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Clinicopathological Features in Elderly ALK-rearranged Non-small Cell Lung Cancer Patients

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Abstract. *Aim: To clarify the clinicopathological features in elderly anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer (NSCLC) patients. Patients and Methods: A retrospective study was performed in 129 ALK rearranged NSCLC patients diagnosed between April 2008 and March 2019 in fifteen Institutions of the Ibaraki prefecture, Japan. Results: Median age of patients was 63 years. In 59 patients aged 65 and older, the proportions of patients with advanced stage and those treated with ALK-tyrosine kinase inhibitor (TKI) were lower than those younger than 65 years. There was no difference in overall survival (OS) between the two age groups. Among the elderly patients, no difference was observed in OS between the patients aged 65-69 and those aged 70 and older. In 89 patients treated with TKI, no significant differences were observed in the progression-free survival of TKIs and OS between patients aged 65 and older and those younger than 65, respectively. Conclusion: Evaluation of ALK gene status and TKI treatment are desirable even for elderly patients.*

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Key Words: Clinical practice, elderly, non-small cell lung cancer, anaplastic lymphoma kinase fusion gene mutation, ALK.

Advances in molecular biology have led to discovery of specific driver genes in certain cancer types and therefore to development of specific therapeutics (1, 2). This new trend is evident in the clinical practice of NSCLC patients. Mutations in the anaplastic lymphoma kinase (ALK) fusion gene is one such driver gene. Long-term survival can be expected in ALK-rearranged NSCLC patients, but its frequency is very rare (1,

2). Because of the rarity of ALK-rearranged NSCLC, it is important to collect and evaluate data in clinical practice in addition to the results of clinical trials to evaluate its significance. ALK rearranged gene mutation is an oncogenic driver of NSCLC and commonly associated with younger age (3-16). Although under a small number, however, elderly ALK-rearranged NSCLC patients also have been reported (17-19). There exist few reports on the characteristics of these elderly patients (17-19). Recently, we performed a retrospective study in real clinical practice of 129 ALK-rearranged NSCLC patients. This was a study of 15 medical Institutions covering a population of 3 million (20). The study included a considerable number of elderly patients. We conducted this study to clarify characteristics of elderly ALK-rearranged NSCLC patients in in real clinical practice.

Patients and Methods

Fifteen Institutions located in the Ibaraki prefecture (area: 6,095 km^2; population: ~3 million) participated in the present retrospective study. We included patients who were diagnosed as having ALK-rearranged NSCLC between April, 2008 and March, 2019. Patients, who had started treatment before crizotinib was approved in Japan in May 2012 and were diagnosed as having ALK-rearranged NSCLC during the study period, were included in the study. All patients demonstrated histological or cytological evidence of NSCLC. Histopathological diagnoses were defined according to the World Health Organization (WHO) classification system and patients were staged according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system. Metastatic sites were evaluated as bone, lung, brain, liver, extrathoracic lymph nodes, adrenal glands, and other uncommon sites. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease, or not evaluable, according to the response evaluation criteria in solid tumors (RECIST), version 1.1. The patient characteristics, efficacy, safety, progressive-free survival (PFS) and OS were evaluated using patient data extracted from the database of each institution. The sum of PFS in ALK-tyrosine kinase inhibitor (TKI) prescribed was defined as PFSs. Patient survival time was calculated from the date of initiation of first-line therapeutic drug to the date of death or latest follow-up contact of the patient. The present observational study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. This study was approved by the institutional Ethics Committee of each Hospital (Project approval number: NO16-66, 18-15). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

ALK fusion gene analysis methods. ALK fusion gene mutation analysis was performed by the assay method normally used by each institution, such as fluorescence *in situ* hybridization (FISH), real time-reverse transcription polymerase chain reaction, and immunohistochemistry, using biopsy specimens, cytology specimens, and plasma specimens.

Statistical analysis. The survival rate was analyzed by the Kaplan-Meier method and comparisons were performed using the log-rank test. The effects of clinicopathological factors on survival were analyzed using the Cox proportional hazards model. $p<0.05$ was considered to indicate a statistically significant difference.

Table I. *Comparison of the background of 129 ALK-rearranged NSCLC patients who were divided into two groups at 65 years*.

Factors	Patients aged 65 years or older	Patients younger than 65 years	*p*-Value
Gender, M/F	24/35	21/49	0.2660
Performance status			
0/1 or more	31/28	40/30	0.7226
Smoking habit			
Never/Past or current	34/25	45/25	0.4721
Pathology			
AD/Others	57/2	67/3	0.9999
Pleural fluid			
Absent/Present	45/14	48/22	0.4310
Clinical stage			
IA-IIIA/IIIB-IVB	30/29	23/47	0.0486
Surgical resection			
Present/Absent	31/28	27/43	0.1550
ALK-TKI therapy			
Present/Absent	34/25	55/15	0.0131

ALK: Anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer.

Results

Clinicopathological features of the elderly patients. The median age of 129 ALK-rearranged NSCLC patients was 63 years, and 59 (45.7%) patients were 65 years or older. Table I shows a comparison of the background of patients who were divided into two groups at 65 years. The clinicopathological factors in the elderly patients aged 65 and older were not significantly different from those in younger patients except for clinical stage and ALK-TKI therapy. Namely, the proportion of advanced clinical stages was higher in patients aged 65 years or older than that in younger patients ($p=0.0486$). The proportion of ALK-TKI therapy for advanced clinical stages was lower in patients aged 65 years or older than that in younger patients ($p=0.0131$).

Overall survival of elderly and young groups of patients. Figure 1A shows the overall survival curves (OSs) of 59 patients aged 65 and older and 70 patients younger than 65 years ($p=0.9394$). There was no difference in OS between them. As shown in Figure 1B, no difference in OS was observed between 35 patients aged 70 years and older and 94 patients younger than 70 years ($p=0.6835$). Among the 59 patients aged 65 years and older, no difference was observed in OS between 24 patients aged 65-69 years and 35 patients aged 70 years and older ($p=6477$).

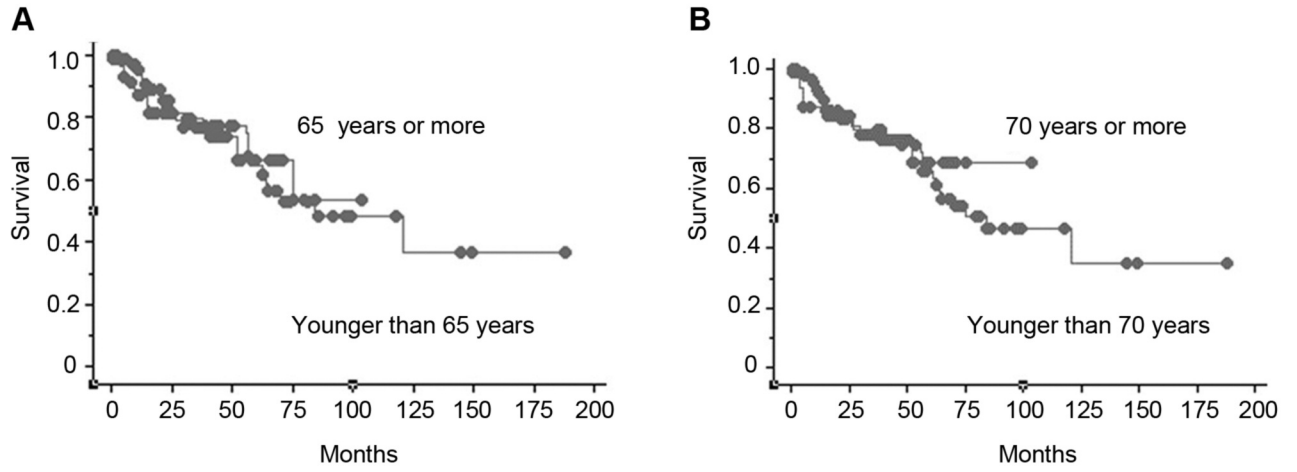

Figure 1. *Comparison of survival between elderly and young patients among the 129 ALK-rearranged NSCLC patients. There was no difference in survival between the two age groups; patients aged 65 years or older and those younger than 65 years (p=0.9394) (A). No difference was found in survival between the two groups: 70 years or older and those younger than 70 years (p=0.6835) (B).*

PFS and OS in patients treated with ALK-TKI. Eighty-nine of the 129 patients with ALK-rearranged NSCLC patients were treated with ALK-TKIs. A total of 34 patients were aged 65 years and older and 55 patients were younger than 65 years. Figure 2A and B shows PFS curves of the two age groups of patients. There was no statistical difference in PFS between them (p=0.5233). No significant difference in OS between them was observed either (p=0.8315). In the 34 patients aged 65 years or older, who were treated with TKIs, no significant differences were observed in PFS and in OS between patients aged 65-69 years and older and those older than 70 years, respectively (p=0.5609, p=0.1782) (A and B).

Prognostic factors in the elderly. We evaluated prognostic factors in the 59 patients aged 65 years or older. In univariate analysis, female gender, PS0, no smoking status and surgical resection were significant prognostic factors, but age was not. In multivariate analysis, however, none of them was a significant favorable prognostic factor (Table II).

Table II. *Comparison of the background of 129 ALK-rearranged NSCLC patients who were divided into two groups at 65 years.*

	Univariate analysis factors (log-rank test)	Multivariate analysis (Cox's proportional hazards model)	
	p-Value	Hazard ratio	*p*-Value
Age less than 70 years	0.6477		
Female	0.0160	0.542	0.3007
Performance status: 0	0.0048	0.374	0.1058
Smoking habit: absent	0.0009	0.373	0.1519
Absence of pleural fluid	0.2276		
Clinical stage IA-IIIA	0.2140		
Surgical resection	0.0211	0.502	0.2573
Presence of ALK-TKI therapy	0.8749		

ALK: Anaplastic lymphoma kinase; NSCLC: non-small cell lung cancer.

Discussion

The clinical meaning of ALK fusion gene mutations in elderly patients is not well understood. In particular, information on the patient characteristics such as the proportion of elderly patients, gender, PS, histology and clinical stage have been currently lacking due to the small number of patients. There is a lack of information on whether ALK rearrangement testing should be performed for elderly patients as well as younger patients. There is also not enough information on the optimal treatment for elderly patients, and it is not clear whether elderly patients should be treated with the same treatment as younger patients.

ALK-rearranged NSCLC patients have been considered to be younger than those without the rearrangement. Many studies from 2009 to 2020 reported that their median or average age was 50 years (3-16). There were no differences in these clinical features of ALK rearranged gene mutation oncogenic drivers among racial and regional groups (3-16). In recent years, however, there have been interesting reports on the age of ALK-rearranged NSCLC patients (21-23). In these reports, all of which occurred since 2015, median age of NSCLC patients was 67, 60, and 63 years (21-23). The

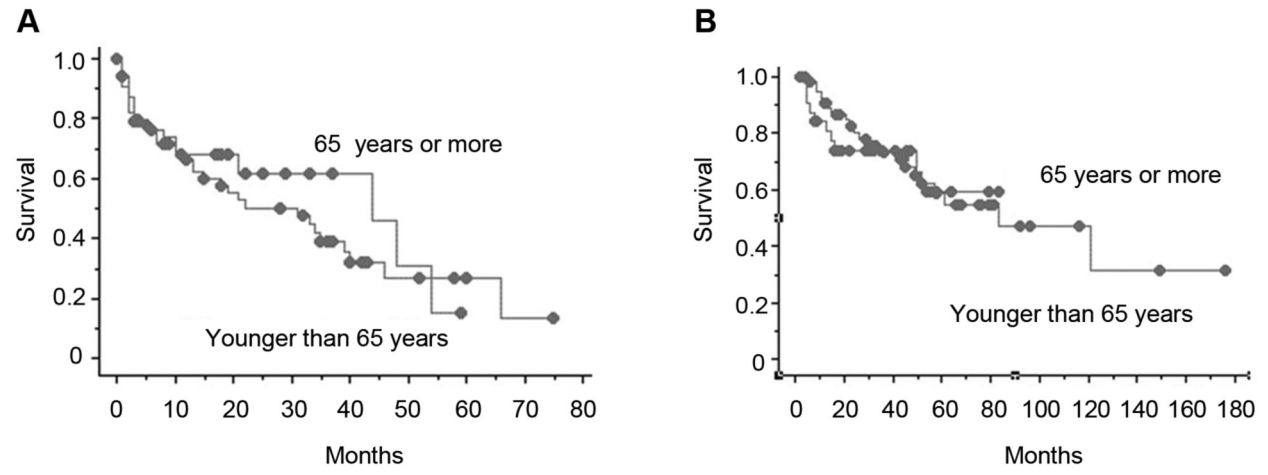

Figure 2. *Comparison of progression-free survivals (PFSs) and overall survival (OS) among ALK-rearranged NSCLC 89 patients treated with ALK-TKIs. There was no difference in PFSs between the two age groups; patients aged 65 years or older and those younger than 65 years (p=0.5233) (A). No difference was found in OS between the two groups: 65 years or older and those younger than 65 years (p=0.8315) (B).*

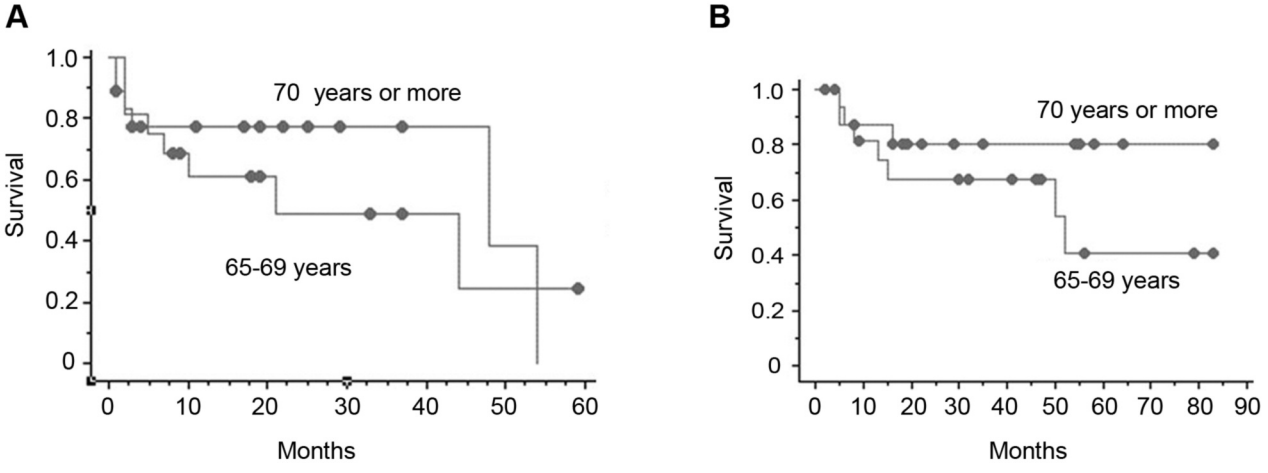

Figure 3. *Comparison of progression-free survival (PFSs) and overall survival (OS) among 34 ALK rearranged NSCLC patients aged 65 years or older, who were treated with TKI. There was no difference in PFSs between the two age groups; patients aged 65-69 years or older and those aged 70 or older (p=0.5609) (A). No difference was found in OS between the two groups either (p=0.1782) (B).*

difference in age could be a notable finding due to either a generalization of ALK-mutant gene assessment or changes related to the aging of the population in developed countries. In addition, there have been few reports with regards to the treatment of elderly ALK-rearranged NSCLC patients (17-19). Therefore, we conducted this study to clarify characteristics of elderly ALK-rearranged NSCLC patients in in real clinical practice. In our study, the median age of 129 ALK-rearranged NSCLC patients was 63 years, and 59 (45.7%) patients were 65 years or older. Our results were consistent with recent reports (21-23), and suggested that a certain percentage of ALK-rearranged NSCLC patients existed in NSCLC patients aged 65 years and older. Bedas *et al*. recently reported a study of 53 ALK-rearranged NSCLC patients (19). Of their patients, 36% were older than 65 years, and all of them had locally advanced or distant metastases. More than half of the patients had brain metastases. In our patients, 45.7% were older than 65 years, and 58 of 129 patients had resectable tumors. Brain metastases were found only in 13.2% of patients. Thus, our patients differed from those of Bedas *et al*. (19). The proportion of ALK patients 65 years and older in clinical trials was about 10-20% (24-26). In Bedas *et al*. and our study, patient characteristics were different, and our study had a higher percentage of elderly patients. However, their study and ours were consistent with a higher percentage of

patients aged 65 and older than those in clinical trials. With regard to gender in ALK-rearranged NSCLC patients, previous studies reported that patients had slightly higher or the same percentage of women as men (5, 8, 10, 12-14, 16, 27). On the other hand, there was a report that the proportion of men was slightly higher than women (7). In addition, recent studies showed that 69% and 65.8% were male patients (9, 11). Ke *et al*. reported that the percentage of women was significantly higher in patients younger than 60 years compared to those older than 60 years (28). In our study, 84 (65.1%) of the 129 patients were female. There was no statistically significant difference in gender between 59 patients aged 65 years or older and 70 patients younger than 65 years (p=0.2660).

In a review of 1,178 patients by Daste *et al*. in 2016, it was reported that ALK rearrangements tended to be present in NSCLC patients with no smoking habit (29). DiBonaventura *et al*. reported treatment of 207 patients, including a median age of 60 and 25 (12%) current smokers (30). In our study, there was no difference in the proportion of smokers aged 65 years or older and those younger than 65 years (p=0.4721). Twenty-five (42.4%) of the 59 patients aged 65 years or older were past or current smokers. This result suggested that there might be ALK-rearranged NSCLC patients among elderly NSCLC patients who had a history of smoking. NSCLC patients aged 60 years or older who have smoked. Therefore, physicians had better not excluded the elderly NSCLC patients from assessment of ALK fusion mutation.

Regarding the efficacy of ALK-TKIs, Bedas and colleagues attempted to perform an evaluation in 53 ALK-rearranged NSCLC patients (19). They divided them into 19 patients aged 65 years and older and 53 patients younger than 65 years to compare the efficacy of ALK-TKI. There was no difference in efficacy among the two groups (19). In our study, there was no significant difference in the proportion of patients receiving TKI between patients older than 65 years and those younger than 65 years. There was also no significant difference between the two groups in terms of PFS. The lower proportion of TKI therapy in the elderly patients might have been influenced by concerns about the adverse effect of crizotinib, which was the first ALK-TKI approved by the Food and Drug Administration of the United States. Common adverse events associated with crizotinib were visual disorder, gastrointestinal side-effects, and elevated liver aminotransferase levels. It seemed that elderly patients concerned about exacerbation of complications did not receive crizotinib treatment. It is considered difficult to conduct clinical trials of TKI in the elderly patients from the viewpoint of accumulation of patients because of the rarity of this disease. At present, however, as TKIs such as alectinib with fewer side-effects exist, administration is feasible (29, 30), and it might be desirable to perform the same TKI treatment as in younger patients.

Finally, we would like to discuss the prognosis of elderly ALK-rearranged NSCLC patients. In our evaluation of prognostic factors in 59 patients aged 65 or older, univariate analysis showed that women, PS0, no smoking history, no pleural effusion, stage IA-IIIA, and surgical resection were favorable prognostic factors. However, there was no significant factor in the multivariate analysis. This result might be related to the small number of analyzed patients. The result that ALK-TKI therapy was not a favorable prognostic factor might be related to the fact that this study included a big number resectable patients. Of interest was the comparison between groups of aged patients. When patients were divided into two groups, ≥65 years and <65 years, age was not a prognostic factor. Similar results were obtained when the age cutoff was set at 70 years. In addition, there was no difference in OS when 59 patients aged 65 or older were divided into two groups; those aged 70 or older and those aged 65-69. Taking the abovementioned results into consideration, showing that the PFS of ALK-TKI did not differ by age, it might be reasonable to determine that no special age-related distinction was necessary in treatment.

Despite some meaningful results, this study had certain limitations. Firstly, it was a retrospective study with patients from miscellaneous backgrounds. Secondly, the methods for examining ALK-fusion gene mutations were not unified. Thirdly, the limited number of patients and the short period of investigation were also limitations. These matters were the limitations of this study. Despite these limitations, we do believe that our information in ALK-rearranged NSCLC patients collected by multiple institutions covering the residents with a population of 3 million will provide clinically meaningful information.

ALK rearranged NSCLC is a rare entity of NSCLC. Therefore, there may be “facts” regarding the treatment that cannot be grasped by clinical trials alone. In order to clarify these facts, it must be meaningful to accumulate, collect and publish clinical practice data. This study was conducted from this point of view. Similarly to characteristics of the patient's background and prognostic factors in the elderly ALK-rearranged NSCLC patients obtained in this study, information obtained in this study should be verified in larger-scale clinical practice studies.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors’ Contributions

HS and NH designed the study. KM, SS, TK, TN, TE, YY, KS, HY, KH, SO, YY, TT, KS, NK, KK, HI, HW, TS, YF, SH, and TY collected the data. KM, SS, TK, HN, and HS analyzed the data and prepared the manuscript. All Authors approved the final version of the article.

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