

Five-year Disease Control With Alectinib in a Patient With Metastatic ALK-rearranged Lung Adenocarcinoma

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Abstract. *Background/Aim:* Therapy with alectinib could achieve prolonged progression-free and overall survival in patients with anaplastic lymphoma kinase gene (ALK)-rearranged non-small-cell lung cancer (NSCLC). However, a large proportion of the patients discontinue alectinib treatment due to recurrence. *Case Report:* A 41-year-old male patient presented with cellulitis of the right upper extremity that had developed in the past 3 weeks. Chest radiograph at the time of admission incidentally revealed a nodule in the right lung. At diagnosis, the patient had spinal bone metastases and thrombosis in the common jugular vein subclavian veins. Therefore, in addition to warfarin therapy and irradiation to the bone metastases, chemotherapy was started. After identifying the presence of the ALK rearranged gene, alectinib therapy was initiated. Since then, alectinib treatment has been continued for more than 5 years. *Conclusion:* Although very rare, there are patients who might be able to maintain a long-term response to alectinib. It is important for chest physicians to manage such patients so that the effects of alectinib can be maintained for a long time.

The discovery of driver gene mutations and the emergence of drugs to treat these genetic abnormalities have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC) (1). The anaplastic lymphoma kinase (ALK)

rearranged mutation is one of them, and many patients carrying this mutation have been benefiting from ALK-tyrosine kinase inhibitors (TKIs) (2). The ALK-TKI crizotinib, has adverse events including vision disorders, hepatotoxicity, interstitial lung toxicity, and electrocardiographic abnormality (2). Alectinib, another ALK-TKI, has a longer duration of response and lower frequency of adverse events than crizotinib (3, 4). At present, alectinib is a widely used drug in clinical practice (5-8). Despite the initial excellent efficacy of alectinib, treatment is usually discontinued (3, 4) owing to acquired resistance. Acquisition of secondary mutations in target genes is one of the major mechanisms of resistance (9).

We present herein a patient with metastatic ALK-rearranged NSCLC who had over a five-year disease control with alectinib, although the reasons are unknown. At the time of diagnosis, the patient had spinal bone metastases and thrombosis in the common jugular vein subclavian veins. Therefore, in addition to warfarin therapy and irradiation to the bone metastases, chemotherapy was started. Soon after the ALK mutation was identified, alectinib therapy was initiated. Since then, alectinib treatment has been continued for more than 5 years. This case demonstrates that, although rare, a small percentage of patients might continue to benefit from alectinib over a long-term period.

Case Report

A 41-year-old male patient presented with cellulitis of the right upper extremity that had developed in the past 3 weeks. Chest radiograph at the time of admission incidentally revealed a nodule in the right lung. He smoked around 30 packs per year. His physical examination was unremarkable. The patient underwent a chest computed tomography (CT) scan, which revealed a nodule in the right lower lobe (Figure 1A) and bilateral mediastinal lymph node enlargement. A transbronchial biopsy was performed and the histological examination confirmed the diagnosis of adenocarcinoma. CT and bone scan confirmed metastatic lesions in the cervical and thoracic vertebrae. The final diagnosis was T2N3M1b (OSS) stage IVB. In addition to this, thrombosis was

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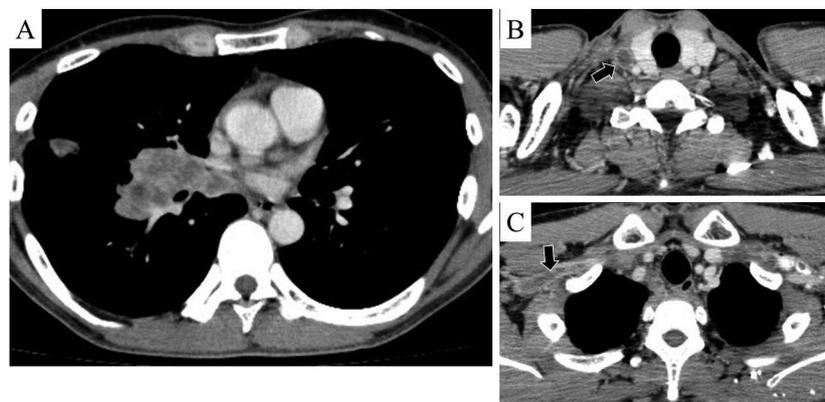


Figure 1. Chest computed tomography scan obtained at the time of admission showed a nodule in the right lower lobe (A). Thrombosis was found in the common jugular vein subclavian veins (B and C).

confirmed in the common jugular vein subclavian veins (Figure 1B and C). In addition to warfarin therapy and irradiation to the bone metastases, chemotherapy with carboplatin and paclitaxel was immediately started. Irradiation to metastatic lesions of the vertebral bodies was also initiated. Shortly after these treatments were initiated, fluorescence *in situ* hybridization of the resected specimen revealed the *ALK* rearrangement. The initial chemotherapy resulted in 'partial response' but CT performed 3 months after the start of the therapy showed regrowth of the primary lesion. Therefore, alectinib (600 mg orally twice daily) was started. 'Complete response' was obtained with this treatment. Warfarin was administered for 63 months and then terminated. Imaging tests were performed regularly after the initiation of alectinib. Chest CT scan obtained 65 months after the initiation of alectinib showed disappearance of the lung nodule (Figure 2A) and thrombosis in the common jugular vein subclavian veins (Figure 2B and C). There were no adverse effects requiring discontinuation of alectinib treatment. The patient is currently doing well without any symptoms. This study was approved by the institutional ethics committee of our institute. Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Discussion

The treatment of NSCLC has made remarkable progress in relation to the rapid expansion of knowledge on the molecular basis of the disease (1). The discovery of several driver genes and drugs that are expected to have specific responses to them in clinical practice is significantly changing the treatment of patients with advanced NSCLC (1). Among these driver genes, *ALK* rearrangement has been found in approximately 5% of patients with NSCLC (2).

Alectinib, one of the highly selective second-generation *ALK* inhibitors, is a drug with a longer duration of response and lower frequency of adverse events compared to crizotinib (3, 4). Common adverse events associated with crizotinib include visual disorders, gastrointestinal side effects, and pulmonary toxicity (2). Although pulmonary toxicity has been reported with alectinib (10), the toxicity profile of alectinib has been shown to be milder compared to that of crizotinib (3, 4). Alectinib is currently positioned as a first-line drug for NSCLC patients with the *ALK* rearranged mutation, but many of these patients develop resistance to alectinib (9). For this reason, evaluation of disease activity using tumor markers (11) and treatments after the emergence of alectinib resistance have recently been researched (12). Basic studies of combination therapies that enhance the efficacy of alectinib are also being conducted (13).

Although there are advances in genetic testing methods that can measure multiple genes simultaneously, their accuracy and 'turnaround time' are still problematic at this time (14). In this patient, the *ALK* rearrangement was evaluated using fluorescence *in situ* hybridization. Since the complication of thrombosis was found at the time of lung cancer diagnosis and the treatment had to be started immediately, chemotherapy preceded the identification of the *ALK* mutation. Phase III trials of alectinib in treatment-naïve patients reported a median progression-free survival (PFS) of 34.1–34.8 months (3, 4). There are also some reports on the PFS of patients treated with alectinib after administration of crizotinib (5, 6). Hizal *et al.* recently reported a median PFS of 28.8 months for alectinib in 177 treatment-naïve patients (7). In our previous study, PFS for alectinib was 31 months (95%CI=30-56 months) (8). To the best of our knowledge, there is only one case report in the English literature regarding a patient treated with alectinib for more than 5 years (15). The patient received radiosurgery for brain metastasis followed by chemotherapy with cisplatin and

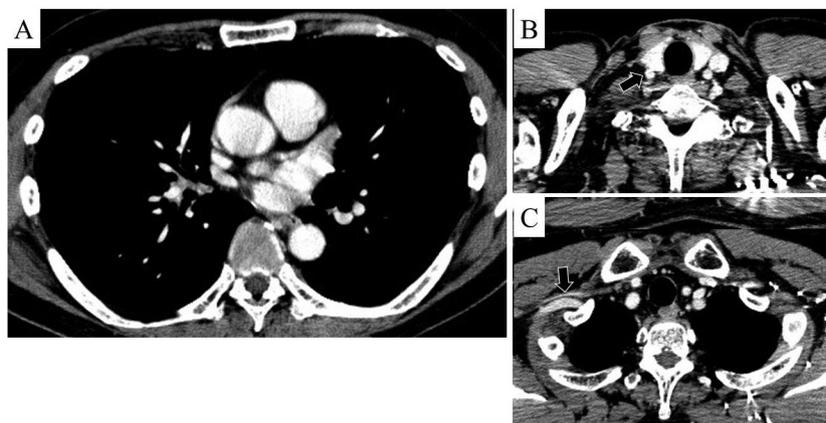


Figure 2. Chest computed tomography scan obtained 65 months after the initiation of alectinib showed disappearance of the lung nodule (A) and thrombosis in the common jugular vein subclavian veins (B and C).

gemcitabine before introduction of alectinib therapy, which continued for approximately 5.5 years with marked efficacy. Then, he experienced recurrence of a bulbar metastasis after discontinuation of alectinib. Reintroduction of alectinib therapy resolved the lesion again (15). Our patient also received chemotherapy first because of the oncology emergency of coagulopathy and 'laboratory turn-around-time' of the *ALK* rearranged gene. The chemotherapy administered was also successful in our patient. It is interesting that "preceding chemotherapy" and "response to preceding chemotherapy" in our patient were consistent with the clinical course of the patient reported by Kawamura *et al.* (15). It is not clear why this patient was able to achieve disease control with alectinib for more than 5 years. However, it seems to be related to the following positive factors regarding prognosis: 1) detection before intravenous thrombosis causes complications, 2) good control of thrombosis with warfarin combination, 3) no complications associated with the administration of warfarin, and 4) no recurrence of thrombosis. There were no adverse events that forced the patient to discontinue alectinib. This also seems to be a good factor.

Although research on the mechanism of drug resistance has progressed, currently, no definitive means of overcoming resistance have been established. The reason why alectinib could be administered for a long period of time is unknown, but this study showed that there are patients who are responsive for more than 5 years.

Conclusion

Although rare, a small percentage of patients might continue to benefit from alectinib over a long term. At present, the favorable conditions associated with the possibility of long-term survival are unknown, but future clarification is expected.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

GO and HS designed the study. GO, SO, YS and HS collected the data. GO and HS analyzed the data and prepared the manuscript. All Authors approved the final version of the article.

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