Successful Treatment with Crizotinib in Mechanically Ventilated Patients with ALK Positive Non–Small-Cell Lung Cancer

Hee Kyung Ahn, MD, Kyeongman Jeon, MD, PhD,† Hongseok Yoo, MD,† Boram Han, MD,* Su Jin Lee, MD,* Hyeyon Park, MD,‡ Min Ji Lee, MD,‡ Sang Yun Ha, MD,§ Joung Ho Han, MD, PhD,§ Jong-Mu Sun, MD, PhD,* Jin Seok Ahn, MD, PhD,* Myung-Ju Ahn, MD, PhD,* and Keunchil Park, MD, PhD**

Lung cancer is the most common solid tumor in critically ill cancer patients admitted to intensive care units and is associated with a poor prognosis. Crizotinib is an anaplastic lymphoma kinase (ALK) inhibitor, which is active for advanced non–small cell lung cancer (NSCLC) patients harboring ALK rearrangements. We report three cases of NSCLC patients who required mechanical ventilation for respiratory failure and were successfully weaned from mechanical ventilation after treatment with ALK inhibitors. These responses were accompanied by minimal toxicities and an overt improvement in performance status. These results suggest that ALK inhibitors may be safe and effective in critically ill patients on mechanical ventilation for respiratory failure resulting from *EML4-ALK* translocated NSCLC progression.

Key Words: Non–small-cell lung carcinoma, Crizotinib, Mechanical ventilation, Weaning.

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Lung cancer is the most common solid tumor in critically ill cancer patients with cancer- or treatment-related complications admitted to intensive care units (ICUs).[1] The most common reason for ICU admission in these patients is respiratory failure, necessitating mechanical ventilation.[2] Despite recent improvements in the intensive care of critically ill cancer patients, the outcome of patients with lung cancer admitted to the ICU is poor, especially in those requiring mechanical ventilation as a result of respiratory failure.[1]

Divisions of *Hematology-Oncology and †Pulmonology and Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and Departments of ‡Medicine and §Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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The first two authors contributed equally to this work.

Address for correspondence: Keunchil Park, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135–710, Korea. E-mail: kpark@skku.edu

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Crizotinib is an orally active, small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), and it has efficacy for non–small-cell lung cancer (NSCLC) with echinoderm microtubule-associated protein-like4 - anaplastic lymphoma kinase (EML4-ALK) rearrangements. Treatment with crizotinib resulted in a rapid and dramatic response with few instances of major toxicity,[3] enabling its safe administration as a salvage treatment for patients with poor performance status. Here, we report three Korean ALK-positive NSCLC patients with respiratory failure caused by lung cancer progression, who were successfully treated with crizotinib during mechanical ventilatory care.

CASE 1

A 40-year-old nonsmoker woman had been diagnosed with adenocarcinoma of the lung with multiple metastases in both the lung and the liver in April 2010. Analysis of the *EGFR* and *KRAS* genes did not indicate any mutation. She did not respond to combined chemotherapy involving pemetrexed and cisplatin, and she was referred to our hospital in July 2010 and erlotinib treatment was initiated for her rapidly progressing disease.

After 1 week, she was hospitalized because of respiratory failure and progression of bilateral infiltrates on chest radiographs. Empirical antibiotics for suspected pneumonia were initiated, but oxygenation continued to worsen. She was subsequently transferred to the ICU and was intubated 2 days later, but she required both a high fraction of inspired oxygen (FiO_2) and elevated positive end-expiratory pressure. However, her refractory hypoxemia and hypercapnia persisted, and she failed to respond to conventional mechanical ventilation using inhaled nitric oxide even after her pneumonia symptoms improved. In the absence of evidence of another cause, the progression of bilateral infiltrates on chest radiography led us to conclude that the advancing lung cancer was responsible for the hypoxemia and hypercapnia. Immunohistochemical (IHC) staining for ALK protein was positive, but fluorescence in situ hybridization analysis could not be performed because of insufficient amounts of tumor tissue. Crizotinib was initiated 21 days after intubation for mechanical ventilation (August 24, 2010) that was administered in powdered form through a feeding tube. Two days after the initiation of crizotinib, ventilation had improved enough to correct hypercapnia. Ten

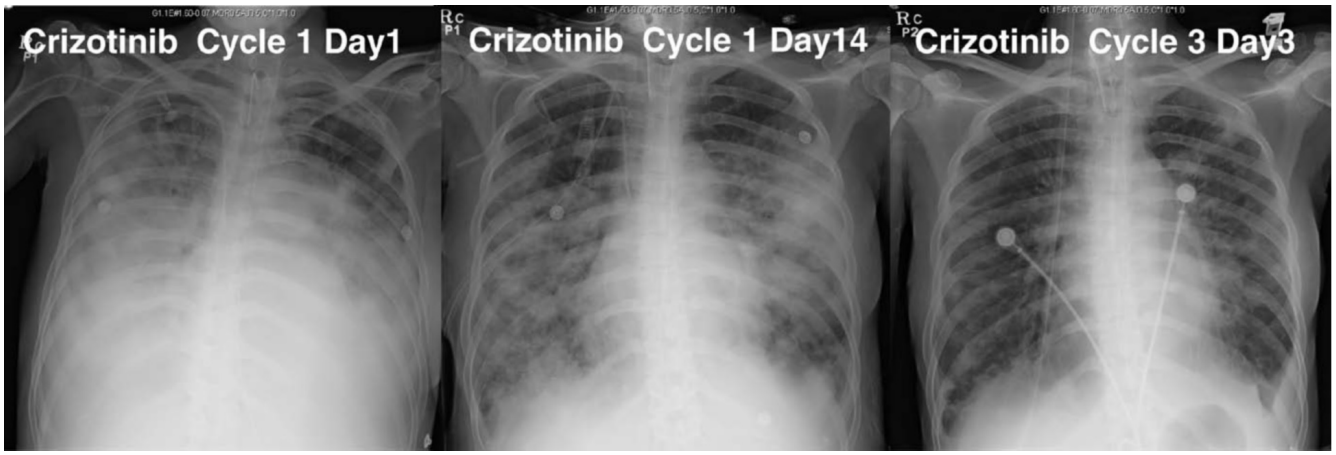

FIGURE 1. Chest radiographs before and after crizotinib treatment in case 1.

days after treatment initiation, oxygenation had improved enough to taper out inhaled nitric oxide doses and to reduce FiO_2. The progressive bilateral infiltrates seemed to undergo amelioration as well (Fig. 1). During the second treatment cycle, that is, on the 25th day of treatment, weaning from mechanical ventilation was attempted for the first time. She was eventually weaned from mechanical ventilation entirely on the 42nd day and was weaned from tracheostomy on the 57th day of treatment. She recovered fully and was discharged 60 days after the initiation of crizotinib.

Her response persisted for 84 days until the fifth cycle of treatment, when multiple brain metastases were diagnosed. Eventually, she died because of rapidly progressing brain metastases.

CASE 2

A 44-year-old nonsmoking woman was diagnosed with adenocarcinoma of the lung with intraabdominal lymph node metastases in May 2010. *EGFR* and *KRAS* gene analysis revealed wild-type genes. After failure to respond to four lines of palliative chemotherapy (pemetrexed with cisplatin, erlotinib, gemcitabine, and vinorelbine with cisplatin), she was admitted to our hospital because of rapidly progressive dyspnea with extensive consolidation in both the lungs. On July 10, 2011, intubation and mechanical ventilation were initiated for respiratory failure. Infectious bronchoalveolar lavage did not reveal any microbial growth, and therefore, lung cancer progression was suspected as the main cause of respiratory failure. A transbronchial lung biopsy was performed, and IHC staining results were positive for ALK protein in the cytoplasm (Fig. 2). Crizotinib was initiated on July 21, 2011. At that time, her arterial oxygen saturation (SaO_2) was approximately 87% to 90%, with an oxygen supply of FiO_2 1.0. After 1 week, FiO2 was reduced to 0.5. On the 20th day of treatment (Fig. 3), the patient was completely weaned from the mechanical ventilator and was weaned from tracheostomy on the 36th day of treatment. A chest computed tomography scan after one cycle (August 10, 2011) revealed that the multiple metastatic lesions in the lung had greatly reduced. Therefore, she was discharged from the hospital on the 38th day of treatment, and the response was maintained until April 4, 2012, which indicates a progression-free survival of 8 months.

CASE 3

A 49-year-old nonsmoking woman was diagnosed with stage IV adenocarcinoma of the lung in October 2010. Gene sequencing revealed that both the *EGFR* and *KRAS* genes were of the wild type. One year since her diagnosis, all three lines of palliative chemotherapy (gemcitabine with cisplatin, pemetrexed with afatinib, and gefitinib) and palliative radiotherapy for cervical and mediastinal metastatic lymphadenopathy had failed. The IHC staining indicated positive results for ALK protein; however, the EML4-ALK

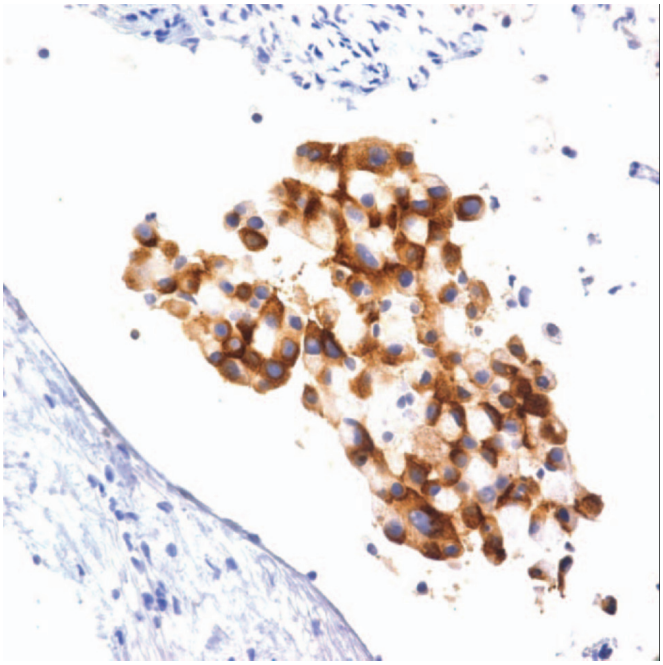

FIGURE 2. Positive immunohistochemical staining for anaplastic lymphoma kinasein the cytoplasm of lung cancer cells (NCL-ALK [clone 5A4], Novocastra, United Kingdom).

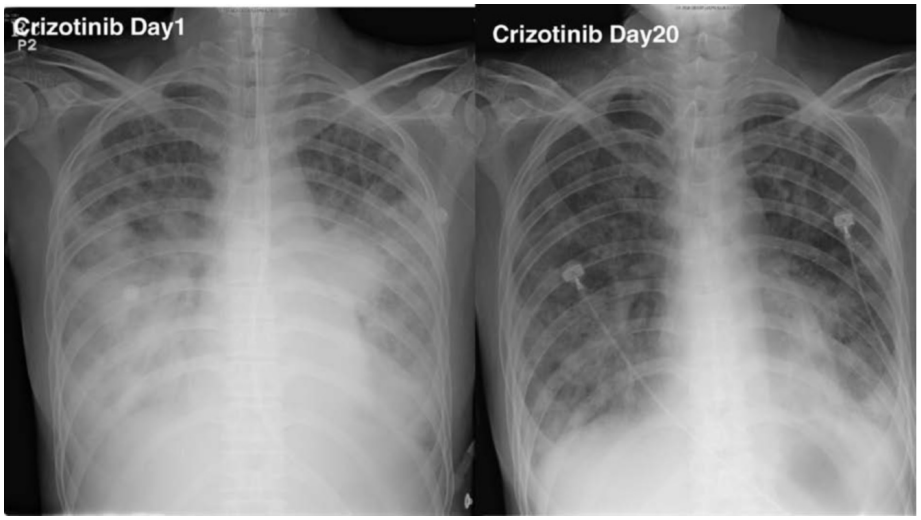

FIGURE 3. Chest radiographs before and after crizotinib treatment in case 2.

fluorescence in situ hybridization analysis did not give a clear result. On November 12, 2011, intubation was performed, and mechanical ventilation was initiated for upper airway obstruction. On the next day, bilateral vocal cord paresis with paradoxical vocal cord movement caused by mediastinal lymph nodes metastasis was noted, and tracheostomy was performed on the fifth day of initial intubation. An attempt to wean through a T-piece failed because of carbon dioxide retention. Crizotinib was initiated on November 21, 2011 through a feeding tube. On the 10th day of treatment, the patient was transferred to a general ward and was placed a mobile ventilator, and on the 17th day of treatment, complete weaning from the ventilator was achieved. On the 31st day of treatment (December 21, 2011), a chest computed tomography scan revealed a partial response to multiple cervical, axillary, and mediastinal metastatic lymphadenopathy (Fig. 4). In March 2012 (cycle 5, day 1), although the removal of the tracheostomy tube still could not be attempted because of persistent saliva aspiration and a glottis gap, no evidence of lung cancer progression was observed. Therefore, she was discharged from the hospital. Further information on this patient's progress is unavailable because she was lost to follow-up.

DISCUSSION

Although the main reasons for admission to the ICU are treatment related and other complications associated with cancer, some patients are admitted to the ICU for chemotherapy because of cancer-related, life-threatening conditions.[4–6] However, the decision to initiate chemotherapy in critically ill cancer patients is extremely complex because the expected outcomes or prognostic factors are unclear. Only a few studies describing the benefits of administrating chemotherapy to critically ill cancer patients[4–6] have been reported. Moreover, respiratory failure requiring mechanical ventilation was significantly associated with a poor outcome.[4–6] However, most patients included in these studies had hematologic malignancies. Therefore, a decision to start chemotherapy for advanced solid cancer in the ICU generally carries reluctance because of two reasons. First, solid malignancies, including lung cancer, are usually less sensitive to chemotherapeutic drugs than

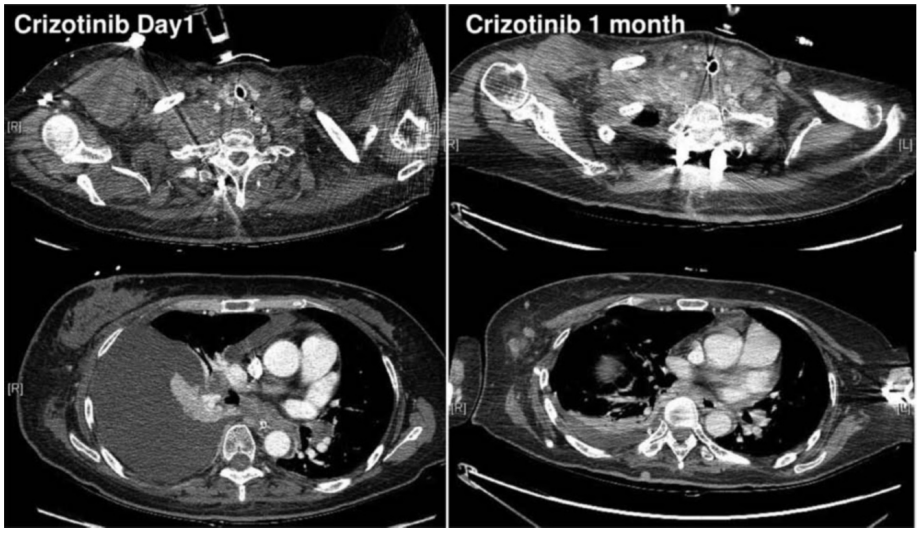

FIGURE 4. Response to crizotinib in case 3. A chest wall metastatic mass and malignant pleural effusion on the right side reduced after 1 month of treatment.

TABLE 1. Outcome of the ICU-Admitted Three Non–Small-Cell Lung Cancer Patients

	Age	Histology	ALK Over expression by IHC	EML4-ALK Translocation	EGFR/KRAS mutation	Time from the First Diagnosis of NSCLC to ICU Admission (mo)	Number of Previous Chemotherapies	Timing of Crizotinib Initiation from MV Initiation (days)	Weaning from MV/T-tube (days)	Discharge from Hospital (days)	ECOG PS at Discharge from Hospital	PFS (mo)
1	F/40	Adenoca	Positive	Failed FISH test because of tissue insufficiency	WT/WT	4	2	21	42/57	60	2	3
2	F/44	Adenoca	Positive	Failed FISH test because of tissue insufficiency	WT/WT	13	4	12	20/36	38	2	8
3	F/49	Adenoca	Positive	Failed FISH test because of tissue insufficiency	WT/WT	13	3	10	17/-	92	3	3

NSCLC, non–small-cell lung cancer; ICU, intensive care unit; MV, mechanical ventilation; T-tube, tracheostomy tube; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; adenoca, adenocarcinoma; FISH, fluorescence in situ hybridization; WT, wild type.

hematologic malignancies were. Second, poor performance status of the Eastern Cooperative Oncology Groups 3 and 4 is usually considered a contraindication of cytotoxic chemotherapy. Cytotoxic chemotherapeutic agents invariably have toxicities, including myelosuppression, resulting in an increased risk of infection, which in turn is thought to be associated with poor outcome, particularly in patients with poor performance status.

Recently various types of molecularly targeted agents have been developed. In many cases the response to these agents can be predicted through genetic analysis, and the profiles of major adverse events are significantly different from those of cytotoxic chemotherapeutic agents, among which myelosuppression is less common. Therefore, these molecularly targeted agents can be considered for use in cancer patients with poor performance status, even when patients are receiving critical care because of cancer progression-induced organ failure.

In this report, three critically ill patients with metastatic NSCLC who required mechanical ventilation for respiratory failure in the ICU were treated with crizotinib and were successfully weaned from mechanical ventilation. This report gives an insight into successful chemotherapy with a molecularly targeted agent in the ICU. Although we have reported only three cases, this study is noteworthy because mechanical ventilation is strongly associated with increased hospital mortality in lung cancer cases,[7] and all the patients in the present case study experienced respiratory failure caused by heavily pretreated lung cancer progression. Thus, the present cases can be a reference in reappraisal and decision making for lung cancer patients requiring ICU care because of cancer progression.

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REFERENCES

1. Soubani AO, Ruckdeschel JC. The outcome of medical intensive care for lung cancer patients: the case for optimism. *Journal of thoracic oncology* 2011;6:633–638.
2. Adam AK, Soubani AO, Outcome and prognostic factors of lung cancer patients admitted to the medical intensive care unit. *The European respiratory journal* 2008;31:47–53.
3. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *The New England journal of medicine* 2010;363:1693–1703.
4. Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. *Intensive Care Med* 2006;32:93–99.
5. Darmon M, Thiery G, Ciroldi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Critical care medicine* 2005;33:2488–2493.
6. Song JU, Suh GY, Chung MP, et al. Risk factors to predict outcome in critically ill cancer patients receiving chemotherapy in the intensive care unit. *Support Care Cancer* 2011;19:491–495.
7. Slatore CG, Cecere LM, Letourneau JL, et al. Intensive care unit outcomes among patients with lung cancer in the surveillance, epidemiology, and end results-medicare registry. *Journal of clinical oncology* 2012;30:1686–1691.

