Successful alectinib treatment for a mechanically ventilated patient with ALK-positive non-small cell lung cancer

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Abstract
We report a 38-year-old man with poor performance status (PS) who was diagnosed as stage IV non-small cell lung cancer (NSCLC) harboring the echinoderm microtubule-associated protein like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion gene. Crizotinib, an ALK inhibitor, was administered after a temporary effect of combination cytotoxic chemotherapy. Chest computed tomography showed air space consolidations and diffuse ground glass opacities in both lungs after 5 days of treatment with crizotinib, and the patient required mechanical ventilation due to respiratory deterioration. For tumor progression, crizotinib was switched to alectinib, the other ALK inhibitor, along with short-term corticosteroid therapy for the possibility of crizotinib-induced pneumonitis. After alectinib administration through a nasogastric tube, tumors regressed with weaning from mechanical ventilation. Safe and successful administration of alectinib through a nasogastric tube may be a therapeutic option for the ALK-positive NSCLC patient with poor PS who fails to take oral medications.

Key Words: Lung adenocarcinoma, EML4-ALK fusion gene, mechanical ventilation, nasogastric tube, alectinib
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Introduction
The molecular profile of the tumor currently determines the therapeutic strategy for advanced lung cancer. In 2007, the echinoderm microtubule-associated protein like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion gene was identified as a novel driver oncogene, leading to a potential therapeutic target for ALK-positive NSCLC.

Crizotinib, the first available ALK inhibitor, provided a significant therapeutic response and a survival benefit to patients with ALK-positive NSCLC based on the phase III trial. Furthermore, recent phase I–II study reported that the second-generation ALK inhibitor, alectinib, is a highly selective, oral TKI, showing a high response rate (93.5%) and good progression-free survival (27.7 months) for such patients.

However, in the context of limited data of alectinib compared with that of crizotinib, there is no evidence for its use in patients with poor performance status (PS) who fail to take oral medications. To our knowledge, this is the first report that an ALK-positive NSCLC patient who underwent mechanical ventilation due to severe respiratory failure was successfully treated with alectinib administered through a nasogastric tube.

Case Presentation
A 38-year-old man with no smoking history was admitted to our hospital because of progressive dyspnea and lumbago. Chest X-ray and computed tomography (CT) scans showed a massive tumor lesion in the left upper lung lobe, multiple small nodules and thickened interlobular septa in both lungs, and bilateral pleural effusions (Fig. 1A, B). Bronchoscopy established a pathological diagnosis of adenocarcinoma with a component of signet ring cells. Along with results of a positron emission tomography (PET) - CT scan and a brain magnetic resonance imaging (MRI) scan, the patient was finally diagnosed as having stage IV lung adenocarcinoma (cT4N3M1b; PUL, PLE, OTH, BRA, OSS, HEP, LYM) (Fig. 1C).

Although chemotherapy with carboplatin and albumin-combined paclitaxel yielded temporary tumor regression, progressive liver metastases led to discontinuation of the first-line chemotherapy after the first course. In turn, crizotinib (300 mg daily) was administered...
because of the positive results of EML4-ALK fusion protein and gene from immunohistochemical analysis, fluorescent in situ hybridization examination, and next-generation sequencing (NGS) data for biopsy specimens. After 5 days of crizotinib administration, chest X-ray and CT showed air space consolidations and diffuse ground glass opacities (GGOs) in the both lungs and bilateral pleural effusions (Fig. 2). The patient developed respiratory failure with worse PS (ECOG PS 4), and required mechanical ventilation.

Clinical and laboratory data, sputum culture results, and echocardiographic findings negated the possibilities of infection and congestive heart failure. Along with tumor progression, crizotinib-induced pneumonitis was suspected, whereas his poor PS and severe respiratory insufficiency precluded a bronchoscopic approach. Therefore, crizotinib was discontinued and methylprednisolone (mPSL) pulse therapy (1000 mg daily for 3 days), followed by 1 mg/kg daily of prednisolone (PSL) was initiated. After repetitive informed consents were obtained because the patient and his family hoped for a further antitumor therapy other than palliative care, alectinib (600 mg daily) administration through a nasogastric tube commenced at the same day of the initiation of mPSL pulse therapy and mechanical ventilation. Since the patient failed to take oral medication, powders in the alectinib capsule suspended in water were administered through a nasogastric tube. After 8 days of these treatments, tumor volume and GGOs were substantially reduced, and his respiratory status improved, permitting ventilator weaning. PSL was discontinued after 49 days, and 11-day alectinib administration through a nasogastric tube was changed to oral administration. PS was improved to 0 and the patient was discharged from our

Fig. 1 Chest X-ray (A) and positron emission tomography (PET) - computed tomography (CT) (B) scans at admission demonstrate the primary tumor lesion in the left upper lung lobe and metastases to multiple organs.
Efficacy of alectinib administration through a nasogastric tube 22 days after alectinib treatment was started. Chest X-ray and CT showed markedly decreased bilateral pleural effusions, disappearance of GGOs, and substantial tumor regression in both lungs (Fig. 3A, B). FDG-PET demonstrated marked regression of primary and multiple metastatic tumor lesions (Fig. 3C). The patient continues to be treated with alectinib without critical adverse events.

Discussion

We herein describe the case of an ALK-positive NSCLC patient with severe respiratory failure requiring mechanical ventilation to whom alectinib was successfully administered through a nasogastric tube after crizotinib treatment. There has been little clinical benefit of chemotherapy in NSCLC patients with poor PS, who is often withheld from cytotoxic chemotherapy. However, the previous phase II trial showed that gefitinib, one of the EGFR-TKIs, was safely and effectively used for EGFR-mutated NSCLC patients with poor PS. The indication for molecular targeted therapy for NSCLC patients harboring corresponding target genes therefore needs to be determined separately from that for cytotoxic chemotherapy for non-selected population. In the context of only limited case reports concerning treatment outcomes for ALK-positive patients with poor PS including the recent report, the present case showed that unusual administration of alectinib safely induced marked tumor shrinkage and improved PS in such patients. This report may warrant a prospective clinical trial to confirm the safety and efficacy of alectinib in ALK-positive patients with poor PS.

In the present case, worsened PS and mechanical ventilation settings resulting from acute respiratory failure needed unusual administration of alectinib. The previous case reports showed that patients with ALK-positive NSCLC were successfully treated with crizotinib through a nasogastric tube, but not alectinib. Water-insoluble active ingredients in the alectinib capsule are known to be stable at room temperature and acidic pH. The formulation stability of alectinib may underlie the safety and effectiveness of alectinib administration through a nasogastric tube, although its pharmacokinetics remains unclear.

On the other hand, no definitive diagnosis was established for severe respiratory failure that made further examination difficult and required a prompt response. Crizotinib-induced pneumonitis was considered to be one of possible etiologies of respiratory insufficiency based on the previous reports, some of which showed successful retreatment with an ALK inhibitor after the

Fig. 2 Chest X-ray (A) and chest CT (B, C) scans after 5 days of crizotinib administration demonstrate diffuse ground glass opacities with thickened interlobular septa in the entire right lung, massive atelectasis of the left lung, and bilateral pleural effusions.
development of pneumonitis\textsuperscript{10,13}. Particularly, Chino et al. reported an ALK-positive patient who had undergone crizotinib-induced pneumonitis was successfully treated with alectinib thereafter\textsuperscript{13}. We concurrently used corticosteroids and alectinib for the possibilities of crizotinib-induced pneumonitis and tumor progression, respectively. Although alectinib administration is rechallenge of an ALK inhibitor, alectinib, a highly selective ALK inhibitor, may have different toxicity profiles and therapeutic benefits from crizotinib\textsuperscript{14}.

In conclusion, the present report shows significant beneficial effects of alectinib administration through a nasogastric tube on a mechanically ventilated patient. Alectinib may be a therapeutic option for ALK-positive NSCLC patients with poor PS who had a history of preceding crizotinib treatment and failed to take oral medications.

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Conflict of interest
Nobuyuki Koyama has received honoraria and/or lectures from Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., and Taiho Pharmaceutical Co., Ltd., and payment for the development of educational presentations from Pfizer Japan Inc.
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