Published in final edited form as:

Clin Lung Cancer. 2016 November ; 17(6): 523–527. doi:10.1016/j.clcc.2016.04.004.

Treatment of Lung Cancer Patients With Actionable Mutations in the Intensive Care Unit

Kathleen Kerrigan¹, Abigail Shoben², and Gregory Otterson³

¹Department of Internal Medicine, The Ohio State University, Columbus, OH

²Department of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH

³Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, OH

Abstract

Lung cancer patients with acute respiratory failure in the intensive care unit have a poor prognosis. Molecular targeted therapy, in concert with best critical care practices, can result in extubation and improved performance status and overall survival in these patients. Empiric molecular targeted therapy should be considered in this setting for those patients with a high likelihood of having an activating mutation.

Background—Patients with advanced-stage non–small-cell lung cancer (NSCLC) have high mortality rates in the intensive care unit (ICU). Although the benefit of chemotherapy for hematologic malignancies in the ICU has previously been explored, few data exist regarding the use of targeted therapy for NSCLC in such settings. The primary objective of the present study was to report our experience with the use of targeted therapy in patients with NSCLC in the ICU.

Materials and Methods—We performed a single-institution, retrospective medical record review. The eligibility criteria included patients with NSCLC with targetable mutations who had received tyrosine kinase inhibitors (TKIs) in the ICU. Cases were identified by queries of our institution's information warehouse database and pharmacy dispensary records from 2010 to 2015.

Results—All 9 patients who had received TKIs in the ICU had acute respiratory failure. Three patients were successfully extubated after initiating TKI therapy, although 1 required later tracheostomy. TKI therapy stabilized another patient's refractory disseminated intravascular coagulation. The remaining 5 patients showed no measurable clinical improvement and were transitioned to comfort care. The overall ICU mortality rate was 56%.

Conclusion—Patients with metastatic NSCLC requiring mechanical ventilation have high mortality rates. Cytotoxic chemotherapy is generally contraindicated for poor performance status patients. However, targeted TKI therapy should be considered, given its proven efficacy and few systemic side effects. We recommend the empiric use of targeted therapy for NSCLC patients with

Address for correspondence: Kathleen Kerrigan, DO, Department of Internal Medicine, The Ohio State University, 395 West 12th Avenue, Third Floor, Columbus, OH 43210, kathleen.kerrigan@osumc.edu.

Disclosure: There are no conflicts of interest or sources of support to disclose for Drs. Kerrigan and Shoben. Dr. Otterson is a consultant for Boehringer Ingelheim and Genentech. Dr. Otterson has received grants from Pfizer, Genentech, BMS, Clovis, Novartis, Daiichi Sankyo, and Boehringer Ingelheim.

suspected and/or known actionable mutations presenting with multifactorial respiratory failure to the ICU, with aggressive determination of the mutation status if not known.

Keywords

Acute respiratory failure; Intensive care unit; Molecular targeted therapy; Non; small-cell lung cancer; Tyrosine kinase inhibitors

Introduction

Recent advances in cancer genomics have changed our understanding of the multistep process of tumorigenesis that leads to the development of non-small-cell lung cancer (NSCLC). Furthermore, the identification of reproducible genetic alterations in growth signaling kinases that can be targeted pharmacologically has dramatically altered the treatment landscape of NSCLC. The epidermal growth factor receptor (EGFR) is a tyrosine kinase that can have altered regulation in NSCLC.¹ Additionally, chromosomal rearrangements in anaplastic lymphoma kinase (ALK) and the *c-ros* oncogene 1 receptor tyrosine kinase (ROS1) have been identified as potential targets for molecular therapy in NSCLC.^{2,3} The Food and Drug Administration (FDA)-approved agents erlotinib, gefitinib, afatinib, crizotinib, and ceritinib act as tyrosine kinase inhibitors (TKIs), and those patients with mutations and/or rearrangements in the *EGFR*, *ALK*, or *ROS1* genes have been shown to be sensitive to these agents.³⁻⁵ In patients with the targeted alteration, the response rates and progression-free survival (PFS) have been shown to be superior to cytotoxic chemotherapy.⁶ Furthermore, the time to response has typically been quite rapid.

Advanced-stage lung cancer patients have high mortality in the intensive care unit (ICU) setting.⁷⁻¹¹ Acute respiratory failure, advanced-stage cancer, and poor performance status (PS) have all been associated with significant mortality in lung cancer patients admitted to the ICU.⁷⁻¹¹ Although data from different studies have varied, the overall reported mortality in the ICU setting has been in the range of 40% to 55%,^{7,8} and in those patients who develop acute respiratory failure requiring mechanical ventilation, the mortality increases substantially to 70%.⁷⁻¹⁰

In a review of the published data, only a few case reports have detailed the successful use of empiric molecular targeted therapy in advanced-stage, mechanically ventilated NSCLC patients in the ICU.^{12,13} Although the benefit of chemotherapy for hematologic malignancies in the ICU has previously been explored,¹⁴ few data are available regarding the use of molecular therapy in NSCLC in this setting. The primary objective of the present study was to report our institution's experience in the management of acute respiratory failure in those NSCLC patients with actionable mutations who received TKI therapy in the ICU.

Materials and Methods

The institutional review board at our academic medical center approved the study protocol, and the study was performed in accordance with the Declaration of Helsinki. Our study was designed as a single-institution, retrospective medical record review. The main eligibility

criteria were advanced NSCLC with targetable *EGFR*, *ALK*, *ROS1*, or *MET* mutations and the use of molecular targeted therapy in the ICU. We identified the appropriate patients by queries of both our institution's information warehouse database and the pharmacy dispensary records for 2010 to 2015. Data were included only if both the pharmacy had dispensed the medication and medication reconciliation documentation was available showing that the patient had received the therapy during their ICU stay. We focused on the targeted agents erlotinib (approved by the FDA throughout the study period) and crizotinib (approved by the FDA in 2013), which the patients received in either oral or crushed formulation by way of an orogastric tube, depending on the need for intubation. Mutation analysis was performed in-house using Clinical Laboratory Improvement Amendments-certified tests. Fluorescence in situ hybridization was performed using the FDA-approved probe for *ALK* analysis, and polymerase chain reaction-based fragment analysis was used for *EGFR* mutation analysis until 2012. In 2012, our molecular analysis technique was changed to a targeted next-generation sequencing platform. We included the diagnoses requiring admission to the ICU identified using the International Classification Diseases (9th revision) codes, the need for mechanical ventilation, vasopressor support, continuous renal replacement therapy, and antibiotics in our analysis as a method to detect the severity of illness in our study population (Tables 1 and 2). In addition to the patients' tumor histologic features, we collected information regarding age, smoking status, previous chemotherapy regimens, comorbid conditions, and the cause of death from the medical record review (Tables 1 and 2). The primary objective of the present study was to examine overall survival (OS) and ICU survival in patients with a history of advanced NSCLC with actionable mutations treated with molecular targeted therapy in the ICU.

Results

From 2010 to 2015, we identified 48 patients admitted to our academic medical center who had received targeted TKI therapy during their inpatient stay for actionable mutant NSCLC. Of these 48 patients, 9 had been admitted to the ICU for acute respiratory failure requiring either invasive or noninvasive mechanical ventilation (Tables 1 and 2). Of the 9 patients, 4 had received empiric TKIs for an unknown mutational status at ICU admission (Table 1). In this setting, the clinical characteristics suggested a high likelihood of *EGFR* or *ALK* alterations (eg, nonsmoker, adenocarcinoma, younger age), and empiric use of erlotinib (because *EGFR* mutations were most likely) was determined to be a potentially lifesaving intervention. Of the remaining 5 patients, 2 had a known mutational status and started TKI therapy for the first time in the ICU, 2 continued home TKI therapy, and the final patient received a second-generation ALK inhibitor after previous exposure to crizotinib (Table 2). Many of the patients had comorbid septic shock, venous thromboembolism, acute renal failure, and coagulopathy, which contributed to their illness severity (Tables 1 and 2). In our study, 3 patients were successfully extubated after starting molecular therapy in the ICU, although 1 later required reintubation and tracheostomy. Patient 1 experienced 16 months of PFS after initiation of crizotinib for a *ROS1* translocated (and *BRAF* mutant) lung adenocarcinoma, and patient 9 had 8 months of PFS after initiation of erlotinib for an *EGFR*-mutant lung adenocarcinoma before disease progression (Figure 1). Initiation of ceritinib stabilized patient 3's refractory disseminated intravascular coagulation, and the

patient was successfully discharged without further blood product requirements. Patient 2 was initially extubated but later required reintubation and eventual tracheostomy with discharge to a long-term acute care facility to continue TKI therapy. Patient 5 received empiric erlotinib in the setting of newly diagnosed, metastatic lung adenocarcinoma given the high likelihood of the presence of an activating mutation (never smoker, young female). However, this was before FDA approval of crizotinib for *ALK*-translocated adenocarcinoma. When the mutation analysis demonstrated *ALK* gene rearrangement, erlotinib was discontinued, and the patient elected comfort care. The remaining 4 patients had refractory septic shock, worsening respiratory failure, or the goal of pursuing comfort measures only, resulting in transition to hospice care without measureable clinical improvement with the addition of targeted therapy. No significant treatment toxicities were identified during the ICU admission. The overall ICU mortality rate was 56%, similar to the mortality rates reported in other studies.

Discussion

Metastatic NSCLC patients have a poor prognosis in the ICU setting, with mortality rates approaching 70% in those requiring mechanical ventilation in selected studies.⁶⁻¹⁰ Many patients are diagnosed with respiratory failure secondary to newly diagnosed metastatic disease on admission to the ICU and are treatment naive. Little information is available from published studies about patient selection for, and the use of, targeted TKIs in the critically ill ICU patient. One study suggested that the use of gefitinib, an EGFR TKI, for poor PS NSCLC patients can improve OS and PFS and can even upgrade the PS compared with the best supportive care in this patient population.¹⁵

Although the use of cytotoxic chemotherapy is generally contraindicated for patients with solid tumors and a poor PS who are in the ICU, molecular targeted therapy should be considered as a treatment modality for multifactorial respiratory failure, given its relatively few serious, systemic side effects and proved efficacy. Our data, and others, have shown that the use of targeted TKIs combined with antibiotics and best critical care practice can result in extubation and improved OS in appropriately selected patients.^{12,13} We have also shown that using second-generation TKIs in the ICU can prove useful even in those with disease refractory to first-generation therapy. Therefore, we recommend the empiric use of molecular targeted therapy for NSCLC patients with suspected and/or known actionable mutations presenting to the ICU with multi-factorial respiratory failure, with aggressive determination of mutation status if not previously known. It is difficult to determine which patients will improve; however, we suspect those with strong activating mutations and those with fewer medical comorbidities will be most likely to benefit from the addition of empiric targeted therapy. The rapid diagnosis of cancer and the specific molecular abnormalities in patients presenting to the ICU are critical to the successful application of targeted therapies in this setting.

Conclusion

Given the possibility of significant improvement in PS, PFS, and OS with the use of TKIs compared to best supportive care, we suggest at least a time-limited trial of targeted therapy

in this setting. Thus, future studies should continue to evaluate the outcomes of critically ill NSCLC patients treated with molecular therapy in the ICU to potentially develop patient selection criteria and a more standardized approach to the use of these agents in this setting.

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Clinical Practice Points

- Cases of NSCLC with activating mutations are sensitive to molecular targeted therapy.
- Molecular targeted therapy has been previously used in poor PS patients with known mutation status, although infrequently, and has resulted in ICU discharge and extubation.
- The empiric use of molecular targeted therapy in the setting of unknown mutation status can lead to extubation and improvement in OS and PS, as demonstrated by our data.
- Multifactorial respiratory failure in patients with NSCLC in the ICU should be addressed using a multidisciplinary approach, with consideration of the use of molecular targeted therapy.
- Further evaluation of the use of molecular targeted therapy in patients with NSCLC and a poor PS in the ICU could lead to the development of patient selection criteria and/or guidelines to help direct the use of these agents in critically ill patients.

Figure 1. Swimmers Plot Detailing Time From Cancer Diagnosis to Intensive Care Unit (ICU) Admission and Start of Tyrosine Kinase Inhibitor (TKI)

Table 2
Demographic and ICU Data for Patients With Known Mutation Status Receiving Targeted Therapy

Variable	Patient 1	Patient 3	Patient 6	Patient 7	Patient 8
Mutation status	ROS1 ⁺ , BRAF ⁺	ALK ⁺	EGFR exon 19 ⁺ , Exon 20 resistance mutation-positive	Borderline ALK ⁺ (12%), BRAF ⁺ , PDI ⁺	MET ⁺ , MYC ⁺
Histologic type	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Stage	IV	IV	IV	IV	IV
Smoking status	Never smoker	Never smoker	Light smoker	Former heavy smoker	Former heavy smoker
Previous chemotherapy	Carboplatin, pemetrexed Clinical trial: pazopanib, GSK2118436	Crizotinib Phase I/II clinical trial, next-generation ALK inhibitor, X-396	Carboplatin, paclitaxel, bevacizumab Erlotinib, gemcitabine, cetuximab pemetrexed	None	Carboplatin, paclitaxel, bevacizumab Cisplatin, pemetrexed Gemcitabine
Admission diagnosis to ICU	Acute respiratory failure ARDS Submassive PE Septic shock	DIC, refractory Acute respiratory failure	Acute respiratory failure HCAP Malignant pleural effusions	Acute respiratory failure Septic shock PE Pulmonary aspergillosis	Acute respiratory failure Septic shock HCAP
Molecular therapy in ICU	Crizotinib 250 mg BID by OGT	Ceritinib 750 mg PO	Erlotinib 150 mg by OGT	Crizotinib 250 mg BID by OGT	Crizotinib 250 mg BID PO
Mechanical ventilation	Yes	Yes, only NIPPV	Yes	Yes	Yes
Vasopressor support	Yes	No	No	Yes	Yes
CRRT	No	No	No	Yes	No
Antimicrobial therapy	Yes, 7-d therapy for HCAP	Yes, 7-d therapy for UTI	Yes, 7-d therapy for HCAP	Yes, therapy for HCAP and aspergillosis	Yes, 7-d therapy for HCAP
Charlson comorbid index	6	6	8	8	7
Clinical ICU outcome	Extubated, discharged home	Improvement in refractory DIC, discharge to rehabilitation facility	Transition to DNRCC after tracheostomy	Expired secondary to refractory shock	Transition to DNRCC

Abbreviations: ALK = anaplastic lymphoma kinase; ARDS = acute respiratory distress syndrome; BID = twice daily; CRRT = continuous renal replacement therapy; DIC = disseminated intravascular coagulation; DNRCC = do not resuscitate comfort care; EGFR = epidermal growth factor receptor; HCAP = healthcare-associated pneumonia; NIPPV = noninvasive positive pressure ventilation; OGT = orogastric tube; PE = pulmonary embolism; UTI = urinary tract infection.

Table 1
Demographic and ICU Data in Patients Receiving Empiric Targeted Therapy

Variable	Patient 2	Patient 4	Patient 5	Patient 9
Mutation status	EGFR exon 21 ⁺	Unknown ^a	ALK ⁺	EGFR exon 19 ⁺
Histologic type	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Stage	IV	IV	IV	IV
Smoking status	Never smoker	Never smoker	Never smoker	Never smoker
Previous chemotherapy	None	None	None	None
Admission diagnosis to ICU	Acute respiratory failure Septic shock Malignant pleural, pericardial effusions	Acute respiratory failure Pulmonary aspergillosis	Acute respiratory failure Cardiac tamponade Malignant pleural effusions	Acute respiratory failure HCAP
Molecular therapy in ICU	Erlotinib 150 mg by OGT	Erlotinib 150 mg by OGT	Erlotinib 150 mg PO	Erlotinib 150 mg by OGT
Mechanical ventilation	Yes	Yes, only NIPPV	Yes, only NIPPV	Yes
Vasopressor support	Yes	No	No	No
CRRT	No	No	No	No
Antimicrobial therapy	Yes, 7-d therapy for HCAP	Yes, antifungal therapy for aspergillosis	Yes, 7-d therapy for HCAP	Yes, 7-d therapy for HCAP
Charlson comorbid index	10	10	6	6
Clinical ICU outcome	Extubated; reintubated with tracheostomy	Transition to DNRCC	Transition to DNRCC	Extubated, discharged home

Abbreviations: ALK = anaplastic lymphoma kinase; BID = twice daily; CRRT = continuous renal replacement therapy; DNRCC = do not resuscitate comfort care; EGFR = epidermal growth factor receptor; HCAP = healthcare-associated pneumonia; NIPPV = noninvasive positive pressure ventilation; OGT = orogastric tube; PE = pulmonary embolism.

^a Mutation status unknown because no samples were available; patient 4 presented from an outside hospital, and pathology reports were not readily available and were not in the electronic medical records or our pre-electronic medical record information warehouse database.