의학석사 학위논문

Comparative Analysis of Overall Survival of Patient with Non-Small Cell Lung Cancer Harboring Anaplastic Lymphoma Kinase Fusion

역형성 림프종 인산화효소 융합-양성 비소세포폐암 환자의 전체생존기간에 대한 비교연구

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지도교수 허 대 석

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이 준 구

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위 원 장 우 홍 균 (인)

부위원장 허 대 석 (인)

위 원 김 동 완 (인)

Comparative Analysis of Overall Survival of Patient with Non-Small Cell Lung Cancer Harboring Anaplastic Lymphoma Kinase Fusion

by

June Koo Lee

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Professor _____Chairman

Professor _____Vice chairman

Professor _____

Abstract

Comparative Analysis of Overall Survival of Patient with Non-Small Cell Lung Cancer Harboring Anaplastic Lymphoma Kinase Fusion

June Koo Lee, M.D.

Medicine (Molecular Oncology)

The Graduate School

Seoul National University College of Medicine

Background and purpose:

The aim of this study was to examine the overall survival (OS) of patient with non-small cell lung cancer (NSCLC) harboring anaplastic lymphoma kinase (ALK) fusion, who were treated in the pre-ALK inhibitor era and to compare the survival with a matched case cohort of ALK-wildtype (WT) patients.

Methods:

Data from 1,166 stage IIIB/IV patients with non-squamous histology were collected from the NSCLC database of Seoul National University Hospital between 2003 and 2009. ALK FISH was performed on 262 cases that were either EGFR wild-type (WT) or non-responders to prior EGFR tyrosine kinase inhibitor (TKI) therapy. Survival analysis was conducted to compare the OS between 3 groups: 1) ALK fusion-positive, 2) EGFR mutation-positive and 3) ALK-WT/EGFR-WT (WT/WT). Progression-free survival (PFS) of 1st-line platinum-based doublet chemotherapy and EGFR TKIs was also analyzed.

Results:

Twenty-three cases were ALK fusion-positive by FISH and did not receive ALK inhibitors during the follow-up period. The median OS of ALK fusion-positive, EGFR mutation-positive and WT/WT patients was 12.2, 29.6, and 19.3 months, respectively (P-value; vs. EGFR mutation-positive: 0.001, vs. WT/WT: 0.127). The PFS of 1st-line platinum-based chemotherapy for the 3 groups was not different. However, the PFS of EGFR TKIs was shorter in ALK fusion-positive patients, compared with the other two groups (P-value; vs. EGFR mutation-positive: < 0.001, vs. WT/WT: 0.021).

Conclusion:

Before the introduction of ALK inhibitors, ALK fusion-positive patients experienced the shortest survival, albeit not statistically different from WT/WT patients. Although their responses to platinum-based chemotherapy were not different from comparator groups, ALK fusion-positive patients were even more resistant to EGFR TKI treatment than were WT/WT patients.

Key words:

Anaplastic lymphoma kinase, epidermal growth factor receptor, non-small cell lung carcinoma, overall survival, tyrosine kinase inhibitor

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Introduction

It has become obvious that non-small cell lung cancer (NSCLC) has distinct genetic alterations that are crucial for tumor initiation and maintenance. These molecular changes, called driver mutations, allowed a new way to categorize lung cancer into clinically relevant subgroups.[1-3] One of them is the ALK fusion, which was identified in 2007.[4,5] A small inversion within chromosome 2p produces a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene.[6] The product of this fusion gene overexpresses ALK protein and works as a driver for proliferation in lung cancer cells harboring this fusion, demonstrating the phenomenon of oncogene addiction.[7,8] Fewer than 3 years after the identification of the ALK fusion, a phase I trial of crizotinib (PF-02341066, Pfizer), an orally active ALK and MET dual inhibitor, resulted in a significant response in patients with ALK fusion. In a pretreated patient population that usually has a 10% response rate to conventional chemotherapy; treatment with crizotinib yielded an overall response rate (ORR) of 55% and estimated 6-month progression-free survival (PFS) rate of 72%.[9,10] Furthermore, a gatekeeper mutation which could explain the resistance to crizotinib was also identified at the same time.[11]

In the center of this rapid advance of translational research, there has been an early understanding of the clinical and pathologic characteristics of patients with ALK fusion.[12] Prevalence of the ALK fusion in unselected NSCLC patients ranges from 3% to 5%.[13-16] The ALK fusion is strongly

related with younger age, and never- or light-smoking history.[15,17] The pathologic features of ALK fusion-positive tumors are also distinct. Almost all of them are adenocarcinomas; signet-ring cell histology and acinar pattern were commonly identified.[13,18-20] Recent studies have proposed use of these clinicopathologic characteristics as screening strategies to enrich for likelihood of ALK fusion-positive tumors.[3,21-23]

Now, ALK fusion is a positive predictive marker for ALK inhibitor treatment.[9,24] However, the prognostic value of ALK fusion is not fully understood. Previous studies tried to analyze overall survival (OS) in patients with EML4-ALK fusion, but the clinical significance was in question due to small numbers of events in enrolled patients, and confounding from the use of crizotinib in the ALK fusion-positive group.[12,23] Therefore, this study was performed to elucidate the clinical course of ALK fusion-positive patients who did not receive ALK inhibitors, compared to ALK-WT patients

Materials and Methods

Study Population

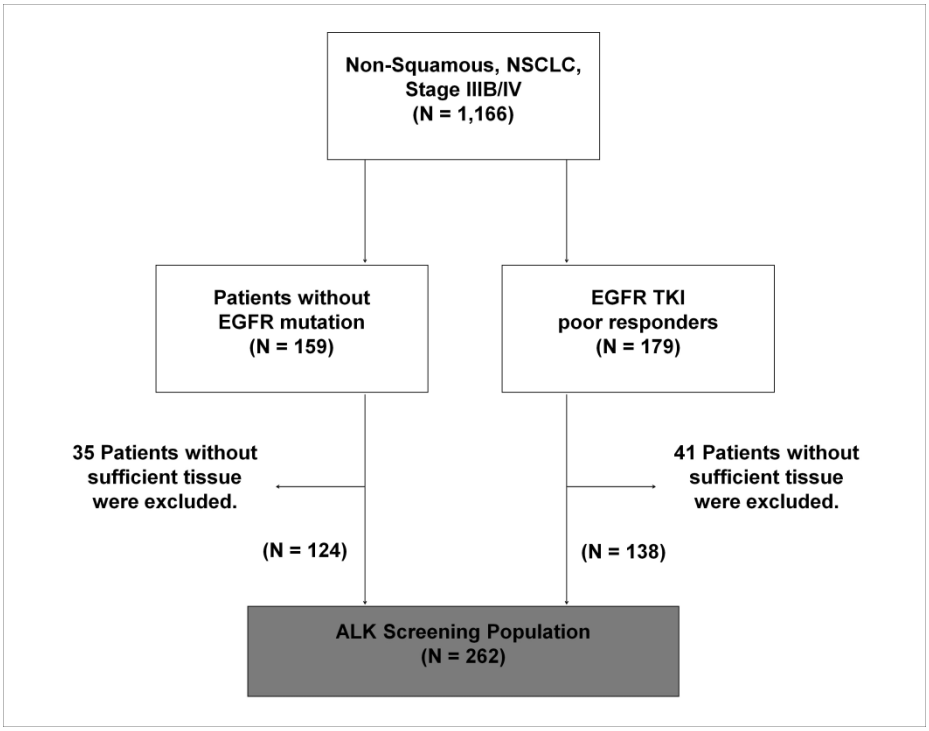
A total of 1,166 patients with stage IIIB/IV, non-squamous NSCLC were collected from the database of Seoul National University Hospital (SNUH), Seoul, Korea, between January 1st, 2003 and August 31st, 2009. To enrich for ALK fusion-positive cases, we excluded patients harboring EGFR mutations because ALK fusion is rarely coexistent with EGFR mutation.[14,25] Among the patients with unknown EGFR mutation status, patients who showed objective

response to gefitinib or erlotinib were excluded, using this history as a proxy for likelihood of harboring EGFR mutation (Figure 1).[12] Patients with insufficient tissue for pathologic examination, or patients whose tissue produced an inconclusive result in ALK fluorescence in situ hybridization (FISH) were also excluded. Therefore, a total of 262 patients with examinable tissue were enrolled. Patients who had received crizotinib were not included in this analysis. The study protocol was reviewed and approved by the institutional review board of SNUH (IRB No.: H-1008-035-326).

Data Collection

Electronic medical records of enrolled patients were reviewed to collect demographic, clinical and pathologic information. Chemotherapy regimens, treatment responses, sites of metastases, and survival outcomes were abstracted. EGFR mutation status of patients was also recorded, which had been examined with a direct sequencing method of EGFR exon 18 to 21. Radiologic responses were evaluated according to RECIST criteria, version 1.0.[26] OS was defined from the diagnosis of metastatic disease to the date of death. PFS was measured from the first day of chemotherapy until radiologic or clinical progression of disease.

Figure 1. Sample Enrichment Strategy



Pathologic Examination and Molecular Diagnostics

A total of 262 cases with examinable formalin-fixed paraffin-embedded (FFPE) tissue were included in this study. 206 samples were biopsied by percutaneous technique; 56 samples were surgically resected. All histological diagnoses were reviewed based on the latest WHO classification.[27]

ALK FISH was performed using a dual-color break-apart probe (Abbott Molecular, Abbott Park, USA) which hybridizes the 2p23 band (red signal) and ALK gene breakpoint (green signal). All procedures were conducted according to manufacturer's instructions. Three micron-sectioned FFPE tissue was deparaffinized, dehydrated, immersed in 0.2 N HCl, and incubated in 1M NaSCN at 80°C for 30 minutes. Pepsin solution was added to treated sections, then dual-probe hybridization for ALK was performed. After application of probe mixture, slides were treated with protease, and then incubated in a humidified atmosphere with HYBriteTM (Abbott Molecular) at 77°C for 5 minutes for denaturation. Subsequently, slides were incubated at 37°C for 16 hours for hybridization. Slides were then immersed in 0.3% NP-40 (Abbott Molecular)/0.4× saline sodium citrate (SSC) for 5 minutes at room temperature, followed by 0.3% NP-40/0.4× SSC for 5 minutes at 72°C. For the counterstaining of nuclei, 4,6-diamidino-2-phenylindole was used. FISH was regarded as positive when the break-apart signals or 5'-deletions were seen in more than 15% of 50 or more tumor cells. All specimens of FISH assay were examined by one trained pathologist in a blinded manner.

Case-Case Matching and Statistical Analysis

To control for known prognostic factors in lung cancer survival, each ALK fusion-positive case was matched to 2 EGFR mutation-positive patients, and 2 WT/WT patients. All patients of matched cohort were also restricted to non-squamous histology. Matching variables were age at diagnosis, sex, stage of the disease, and smoking status. The data cut-off point of survival analysis was January 13th, 2011.

Statistical analyses of categorical variables were performed using Pearson's chi-square test or Fisher's exact test, as appropriate. The t test was performed to compare continuous variables between groups. The median duration of OS and PFS were calculated using the Kaplan-Meier method. Comparisons between groups were done using the log-rank test. Multivariate analysis was carried out using the Cox proportional hazard model. Two-sided P-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc. Chicago, USA).

Results

Clinicopathologic Characteristics

Among 262 examined tumors, 23 cases were identified as ALK fusion-positive by FISH. As mentioned above, One ALK fusion-positive case was matched to 2 EGFR mutation-positive and 2 WT/WT patients (Table 1). All 3 groups included patients with stage IV disease or recurred tumor; except for 1

Table 1. Clinicopathologic Characteristics

	ALK fusion+ (n=23)		EGFR mutation+ (n=46)		WT/WT (n=46)		*P*	
Characteristics	No.	%	No.	%	No.	%	ALK vs. EGFR	ALK vs. WT/WT
Age at diagnosis								
Mean (SD)	47.4 (11.4)		49.6 (6.0)		50.9 (8.1)		.383*	.140
Median	47.8		51.1		52.0			
Sex								
Male	9	39.1	17	37.0	19	41.3	.861†	.862
Female	14	60.9	29	63.0	27	58.7		
Smoking history								
Never or light-smoker	18	78.3	37	80.4	34	73.9	.832	.693
Heavy smoker‡	5	21.7	9	19.6	12	26.1		
Pathology								
Adenocarcinoma	16	69.6	41	89.1	37	80.4	.043	.313
Non-small cell carcinoma, NOS	7	30.4	5	10.9	9	19.6		
Stage								
IIIB	0	0	1	2.2	0	0	.476	
IV	23	100.0	45	97.8	46	100.0		
ECOG performance status								
0	7	30.4	12	26.1	12	26.1		
1	13	56.5	26	56.5	27	58.7		
2	3	13.1	7	15.2	6	13.0		
3	0	0	1	2.2	1	2.2		
4	0	0	0	0	0	0		

Table 1. Clinicopathologic Characteristics (continued)

	ALK fusion+ (n=23)		EGFR mutation+ (n=46)		WT/WT (n=46)		*P*	
Characteristics	No.	%	No.	%	No.	%	ALK vs. EGFR	ALK vs. WT/WT
1st line cytotoxic chemotherapy								
Total	21	91.3	34	73.9	37	80.4		
Gemcitabine /Cisplatin	6		14		12			
Paclitaxel /Carboplatin	3		12		18			
Others	12		8		7			
EGFR TKI, any line								
Total	17	73.9	42	91.3	27	58.7		
Gefitinib	14		31		12			
Erlotinib	3		11		15			
Pemetrexed, any line	12	52.2	20	43.5	22	47.8		

Abbreviations: SD, standard deviation

* T test

† Chi-square test

‡ Heavy smoker means smoker who have smoked ≥ 10 pack years

EGFR mutation-positive patient with stage IIIB disease. Consequently, a total of 115 patients (23 ALK fusion-positive, 46 EGFR mutation-positive, 46 WT/WT) were included in survival analysis. In pathologic examination, the ALK fusion-positive group included more unspecified non-small cell carcinomas (30%) than the EGFR mutation-positive and WT/WT groups (11% and 20%, respectively). Three ALK fusion-positive patients (13.0%) and one WT/WT patient (2%) had signet ring cell carcinoma. In terms of metastatic site, 30% of both ALK fusion-positive and WT/WT patients had CNS metastases proven in radiologic or cerebrospinal fluid cytopathologic examinations during treatment. However, EGFR mutation-positive patients showed higher rate of CNS metastasis of 63% (Table 2. $P<0.001$). Fewer numbers of liver metastases were observed in WT/WT group ($P=0.035$).

Treatment Responses and Survival Analyses

Treatment response and survival outcome to chemotherapy and EGFR TKI treatment were evaluated by reviewing medical records (Table 3, Table 4). Among 115 patients, 92 patients (80%) were initially treated with a cytotoxic chemotherapy for the first-line treatment. All these patients were treated with a platinum-based doublet regimen, except for 2 patients who were treated with gemcitabine/vinorelbine and with docetaxel. Various doublet combinations were identified; the most common regimen was paclitaxel/carboplatin, used in 33 patients, followed by gemcitabine/cisplatin used in 32 patients. Response rates to cytotoxic chemotherapy were not different between the three groups

Table 2. Distribution of Metastasis Sites

	At the point of initial evaluation				Including sites of disease progression			
Site of Metastasis	**ALK fusion+ (n=23)**	**EGFR mutation+ (n=46)**	**WT/WT (n=46)**	***P****	**ALK fusion+ (n=23)**	**EGFR mutation+ (n=46)**	**WT/WT (n=46)**	***P****
Lung to lung	14	32	25	0.322	16	33	33	0.979
Liver	2	9	3	0.136	8	16	6	0.034
Adrenal	1	3	5	0.581	5	4	6	0.317
Bone	8	16	17	0.972	12	23	26	0.818
CNS	6	15	9	0.363	7	31	14	< 0.001
Pleural effusion	4	8	6	0.821	7	12	16	0.663
Pericardial effusion	2	2	1	0.457	3	3	4	0.663

* Chi-square test

Table 3. Treatment Responses by Molecular Subtypes

	ALK fusion+ (n=23)		EGFR mutation+ (n=46)		WT/WT (n=46)		*P**	
Variables	No.	%	No.	%	No.	%	ALK vs. EGFR	ALK vs. WT/WT
Best response to 1st line cytotoxic chemotherapy								
Total	21	91.3	34	73.9	37	80.4		
CR	0	0	0	0	0	0		
PR	6	28.6	11	32.4	13	35.1		
SD	8	38.0	12	35.3	15	40.5		
PD	6	28.6	11	32.4	9	24.4		
Unevaluable	1	4.8	0	0	0	0		
Best response to EGFR TKI								
Total	10†	21.7	42	91.3	27	58.7		
CR	0	0	3	7.1	0	0		
PR	0	0	31	73.8	4	14.8		
SD	2	20.0	6	14.3	7	25.9		
PD	8	80.0	2	4.8	16	59.3		
Unevaluable	0	0	0	0	0	0		
Response rate, %								
Chemotherapy	28.6		32.4		35.1		.857	.695
EGFR TKI	0		80.9		14.8		<.001	.096

* Chi-square test

† Excludes patients that were enrolled due to previous non-response to EGFR TKIs

Table 4. Survival Analysis by Molecular Subtypes

	ALK fusion+ (n=23)	EGFR mutation+ (n=46)	WT/WT (n=46)
Overall survival (months)			
N	23	46	46
Median (95% CI)	12.23 (6.60, 17.87)	29.63 (24.73, 34.53)	19.33 (9.11, 29.55)
***P*-value* vs. ALK+**		.001	.127
PFS of 1st line chemotherapy (months)			
N	21	34	37
Median (95% CI)	3.87 (0.43, 7.31)	4.93 (4.40, 5.46)	3.73 (2.32, 5.14)
***P*-value* vs. ALK+**		.825	.474
PFS of EGFR TKI (months)			
N	10†	42	27
Median (95% CI)	1.37 (1.07, 1.67)	9.80 (4.94, 14.66)	2.07 (0.15, 3.99)
***P*-value* vs. ALK+**		<.001	.037

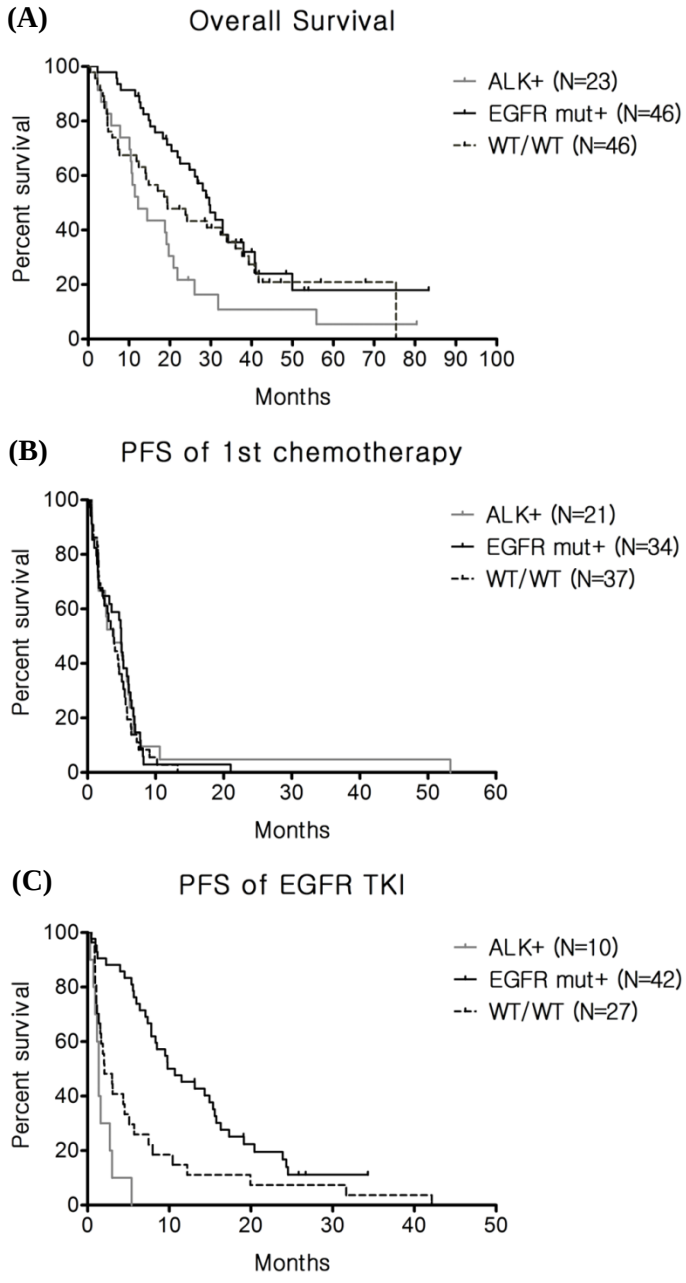
* Log-rank comparison of Kaplan–Meier estimates for patients with ALK-positive tumors compared with patients having other tumor types.

† Excludes patients that were enrolled due to previous non-response to EGFR TKIs.

(ALK fusion-positive, EGFR mutation-positive, and WT/WT; 27%, 32%, and 35%, respectively). While PFS of EGFR mutation-positive patients was longer than the other two groups (Figure 2, ALK fusion-positive, EGFR mutation-positive, and WT/WT; 3.87, 4.93, and 3.73 months, respectively), this difference was not statistically significant. (P-value; vs. ALK-positive: 0.825, vs. WT/WT: 0.505). A total of 73 patients (63%) received subsequent cytotoxic chemotherapy. Proportion of patients who received second-line chemotherapy was well balanced between the groups (ALK fusion-positive, EGFR mutation-positive, and WT/WT; 70%, 59%, and 65%, respectively). Pemetrexed (32) was the most commonly used agent as second-line chemotherapy, followed by gemcitabine/ vinorelbine combination (18), and docetaxel (8). PFS of second-line chemotherapy was not different among the three groups (2.07, 1.63 and 2.93 months, respectively, P=0.353).

Eighty-six patients were treated with EGFR TKI. For specific agents, gefitinib was used in 57, erlotinib in 29, and both were used in 4 patients. For appropriate comparison of PFS of EGFR TKI treatment, ALK fusion-positive patients who were enrolled due to their non-responses to EGFR TKI treatments were excluded. Because these ALK fusion-positive patients were already pre-selected on the basis of non-response to EGFR TKI, it is inappropriate to measure their PFS since this was a selection criterion. If included, it would bias the group based on non-response to TKI. For this reason, nine ALK fusion-positive patients were excluded in this analysis. The EGFR mutation-positive group showed a much higher response rate than the two other groups: ALK fusion-positive, EGFR mutation-positive, and WT/WT:

Figure 2. Kaplan-Meier Estimates of Survival Outcomes



Kaplan-Meier estimates of (A) overall survival, (B) progression-free survival of 1st line chemotherapy, (C) progression-free survival of EGFR TKI among study patients

0%, 81%, and 15%, respectively. ALK fusion-positive patients who were treated with EGFR TKI showed immediate progression, not responding to EGFR TKI treatment. Median PFS of ALK fusion-positive patients was shorter than the other two groups (Fig. 2): ALK fusion-positive, EGFR mutation-positive, and WT/WT; 1.37, 9.80, and 2.07 months, respectively; (P=0.037 vs. WT/WT)

The median OS of ALK fusion-positive patients was 12.2 months compared to 29.6 months for EGFR mutation-positive patients (P=0.001) and 19.3 months for WT/WT patients (P=0.127). In multivariate analysis including age, gender, stage, smoking status, and histology with Cox-proportional hazard model, the calculated hazard ratios of EGFR mutation-positive patients and WT/WT patients were 0.446 and 0.631, respectively. Other variables including histology did not significantly affect the overall survival of patients. In conclusion, ALK fusion-positive patients had the shortest, albeit, not statistically significant, median overall survival in a pre-ALK inhibitor era. They were not different in response to conventional cytotoxic chemotherapy, compared with ALK-WT patients. However, they were more resistant to EGFR TKI treatment, even compared with WT/WT patients.

Discussion

Using FISH, a historical cohort of ALK inhibitor-naïve patients was constructed to examine a possible prognostic role for ALK fusion in NSCLC

clinical outcomes. As a result, the overall survival of ALK fusion-positive patient was not statistically different from their WT/WT matched comparators, although the survival was numerically smaller. Shaw et al.[12] examined survival outcome of 17 metastatic ALK fusion-positive patients by determining PFS and OS. In this study, ALK fusion-positive patients showed inferior clinical outcome compared with EGFR mutation-positive patients, resembling survival of WT/WT patients. However, there were a small number of events within the ALK fusion-positive patient group, relatively short follow-up duration, and differences in age and smoking status between comparator groups in this study. Moreover, seven ALK fusion-positive patients out of 17 enrolled in the phase I crizotinib clinical trial; which may have, as acknowledged by the author, influenced the overall survival outcome of this study. To minimize imbalances in potential prognostic, clinicopathologic variables, a 2:1 case matching of ALK-WT to ALK fusion-positive patients was used in this study. This matching took into account age at diagnosis, sex, disease stage, and smoking status. Although we did not include patients' performance status in the matching variables, the performance statuses were well-balanced between the three groups. The follow-up period of our study was relatively long, with a median follow-up of 26 months. Additionally, ALK inhibitor-related effects on survival were fundamentally ruled out in this study. Although this study had the limitations of a single-center, retrospective design, and restriction of statistical power due to small sample size, we carefully controlled for confounding factors in our analyses in an effort to present the comparative clinical course of ALK fusion-

positive patients (treated without ALK inhibitors) and ALK-WT patients.

Primary Resistance to EGFR TKIs

The predictive role of ALK fusion to response to EGFR TKI therapy, which has been described in several studies[12,22,28,29], was affirmed in this study. ALK fusion-positive patients were more resistant to EGFR TKI treatment. This result is also in concordance with the laboratory data published in 2008, which showed the resistance of an ALK fusion-positive lung cancer cell line to erlotinib.[8] Recent studies repeatedly reported similar data of ALK fusion-positive tumor's primary resistance to EGFR TKI, and a screening strategy for ALK fusion-positivity has been proposed based upon this characteristic.[12,22,23] However, the inferior progression-free survival for EGFR TKI in ALK fusion-positive patients than WT/WT patients should be interpreted cautiously. Considering the low sensitivity of direct sequencing in detecting somatic mutation, the four WT/WT patients who exhibited partial response to EGFR TKI might have EGFR mutation, which was not detected in our tests. By applying more sensitive method such as targeted deep sequencing, the mechanism of response to EGFR TKI in these patients can be more clearly understood.

Sensitivity to Cytotoxic Chemotherapy

As was reported by Shaw et al, as well as a previous report from our group, we here show an objective response rate to conventional chemotherapy that

was numerically smaller in ALK fusion-positive vs. ALK-WT patients.[12,22] In none of these studies was this finding statistically significant, which may either be a true result or be a function of the limited sample size of ALK fusion-positive patients in each study. Larger sample sizes or pooled analyses may answer this question more definitively.

Recent retrospective analyses have shown that ALK fusion-positive patients were more sensitive to pemetrexed compared to ALK-WT comparators.[29,30] In this study, the percentage of pemetrexed exposure in any line of ALK fusion-positive, EGFR mutation-positive, and WT/WT groups was 52%, 43%, and 48%, respectively. Despite the relatively high use of pemetrexed in the ALK fusion-positive patients, this group had the shortest overall survival estimate.

Sites of Metastasis

ALK fusion-positive patients had a lower rate (30%) of CNS metastases during the follow-up period compared with EGFR mutation-positive patients (63%), and this rate was identical with WT/WT patients (30%). This result may be due to bias, because EGFR mutation-positive patients had longer survival compared with the other two groups. Six (26%) ALK fusion-positive, fifteen (33%) EGFR mutation-positive and nine (20%) WT/WT patients had CNS metastases proven in initial staging workup. To compare the rate of CNS metastasis in consideration of a survival-related effect, prospective study would be helpful.

Relationship with Smoking History

A significant portion of ALK fusion-positive patient (22%) had smoking history, although three patients in heavy smoker group had 10 pack-year smoking history, a borderline value of heavy smoker (defined as smoking history of 10 pack-year or more). Similarly, recent study of our group with different patient population also reported large number of smokers (31%) in ALK fusion-positive group.[22] These finding suggests smoking status is not appropriate for patient selection in ALK testing. Smoking history would be approached and interpreted with caution, because it can vary in different cultural and social contexts.

Histologic Considerations

While excluding squamous cell histology in patient selection, our cohort had significant portion of non-small cell carcinoma, not otherwise specified (NOS). Seven ALK fusion-positive patients with NOS histology were identified in this study; three of them had immunophenotype of lung adenocarcinoma, demonstrating expression of thyroid transcription factor-1 (TTF-1) and cytokeratin 7 (CK7). Several previous studies also have been reported small number of ALK fusion-positive patients with non-adenocarcinoma histology.[12,29-31] In addition, misclassification in histology can occur in cases difficult to specify; especially in cases with small amount of specimens harvested by needle biopsy or aspiration.[32] Therefore, we should be careful to restrict ALK testing in patients with adenocarcinoma histology,

since we can miss small number of ALK fusion-positive patients with large cell, NOS, or other minor histology.

Conclusion

In this study, ALK fusion-positivity was suggestive of poor prognosis, albeit not statistically significant, and predictive for poor EGFR TKI outcomes. With the historically dismal survival observed across the unselected NSCLC patient population, this finding may signify an even greater unmet medical need within the ALK fusion-positive subset of NSCLC. Proper targeted therapy such as crizotinib is needed for advanced NSCLC patients harboring ALK fusion, to improve their outcome as like EGFR mutation-positive patients.

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국문 초록

이 준 구

서울대학교 대학원

의학과 분자종양의학

서론 : 본 연구는 역형성림프종인산화효소 (ALK) 에 대한 선택적 억제제를 도입하기 이전 시기에, ALK 융합을 가진 비소세포폐암 환자의 임상적 경과가 어떠하였는지를 확인하기 위해 시행되었다. 이에 ALK 융합-양성 환자군의 임상적 특성을 고려하여 짝짓기한 ALK-자연형 (WT) 환자군을 형성하여 전체생존기간을 비교하였다.

방법 : 2003년부터 2009년의 기간중 서울대학교병원에서 비편평상피, 비소세포폐암으로 치료 받은 1,166명의 IIIB 혹은 IV 기 암환자들 중 상피세포성장인자수용체 (EGFR) 의 돌연변이 검사에서 WT 으로 확인되었거나, EGFR 티로신 인산화

효소 (TKI) 치료에 반응하지 않은 환자를 추출하였다. 이러한 조건을 만족하는 총 262명의 환자군을 대상으로 ALK 융합을 평가하기 위해 형광동소교잡법을 시행하였다. 이 결과를 바탕으로, 전체 코호트로부터 다음의 세 환자군을 형성하였다. 1) ALK 융합-양성, 2) EGFR 돌연변이-양성, 3) ALK 자연형/EGFR 자연형 (WT/WT). 이들 환자군의 전체생존기간, 1차 백금화합물기반 2제 항암화학요법 및 EGFR TKI 에 대한 무진행생존기간을 측정하였다.

결과 : 형광동소교잡법에 의해 23명이 ALK 융합-양성 환자로 진단되었고, 이들은 모두 ALK 에 대한 선택적 억제제를 투여받지 않은 환자들이었다. ALK 융합-양성, EGFR 돌연변이-양성, WT/WT 군의 전체생존기간 중앙값은, 12.2, 29.6, 19.3 개월이었다 (P-value; vs. EGFR 돌연변이-양성: 0.001, vs. WT/WT: 0.127). 1차 백금화합물기반 2제 항암화학요법에 대한 무진행생존기간은 3개 환자군에서 차이를 보이지 않았다. 하지만, EGFR TKI 에 대한 무진행생존기간은 ALK 융합-양성군에서 가장 짧았다 (P-value; vs. EGFR 돌연변이-양성: <0.001, vs. WT/WT: 0.021).

결론 : ALK 에 대한 선택적 억제제를 도입하기 이전 시기에 치료를 받은 ALK 융합-양성 환자군은 WT/WT 군과 비교하여 전체생존기간에 있어 통계적으로 유의한 차이를 보이지 않았다. 특히, ALK 융합-양성 환자군은 EGFR TKI 에 대한 일차성 내성을 보여, WT/WT 군에 비해 더 짧은 무진행생존기간을 보였다.

주요어 : 역형성림프종인산화효소, 상피세포성장인자수용체, 비소세포폐암, 전체생존기간, 티로신 인산화효소 억제제

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감사문

이 논문이 완성될 수 있도록 도움을 주신 모든 분들께 감사드립니다.

의과대학 학생 때부터 석사 과정에 이르기까지 학자로서 나아갈 방향을 보여 주시고 이끌어 주신 지도교수님이신 허대석 선생님께 깊은 감사의 말씀을 올립니다. 논문의 작성 및 심사의 과정에서 세세한 부분까지도 지도해 주신 우홍균 선생님과, 본 주제와 관련된 최신 지견을 익히는 데에 많은 도움을 주신 김동완 선생님께 진심의 감사를 올립니다.

아울러, 매 순간 많은 배려로 심지를 굳게 해 준, 사랑하는 아내가 곁에 있었기에 이 모든 것이 가능하였습니다. 학업에 집중할 수 있도록 모든 도움을 아끼지 않으신 부모님께도 사랑의 마음을 전합니다. 또한, 함께 연구하고 토론하며 같은 꿈을 키워 간 혈액종양내과 동기들 (김지연, 이은영, 임유주)에게, 추억을 가득 담아 감사의 인사를 전합니다.