High prevalence of gene abnormalities in young patients with lung cancer

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ABSTRACT

Background: Recently, driver oncogenes in adenocarcinoma of the lung were identified, and several molecular target agents were introduced in the clinical setting. However, there are few reports on the frequency of gene abnormalities in young patients with lung cancer.

Materials and methods: Twelve patients with lung adenocarcinoma aged 40 or younger at Juntendo University Urayasu Hospital or Juntendo University Hospital from July 2004 to March 2010 were analyzed for driver oncogene status including *EGFR* activating mutation, *EML4-ALK* fusion gene, and *K-ras* mutation.

Results: Four patients showed *EGFR* gene mutation. Five out of 7 *EGFR* mutation-negative patients showed positive results for *EML4-ALK* gene fusion. One case whose *EGFR* mutation was indeterminate.

Conclusions: Driver oncogene including *EGFR* mutation and *EML4-ALK* fusion gene was identified in 9 of 12 cases (75%). Examination of gene abnormalities is essential in young patients with non-small cell lung cancer to provide the best treatment.

KEY WORDS Young patients; driver oncogene; lung cancer; *EGFR*; *EML4-ALK*

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Introduction

Many young patients with lung cancer at the time of diagnosis are already advanced stage and therefore result in a poor prognosis (1,2). For patients harboring the *epidermal growth factor receptor* (*EGFR*) gene mutation, *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) have been used effectively to prolong progression-free survival and overall survival (3,4). Recently, the powerful driver oncogene, fusion gene of the *anaplastic lymphoma kinase* (*ALK*) with the *echinoderm microtubule-associated protein-like 4* (*EML4*) was identified in non-small cell lung cancer (5). Prolongation of the survival period is expected with the use of the *ALK*-TKI. However, few studies have analyzed the frequency of driver oncogenes in young patients with non-small cell lung cancer aged 40 or younger. Therefore, we performed gene mutation analyses in young patients with lung cancer.

Methods and materials

We retrospectively reviewed medical records of all hospitalized patients with non-small cell lung cancer aged 40 or younger at Juntendo University Urayasu Hospital or Juntendo University Hospital from July 2004 to March 2010. We examined patient background, treatment modalities, and gene abnormalities. First, we examined *EGFR* mutation by performing direct sequencing for tumor biopsy specimens obtained by bronchoscope, resected tumor samples, or cell blocks of bronchoalveolar fluid or pleural effusion. When the *EGFR* mutation was negative, we next performed immunohistochemical analysis [using an intercalated antibody-enhanced polymer (iAEP)] and fluorescence in situ hybridization (FISH) for detection of the *EML4-ALK* fusion protein and gene (6), respectively. In negative cases for both *EGFR* mutation and *EML4-ALK* fusion gene, we analyzed the samples for presence of the *K-ras* mutation. We did not conduct re-evaluation for the *EGFR* gene mutation after recurrence.

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Table 1. Background characteristics of the 12 patients in whom examination was performed for gene abnormalities.

No	Age	Sex	BI	Histology	T	N	M	Stage	PS	EGFR	EML4-ALK	1st line	2nd line	Outcome	Survival time
1	33	m	10	adeno	4	0	1	IV	1	+	n.d.	CBDCA+TXL	Gefitinib	death	1,208 days
2	37	m	800	adeno	4	2	1	IV	1	+	n.d.	Gefitinib	CBDCA+TXL	death	461 days
3	37	m	450	adeno	4	3	1	IV	3	+	n.d.	CBDCA+TXL	Gefitinib	death	379 days
4	39	m	400	adeno	3	3	1	IV	0	+	n.d.	CDDP+PEM	Gefitinib	death	364 days
5	31	f	100	adeno	1	3	0	IIIB	0	±	n.d.	CBDCA+TXL	Gefitinib	alive	2,688+α
6	35	f	0	adeno	4	0	0	IIIB	0	-	+	CBDCA+GEM	PEM	alive	1,456+α
7	37	f	0	adeno	2	1	1	IV	0	-	+	CBDCA+PEM		alive	757+α
8	34	f	0	adeno	4	3	1	IV	2	-	+	CBDCA+TXL	GEM	death	568 days
9	33	m	300	adeno	4	3	1	IV	1	-	+	CBDCA+TXL	CBDCA+PEM	death	175 days
10	35	m	0	adeno	4	3	1	IV	1	-	+	CBDCA+TXL	CBDCA+PEM	death	99 days
11	37	f	0	adeno	2	2	0	IIIA	0	-	-	CBDCA+TXL		alive	365+α
12	36	m	340	non-small	2b	3	1b	IV	1	-	-	CBDCA+TXL		alive	280+α

Abbreviations: BI, brinkman index; PS, performance status; ±, EGFR mutaion indeterminate, but responded to gefitinib; n.d., not done; CBDCA, carboplatin; TXL, pacritaxicel; PEM, pemetrexed; GEM, gemcitabine.

Survival analysis was conducted using the Kaplan-Meier method.

Results

Case profile

We retrospectively studied 12 young patients with non-small cell lung cancer (men, 7; women, 5). The mean age of the patients was 35.3 years (Table 1).

Smoking history

Six patients were smokers. Three out of these patients were heavy smokers over 20 pack pear, and had a long history of smoking. One man and 4 women were non-smokers.

Histology and stage of the disease

All of the patients had non-small cell lung cancer. Eleven patients (91.6%) were diagnosed with adenocarcinoma, while one was with histology not otherwise specified. According to the clinical TMN classification, there were 1 patient with stage IIIA, 2 with stage IIIB cancer; and 9 with stage IV.

Examination of the gene abnormalities

Activating EGFR gene mutations, exon 19 deletion, were detected in 4 cases.

One case whose *EGFR* gene mutations were indeterminate because sample size was not enough for direct sequencing. But she seems to harbor *EGFR* activation mutation because she responded to gefitinib remarkably. Therefore, we considered that she harbored an *EGFR* mutation. Subsequently, we conducted iAEP followed by FISH analyses for 7 patients without *EGFR* mutation to determine EML4-ALK fusion protein and gene. Among 7 patients, 5 patients showed positive for *EML4-ALK* protein or gene. Analysis for the presence of *K-ras* mutation was performed in 2 cases that were negative for both the *EGFR* mutation and the *EML4-ALK* fusion gene. One of the cases was *K-ras* mutation-negative, while the other case was not clear for *K-ras* mutation because of inadequate sample (Figure 1).

Median survival time and survival curve

The patients harboring *EGFR* mutation were treated with gefitinib. The median survival time (MST) was 461 days. The MST for the patients harboring *EML4-ALK fusion gene* was 568 days (Figure 2), because these patients could not be treated *ALK* inhibitors.

Discussion

In this study, all patients were diagnosed as non-small cell lung cancer with advanced stage. Development of metastases without symptoms or prolonged neglect of symptoms could be the reasons for this finding. Gene analysis showed that *EGFR* mutation was clearly identified in 4 of our 12 cases.

The frequency of the EGFR mutation in cases of lung adenocarcinoma has been reported by a previous study (7). There were no significant differences in the frequency for *EGFR* mutation depending on the patient age (8). Five of the 7 *EGFR*-negative cases in our study were detected to have the EML4-ALK fusion gene. According to a previous study, the frequency of the *EML4-ALK* fusion gene is in the range of 1.6% to 8.6% (9-12).

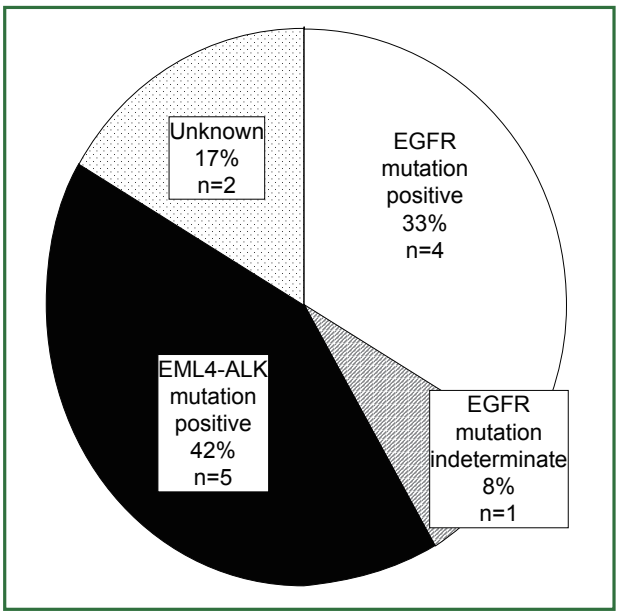

Figure 1. Frequency of gene abnormalities in 12 young patients with lung cancer aged 40 or younger.

The *EML4-ALK* fusion gene is recognized to be associated with the onset of lung cancer in young patients. *EML4-ALK* fusion gene has an exclusive relation with *EGFR* mutation and *K-ras* mutation (13). The frequency for the *EML4-ALK* fusion gene in this study was markedly higher than previous studies. Our sample-size was small, but gene abnormalities were identified in 75% in patients aged 40 and younger with lung cancer. Although all patients with *EGFR* activating mutation were treated with an *EGFR*-TKI, the overall survival was unsatisfactory. Unfortunately, we did not perform a re-examination for the gene abnormalities in the recurrent tumors. One of the potential mechanisms for short survival for these patients could be explained by the fact that 3 patients were heavy smokers, whose *k-ras* could be mutated. Moreover, we could evaluate only one case the *k-ras* status. Furthermore, the overall survival of the patients harboring the *EML4-ALK* fusion gene was also unsatisfactory, probably because *ALK*-TKI was not available at that time for these patients.

The results indicated that driver oncogenes were detected in 75% of our cases and that the frequency of *EML4-ALK* fusion gene was high in the young patients with non-small cell lung cancer. Our finding also suggests that the onset of non-small cell lung cancer in patients aged 40 or younger is more significantly related to gene abnormalities including driver oncogene mutation than to environmental factors.

Conclusions

In this study, we clarified that all 12 patients aged 40 and younger were non-small cell lung cancer and 9 in 12 patients were positive for the *EGFR* gene mutation or the *EML4-ALK* fusion gene. Our study revealed that ALK fusion gene affected carcinogenesis by the young patients in efficiency more than previous reports. Therefore, examination of gene abnormalities is especially important in young patients with lung cancer to provide an appropriate treatment modality.

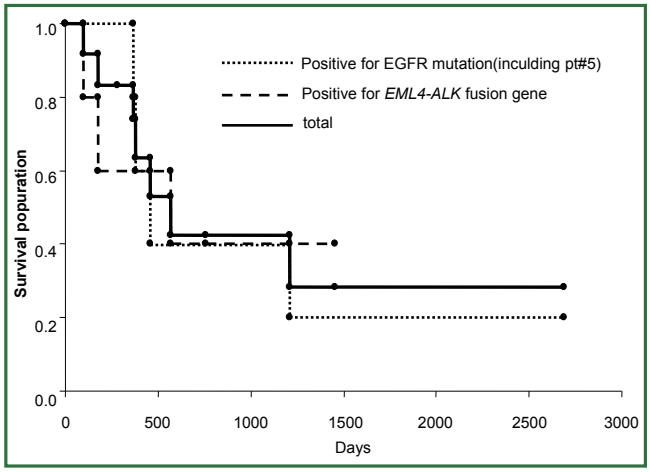

Figure 2. Survival curve of the patients.

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