure. Thus, resistance to second-generation ALK inhibitors is complicated, but the results of this study might suggest that the efficacy of alectinib treatment after ceritinib failure in patients without information about ALK inhibitor resistance-associated mutation could be limited compared with the results of a clinical trial of alectinib in crizotinib-refractory cases. Therefore, identifying ALK mutations associated with inhibitor resistance to second-generation ALK inhibitors, such as F1174L/C or I1171T, might be important for selecting subsequent ALK inhibitors after second-generation ALK inhibitor failure.

The present study has several limitations. Firstly, this was a retrospective study of a case series. In addition, the treatment line and the intervals between ceritinib and alectinib varied among patients. Secondly, the alectinib dose used in Japan (300 mg twice daily) differs from the dose used in the rest of the world (600 mg twice daily). These factors might affect the clinical outcomes of the examined treatment. Further prospective trials, including serial resistance profiles to ALK inhibitors, will be important to evaluate the efficacy and best treatment regimens of novel ALK inhibitors, including the third-generation ALK inhibitor lorlatinib.

Conflicts of Interest

Disclosure: Toyoaki Hida has received research funding and honoraria from Chugai Pharmaceutical. Yasushi Yatabe received honoraria from AstraZeneca, Pfizer, Chugai Pharmaceutical, Novartis and Roche. The other Author has no conflicts of interest.

References

1 Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD and Janne PA: Crizotinib *versus* chemotherapy in advanced alk-positive lung cancer. N Engl J Med *368(25)*: 2385-2394, 2013.

2 Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J and Blackhall F: First-line crizotinib *versus* chemotherapy in alk-positive lung cancer. N Engl J Med *371(23)*: 2167-2177, 2014.

3 Felip E, Crino L, Kim DW, Spigel DR, Nishio M, Mok T, Scagliotti G, Cesic D, Sutradhar S and Shaw AT: 141pd: Whole body and intracranial efficacy of ceritinib in patients (pts) with crizotinib (crz) pretreated, alk-rearranged (alk+) non-small cell lung cancer (nsclc) and baseline brain metastases (bm): Results from ascend-1 and ascend-2 trials. J Thorac Oncol *11(4 Suppl)*: S118-119, 2016.

4 Ou SH, Ahn JS, De Petris L, Govindan R, Yang JC, Hughes B, Lena H, Moro-Sibilot D, Bearz A, Ramirez SV, Mekhail T, Spira A, Bordogna W, Balas B, Morcos PN, Monnet A, Zeaiter A and Kim DW: Alectinib in crizotinib-refractory alk-rearranged non-small-cell lung cancer: A phase ii global study. J Clin Oncol *34(7)*: 661-668, 2016.

5 Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Sutradhar S, Li S, Szczudlo T, Yovine A and Shaw AT: Activity and safety of ceritinib in patients with alk-rearranged non-small-cell lung cancer (ascend-1): Updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol *17(4)*: 452-463, 2016.

6 Marshall H: Ceritinib *versus* chemotherapy in alk-positive lung cancer. Lancet Respir Med *4(12)*: 952-953, 2016.

7 Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Lau YY, Goldwasser M, Boral AL and Engelman JA: Ceritinib in alk-rearranged non-small-cell lung cancer. N Engl J Med *370(13)*: 1189-1197, 2014.

8 Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, Shakespeare WC, Iafrate AJ, Engelman JA and Shaw AT: Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene eml4-alk. Proc Natl Acad Sci USA *108(18)*: 7535-7540, 2011.

9 Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, Jessop NA, Wain JC, Yeo AT, Benes C, Drew L, Saeh JC, Crosby K, Sequist LV, Iafrate AJ and Engelman JA: Mechanisms of acquired crizotinib resistance in alk-rearranged lung cancers. Sci Transl Med *4(120)*: 120ra117, 2012.

10 Sasaki T, Koivunen J, Ogino A, Yanagita M, Nikiforow S, Zheng W, Lathan C, Marcoux JP, Du J, Okuda K, Capelletti M, Shimamura T, Ercan D, Stumpfova M, Xiao Y, Weremowicz S, Butaney M, Heon S, Wilner K, Christensen JG, Eck MJ, Wong KK, Lindeman N, Gray NS, Rodig SJ and Janne PA: A novel alk secondary mutation and egfr signaling cause resistance to alk kinase inhibitors. Cancer Res *71(18)*: 6051-6060, 2011.

11 Lovly CM, McDonald NT, Chen H, Ortiz-Cuaran S, Heukamp LC, Yan Y, Florin A, Ozretic L, Lim D, Wang L, Chen Z, Chen X, Lu P, Paik PK, Shen R, Jin H, Buettner R, Ansen S, Perner S, Brockmann M, Bos M, Wolf J, Gardizi M, Wright GM, Solomon B, Russell PA, Rogers TM, Suehara Y, Red-Brewer M, Tieu R, de Stanchina E, Wang Q, Zhao Z, Johnson DH, Horn L, Wong KK, Thomas RK, Ladanyi M and Pao W: Rationale for co-targeting igf-1r and alk in alk fusion-positive lung cancer. Nat Med *20(9)*: 1027-1034, 2014.

12 Nishio M, Murakami H, Horiike A, Takahashi T, Hirai F, Suenaga N, Tajima T, Tokushige K, Ishii M, Boral A, Robson M and Seto T: Phase i study of ceritinib (ldk378) in japanese patients with advanced, anaplastic lymphoma kinase-rearranged non-small-cell lung cancer or other tumors. J Thorac Oncol *10(7)*: 1058-1066, 2015.

13 Yoshida T, Oya Y, Tanaka K, Shimizu J, Horio Y, Kuroda H, Sakao Y, Hida T and Yatabe Y: Differential crizotinib response duration among alk fusion variants in alk-positive non-small-cell lung cancer. J Clin Oncol *34(28)*: 3383-3389, 2016.

14 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009.

15 Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, Takiguchi Y, Nishio M, Yoshioka H, Imamura F, Hotta K, Watanabe S, Goto K, Satouchi M, Kozuki T, Shukuya T, Nakagawa K, Mitsudomi T, Yamamoto N, Asakawa T, Asabe R, Tanaka T and Tamura T: Alectinib *versus* crizotinib in patients with alk-positive non-small-cell lung cancer (j-alex): An open-label, randomised phase 3 trial. Lancet *390(10089)*: 29-39, 2017.

16 Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T and Investigators AT: Alectinib *versus* crizotinib in untreated alk-positive non-small-cell lung cancer. N Engl J Med *377(9)*: 829-838, 2017.

17 Soria JC, Tan DS, Chiari R, Wu YL, Paz-Ares L, Wolf J, Geater SL, Orlov S, Cortinovis D, Yu CJ, Hochmair M, Cortot AB, Tsai CM, Moro-Sibilot D, Campelo RG, McCulloch T, Sen P, Dugan M, Pantano S, Branle F, Massacesi C and de Castro G Jr.: First-line ceritinib *versus* platinum-based chemotherapy in advanced alk-rearranged non-small-cell lung cancer (ascend-4): A randomised, open-label, phase 3 study. Lancet *389(10072)*: 917-929, 2017.

18 Crino L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, Mok T, Spigel D, Felip E, Nishio M, Scagliotti G, Branle F, Emeremni C, Quadrigli M, Zhang J and Shaw AT: Multicenter phase ii study of whole-body and intracranial activity with ceritinib in patients with alk-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ascend-2. J Clin Oncol *34(24)*: 2866-2873, 2016.

19 Hida T, Satouchi M, Nakagawa K, Seto T, Matsumoto S, Kiura K, Nokihara H, Murakami H, Tokushige K, Hatano B and Nishio M: Ceritinib in patients with advanced, crizotinib-treated, anaplastic lymphoma kinase-rearranged nsclc: Japanese subset. Jpn J Clin Oncol: 1-7, 2017.

20 Gainor JF, Sherman CA, Willoughby K, Logan J, Kennedy E, Brastianos PK, Chi AS and Shaw AT: Alectinib salvages cns relapses in alk-positive lung cancer patients previously treated with crizotinib and ceritinib. J Thorac Oncol *10(2)*: 232-236, 2015.

21 Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, Dagogo-Jack I, Gadgeel S, Schultz K, Singh M, Chin E, Parks M, Lee D, DiCecca RH, Lockerman E, Huynh T, Logan J, Ritterhouse LL, Le LP, Muniappan A, Digumarthy S, Channick C, Keyes C, Getz G, Dias-Santagata D, Heist RS, Lennerz J, Sequist LV, Benes CH, Iafrate AJ, Mino-Kenudson M, Engelman JA and Shaw AT: Molecular mechanisms of resistance to first- and second-generation alk inhibitors in alk-rearranged lung cancer. Cancer Discov *6(10)*: 1118-1133, 2016.

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