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ORIGINAL ARTICLE

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EGFR mutation and *ALK* fusion-positive non-small cell lung cancer: a multicenter prospective cohort study in Nagano Prefecture, Japan

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ABSTRACT

Introduction. We prospectively examined current clinical practices in patients with inoperable epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) fusion-positive (*EGFR*$^+$ and *ALK*$^+$, respectively) non-small cell lung cancer (NSCLC) in Nagano Prefecture, Japan.

Material and methods. The study population consisted of newly diagnosed patients with inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in 14 hospitals in Nagano between May 2016 and March 2019. Both initial and subsequent treatment decisions were made at the discretion of the attending physician.

Results. A total of 281 patients with *EGFR*$^+$ NSCLC (mean age, 74 years, 59.1% female) and 26 patients with *ALK*$^+$ NSCLC (mean age, 66 years, 53.8% female) were included in the study. The study population consisted of 148/107/29/20/3 cases with performance status 0/1/2/3/4 and 6/2/31/194/75 cases with clinical stage I/II/III/IV/recurrence, respectively. First-line therapy with tyrosine kinase inhibitors was performed in 259 (92.2%) and 22 (84.6%) patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC, respectively. The median overall survival rate was 41.2 months (95% CI 36.8–45.6 months) with *EGFR*$^+$. It was not reached with *ALK*$^+$.

Conclusions. This observational analysis represents a valuable resource for evaluating the outcomes of treatment in patients with NSCLC.

Keywords: EGFR-TKI, non-small cell lung cancer, ALK inhibitor, cohort study

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Introduction

Lung cancer is the most common malignant disease and the leading cause of death from cancer both worldwide [1] and in Japan [2, 3]. The most common histological type is non-small cell lung cancer (NSCLC), which is predominantly non-squamous NSCLC [3]. Molecular targeted agents, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and abnormal fusion of anaplastic lymphoma kinase (ALK)-TKIs, have markedly improved overall survival in populations with these targetable genetic alterations [4–12].

The 2016 Japan Lung Cancer Society Guidelines for Treatment of Lung Cancer recommended testing for *EGFR* gene mutation and *ALK* fusion [13], with corresponding TKI treatment as first-line chemotherapy in patients with non-squamous NSCLC whose tumors harbored *EGFR* mutation (*EGFR*$^+$) or *ALK* fusion (*ALK*$^+$). These TKIs have been confirmed to be useful in several clinical studies, especially as first-line therapy [4–11]. In addition, newly developed TKIs targeting *EGFR*$^+$ [10] and *ALK*$^+$ tumors [14, 15] have become available and have been shown to prolong the period of progression-free survival. These new agents could increase the opportunities for choice of first-line or subsequent therapies and may contribute to prolongation of overall survival in *EGFR*$^+$ and *ALK*$^+$ NSCLC. However, real-world data on serial treatment outcomes in patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC are limited [4–8].

This prospective multicenter observational study aimed to evaluate the initial treatment patterns and outcomes in newly diagnosed treatment-naive cases of inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture, Japan. The study evaluated the real-world data of clinical practice and outcomes of patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture.

Material and methods

Patients and data collection

Patients eligible for inclusion in this prospective study were registered at the Cancer Center, Division of Clinical Oncology, Shinshu University School of Medicine, Shinshu University Hospital. The inclusion criteria were newly diagnosed (between May 6, 2016, and March 31, 2019) histologically or cytologically confirmed NSCLC, no prior history of therapy or recurrence following thoracic surgery, or inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC. Patients in whom surgery was inappropriate for medical reasons, such as advanced age, cardiovascular disease, poor pulmonary function, etc., were also enrolled in the study. Consecutive patients were enrolled sequentially in each of the 14 participating hospitals in Nagano prefecture (Tab. S1) to avoid selection bias. Anonymization was performed before registration in each participating hospital, and the anonymized data on baseline demographic and clinical characteristics, including age, sex, smoking history, performance status (PS), histological findings, and clinical stage, were collected from serial case report forms.

The study protocol was approved by the institutional review board of Shinshu University School of Medicine (No. 3407, 10/May/2016, UMIN000003645) and the ethics committee of each participating hospital. Histological diagnosis and NSCLC stage were determined according to the World Health Organization (WHO) classification (version 7 up to 2016, version 8 after 2017), and PS was estimated according to the Eastern Cooperative Oncology Group (ECOG) classification.

EGFR mutations were analyzed using real-time polymerase chain reaction or next-generation sequencing. Patients with any type of *EGFR* mutation were eligible for inclusion in the study; exon 19 deletion and exon 21 L858R susceptibility mutations were classified as common mutations and rare *EGFR* mutations were classified as uncommon. The details of clinical analysis and outcomes in patients with rare *EGFR* mutations were reported previously [16]. ALK fusion was examined by immunohistochemical analysis and/or fluorescence in situ hybridization.

The agents first received after diagnosis were defined as first-line treatments in the present study. Palliative radiotherapy for bone and brain metastases was not included as first-line treatment, but radical radiotherapy, such as stereotactic body radiotherapy (SBRT), was considered first-line treatment. Decisions regarding treatment and choice of TKI were made at the discretion of the attending physician. The types of drugs given as initial treatment were also registered at baseline. We recorded the responses, toxicities, subsequent therapies, and clinical outcomes at 4-monthly intervals. When using individual information, patient privacy was protected in accordance with ethical requirements.

The present study was performed to investigate the real-world first-line treatment practices and survival in patients with inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in the Nagano prefecture, Japan. Survival analysis was censored on December 31, 2021. Analysis of overall survival (OS), defined as the interval from the initial date of induction therapy to the date of death or the last follow-up visit, was performed using Kaplan-Meier plots, and the median and 95% confidence interval (CI) was determined. Statistical analyses were performed using NZR Statistics. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

Clinical characteristics

The study population consisted of 281 patients with *EGFR*$^+$ NSCLC [115 men, 40.9% and 166 women, 59.1%; median age, 74 years (range: 34–93 years)]

Table 1. Patient characteristics

Baseline characteristics	*EGFR* n = 281 (%)	*ALK* n = 26 (%)
Median age (range) [years]	74 (34–93)	66 (33–80)
Sex		
Male	115 (40.9%)	12 (46.2%)
Female	166 (59.1%)	14 (53.8%)
Performance status		
0	131 (46.6%)	17 (65.4%)
1	103 (36.7%)	4 (15.4%)
2	24 (8.5%)	5 (19.2%)
3	20 (7.1%)	0
4	3 (1.7%)	0
Smoking history		
Never	172 (61.2%)	13 (50.0%)
Former	92 (32.7%)	11 (42.3%)
Current	17 (6.1%)	2 (7.7%)
Histological type at initial diagnosis		
Adenocarcinoma	273 (97.2%)	26 (100%)
Other	8 (2.8%)	0
Stage		
I	6 (2.1%)	0
II	2 (0.1%)	0
III	27 (9.6%)	4 (15.4%)
IV	176 (62.6%)	18 (69.2%)
Recurrence	70 (24.9%)	4 (15.4%)

Table 2. Initial and second-line therapies in patients with *EGFR*-mutant (A) and *ALK* fusion-positive (B) non-small cell lung cancer

A. *EGFR*

Initial Therapy	n = 281 (%)	Second therapy (n)
TKIs		
Gefitinib	116 (41.3%)	Chemotherapy (26), osimertinib (22), afatinib (9), eroltinib (7), radiation (1), none (38)
Erlotinib (± bevacizumab)	39 (13.9%)	Chemotherpy (12), osimertinib (14), afatinib (3), gefitinib (3), surgery (1), none (3)
Afatinib	60 (21.3%)	Chemotherpy (24), osimertinib (14), erlotinib (1), gefitinib (7), none (7)
Osimertinib	44 (15.6%)	Chemotherpy (14), gefitinib (3), afatinib (2), none (14)
Cytotoxic chemotherapy	11 (3.9%)	Osimertinib (2), afatinib (2), eroltinib (2), gefitinib (5)
Chemoradiation	2 (0.7%)	Chemotherapy (1)
Radiation	4 (1.4%)	None (3)
Best suportive care	5 (1.8%)	

B. *ALK*

Initial therapy	n = 26 (%)	Second therapy (n)
TKIs		
Alectinib	20 (76.9%)	Chemotherapy (5), loratinib (3), certinib (2), none (3)
Crizotinib	2 (7.7%)	Alectinib (2)
Cytotoxic chemotheraphy	2 (7.7%)	Alectinib (2)
Chemoradiation	1 (3.9%)	Chemotherapy (1)
Radiation	1 (3.9%)	Alectinib (1)

TKI — tyrosine kinase inhibitor

and 26 patients with ALK^+ NSCLC [12 men, 46.2% and 14 women, 53.8%; median age, 66 years (range: 33––80 years)]. The median observation period was 31.3 months (range: 0.2–67.6 months]). The clinical characteristics of the study population are summarized in Table 1. In the $EGFR^+$ group, 131 patients were classified as PS 0, 103 as PS 1, 24 as PS 2, 20 as PS 3, and 3 as PS 4. In the ALK^+ group, 17 patients were classified as PS 0, 4 as PS 1, and 5 as PS 2. The histological type was adenocarcinoma in most cases, but the $EGFR^+$ group also included three cases of squamous cell carcinoma, three cases of adenosquamous cell carcinoma, one case of combined small cell carcinoma, and one case classified as not otherwise specified (NOS). Most cases of $EGFR^+$ NSCLC were locally advanced and metastatic (stage III/IV: 203 cases, 72.2%), and 70 patients (24.9%) had recurrence after surgery. In addition, in the $EGFR^+$ group, six were classified as stage I, and two cases were classified as stage II and were considered medically inoperable. Concerning the types of *EGFR* mutation, 136 cases (48.4%) were positive for Del19 and 130 cases (46.3%) had L858R. Fifteen patients had uncommon *EGFR* mutations: G719X in eight cases, L861Q in four cases, S768I in two cases, and exon 19 duplications in one case. ALK^+ NSCLCs included 4 cases of stage III, 18 cases of stage IV, and 5 cases of recurrence after surgery.

Treatment choice

The first- and second-line therapies in $EGFR^+$ and ALK^+ NSCLC groups are summarized in Table 2. The most commonly used agent in the $EGFR^+$ group was gefitinib (116 cases, 41%) followed by erlotinib (39 cases, 14%), afatinib (60 cases, 21%), and osimertinib (44 cases, 16%). Among the cases treated

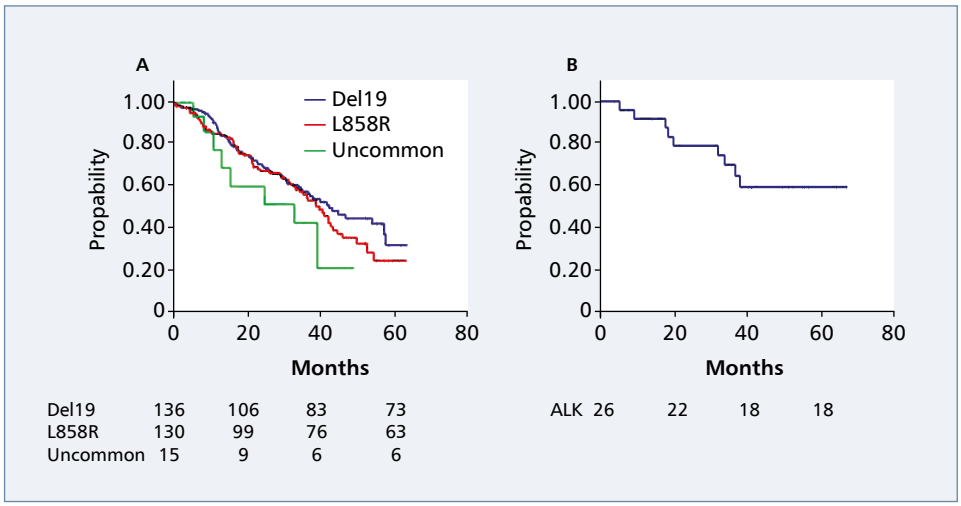

Figure 1. A. Kaplan-Meier plot of overall survival after initial therapy in patients with epidermal growth factor receptor-mutant non-small cell lung cancer; **B.** Kaplan-Meier plot of overall survival after initial therapy in patients with anaplastic lymphoma kinase fusion-positive non-small cell lung cancer

with erlotinib, 12 received bevacizumab combination therapy. Eleven cases (3.9%) were initially treated with cytotoxic chemotherapy. Platinum-doublet chemotherapy was administered in 10 cases, and non-platinum (S-1 monotherapy) was administered in one case. Platinum-based chemoradiotherapy was performed in two cases with clinical stage III. SBRT was performed in four cases classified as stage I (age > 84 years). Best supportive care (BSC), including palliative radiotherapy, was selected in five cases. Therefore, nine patients were not treated with any EGFR-TKIs or cytotoxic chemotherapy. As second-line therapy, chemotherapy was selected in 76 cases (29.3%) initially treated with EGFR-TKIs, and 82 patients (32.8%) were prescribed other TKIs. Osimertinib was used as second-line therapy in 50 cases (19.3%). All patients with *EGFR*$^+$ NSCLC receiving first-line cytotoxic chemotherapy were treated with TKLs as second-line therapy. One patient initially treated with chemoradiotherapy showed no relapse during the follow-up period. Four patients treated with SBRT did not receive further therapy, and three of these patients died.

In the *ALK*$^+$ group, alectinib and crizotinib were administered as first-line therapy in 20 cases (76.9%) and 2 cases (7.7%), respectively. Concurrent chemoradiotherapy was performed in one case classified as stage IIIb, and cisplatin plus pemetrexed chemotherapy was performed in two cases. In addition, one patient received thoracic radiotherapy at a dose of 60 Gy as first-line therapy. Although five cases were treated with chemotherapy as second-line therapy, most patients with *ALK*$^+$ NSCLC were switched to other ALK inhibitors. In one patient treated with chemoradiotherapy as first-line therapy, cytotoxic chemotherapy was selected as second-line therapy followed by ALK inhibitor as third-line chemotherapy.

Survival

The survival curves of the *EGFR*$^+$ and *ALK*$^+$ groups are shown in Figure 1A and 1B, respectively. Median OS in the *EGFR*$^+$ group was 41.3 months (95% CI 36.8–45.7 months) and was similar between the common *EGFR* mutation groups (44.0 months in the Del19 group *vs*. 40.4 months in the L858R group; log-rank test, p = 0.3) (Fig. 1A). However, median OS was significantly lower in patients with uncommon *EGFR* mutations (33.5 months; 95% CI 5.1–61.9 months) than in those with common mutations (log-rank test $p = 2 \times 10^{-5}$) (Fig. 1A). Median OS was not reached in the *ALK*$^+$ group, and the 4-year survival rate was 60.7% (95% CI 40.4–81.1%) (Fig. 1B).

Discussion

This study was performed to determine the current situation in patients with medically treated driver-positive NSCLC in Nagano prefecture, Japan. The analysis included a wide range of criteria for frail NSCLC patients who would likely have been excluded from clinical trials, and so our results reflected daily clinical practice in the treatment and management of driver gene-mutant NSCLC in Japan. We retrospectively examined the number of NSCLC patients treated during the study period in each participating hospital and estimated that 28.8% of NSCLC patients initially received TKIs. This was similar to the proportion obtained by a combined real-world analysis

of hospital-based cancer registries and diagnostic procedure surveys in Japan (33.3%) [17]. Therefore, the data in Nagano prefecture are likely to be close to the daily clinical management of NSCLC in Japan.

We found that non-TKI treatments were applied as initial therapy in 8.0% of *EGFR*$^+$ NSCLC cases and 15.4% of *ALK*$^+$ NSCLC cases, which were slightly higher than the rates of 6.7% and 6.7%, respectively, reported in a previous retrospective observational study of first-line chemotherapy for advanced and metastatic NSCLC (the BRAVE study) conducted at the same time (2017) as our observational study [18]. Non-TKI therapy was applied at high rates in *ALK*$^+$ NSCLC patients in the present study. As newly diagnosed and therapy-naive NSCLC patients were included in the present study and ALK inhibitors were selected as second-line therapy in cases of relapse after first-line chemotherapy, we speculated that the timing of *ALK* testing and/or understanding of *ALK* fusion in certain hospitals may have affected the results. For example, *ALK* testing of samples was performed only after obtaining a negative result for *EFGR* mutation.

In addition, there were nine cases (8.0%) of *EGFR*$^+$ NSCLC with no chance of receiving TKIs in the present study. Our findings in patients with *EGFR*$^+$ NSCLC treated only with BSC were clinically important for understanding the circumstances around lung cancer therapy. The mean age of these patients was 80.8 years and ranged from 68 to 89 years. The youngest patient (68 years old) had stage IV disease and PS 3. Therefore, the selection of BSC was related to advanced age and poor PS. Although EGFR-TKIs were shown to be preferred even in cases of poor PS [19, 20], our experience indicated that this treatment was not applied in some cases in clinical practice. Patients with advanced age and/or poor PS, even with driver gene-mutant NSCLC, must be taken into consideration in daily clinical practice in Nagano prefecture due to the aging of society in this region (https://www.stat.go.jp/data/nihon/02.html).

There have been several observational data studies on the survival of *EGFR*$^+$ NSCLC patients treated with EGFR-TKIs including patients outside of randomized clinical trials [4–8]. Inoue et al. [4] summarized the course of 1660 patients with *EGFR*$^+$ NSCLC treated with TKIs between 2008 and 2012 and reported median OS of 30.8 months. Subsequently, Okamoto et al. [5] reported real-world data for 1656 patients with *EGFR*$^+$ NSCLC treated mainly with first-generation TKIs (99% gefitinib and erlotinib) and reported median OS of 29.5 months. Subgroup analysis of the results of the LUX-Lung 3 phase III trial indicated median OS of 46.9 months in Japanese patients treated with afatinib [6]. Median OS of patients with *EGFR*$^+$ NSCLC in the present study was 41.0 months. As our data included a heterogeneous population of patients, i.e., those receiving only BSC or in the early stages of driver gene-mutant NSCLC, our survival rate was not comparable to those in previous clinical trials and real-world data. However, the survival data in the present study were meaningful to determining the real-world clinical outcomes in patients with *EGFR*$^+$ NSCLC. Further analyses are currently underway to elucidate the differences in survival according to the type of initial EGFR-TKI, TKI treatment sequence pattern, and types of *EGFR* mutations, which will be reported in the near future.

This study had several limitations. First, data on the rates of molecular biomarker testing in participating hospitals were not available. Therefore, our results were unable to reflect daily clinical practice, including the rates of molecular profiling. Second, we could not report a dose reduction and/or suspension of each TKI. Therefore, the clinical outcomes reported here may have been susceptible to physician treatment bias. Finally, the recognition and/or introduction of newly available TKIs may differ between participating hospitals. Nevertheless, a rigorous, and ethical multicenter survey was performed to obtain reference values for clinical practice in patients with inoperable driver-positive NSCLC in Nagano prefecture.

Conclusions

In conclusion, the results of the present study demonstrated real-world clinical outcomes in patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture, Japan. These observational analyses represent a valuable resource for evaluating treatment outcomes in patients with biomarker-positive NSCLC. We are currently planning additional analyses of the treatment sequence in these patients.

Article Information and Declarations

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics statement

The study protocol was approved by the Institutional Review Board of Shinshu University School of Medicine (No. 3407, 10/May/2016, UMIN000003645) and the ethics committee approval from each participating hospital was obtained for the collection of anonymized data and creation of the database. The requirement for written informed consent was waived by the Institutional Review Board of Shinshu University School of Medicine.

Author contributions

T. Kobayashi, S.K., K.T., T. Koizumi: conceived and designed the study, supervised the analysis process, interpreted the data, and drafted the manuscript.
All authors contributed to treatment of enrolled patients and data acquisition.
All authors read and approved the final manuscript.

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Conflict of interest

The authors have no conflicts of interest.

Supplementary material

Supplementary Table S1.

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Supplementary material

Table S1. Participating hospitals

Hospital	Department
Nagano Municipal Hospital	Department of Pulmonary Medicine
Nagano Red Cross Hospital	Department of Pulmonary Medicine
Nagano Prefectural Shinshu Medical Center	Department of Thoracic Surgery
Nagano Matsushiro General Hospital	Department of Pulmonary Medicine
Minami Nagano Iryou Center, Shinonoi Hospital	Department of Pulmonary Medicine
Shinshu Ueda Medical Center	Department of Pulmonary Medicine
Saku Central Hospital Advanced Care Center	Department of Pulmonary Medicine
Aizawa Hospital	Department of Pulmonary Medicine
Shinshu University Hospital	First Department of Internal Medicine, Medical Oncology
Suwa Red Cross Hospital	Department of Pulmonary Medicine
Ina Central Hospital	Department of Pulmonary Medicine, Department of Thoracic Surgery
Showa Inan General Hospital	Department of Thoracic Surgery
Iida Municipal Hospital	Department of Pulmonary Medicine
Iida Hospital	Department of Thoracic Surgery