Critical Care for Patients with Lung Cancer

To the Editor:

I read with interest the recently published concise review by Soubani and Ruckdeschel,[1] which described the main indications for critical care for patients with lung cancer and discusses recent data on their outcome and predictors from which patients with lung cancer are likely to benefit.

The outcome of patients with lung cancer admitted to the intensive care unit (ICU) has improved. Recently, Toffart et al.[2] described 103 consecutive nonsurgical patients with lung cancer admitted to three ICUs in France. In this study,[2] patients who had a poor performance status (PS) at baseline or who developed multiorgan failure early after ICU admission had significantly higher mortality rates with a survival of 37% after 90 days.

During the past 3 years, several studies[2–4] have reported the outcomes of critically ill patients with lung cancer admitted to ICU. These studies[2–4] included a total of 347 patients, and the ICU and in-hospital mortality rate for these patients were 32% and 47.3%, respectively. Two of these studies[2,3] reported, 144/208 (69.2%) patients with stages IIIB/IV and 130/208 (62.5%) patients with metastasis at ICU admission ($n = 63$)[2] or whether already known or evidenced within the first week of ICU stay ($n = 67$).[3] The factors associated with increased mortality in this group of critically ill patients with cancer are poor PS,[2,3] organ dysfunction,[2–4] and metastasis at admission to ICU.[2] Specifically, in this subgroup of critically ill patients with cancer, PS might be a simple tool for oncologists and intensivists as an aid for admitting patients with lung cancer to the ICU.[3] On the other hand, the course of organ dysfunction during the first 3 days of ICU stay could be useful for considering treatment limitation.[2] The patients in whom potential benefits from ICU admission are in doubt should receive a trial of full-code ICU management; this ICU trial has been of help for resolving doubts and conflicts surrounding ICU admission of patients with cancer.[5]

Critically ill patients with lung cancer admitted to the medical ICU have often posed a high-mortality rate but their outcome has been progressively improving and is approximating that of the general critically ill population[1]; however, it should be considered that early integration of palliative care with standard oncologic care in patients with metastatic non-small cell lung cancer led to significant improvements in quality of life and mood.[6]

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Do Complex Mutations of the Epidermal Growth Factor Receptor Gene Reflect Intratumoral Heterogeneity?

To the Editor:

In our clinical practice, two different epidermal growth factor receptor (*EGFR*) gene mutations are occasionally found in a single tumor sample. Such co-occurring *EGFR* mutations have been termed "complex mutations," and we have previously reported the incidence and efficacy of gefitinib for patients with complex mutations.[1] In our previous article, we discussed the cause of complex mutations and speculated on the existence of intratumoral heterogeneity for *EGFR* mutations. We recently encountered three cases that support our hypothesis and herein present these cases.

Case 1 was a 68-year-old man. He received a computed tomography-guided lung biopsy due to a suspicion of lung cancer. We performed a fine needle aspiration, followed by a core needle biopsy through a guide needle to obtain both cytological fluid and histological tissue (Figure 1). Although both cytology and histology revealed adenocarcinoma cells, we accidentally performed *EGFR* mutational analysis on both specimens. Interestingly, only a point mutation in exon 21 (L858R) was detected in the cytology, but complex mutations consisting of a point mutation in exon 18 (G719S) and L858R were detected in the histology. After a diagnosis of locally advanced disease, the patient underwent concurrent chemoradiation therapy. After the treatment, he has been observed and

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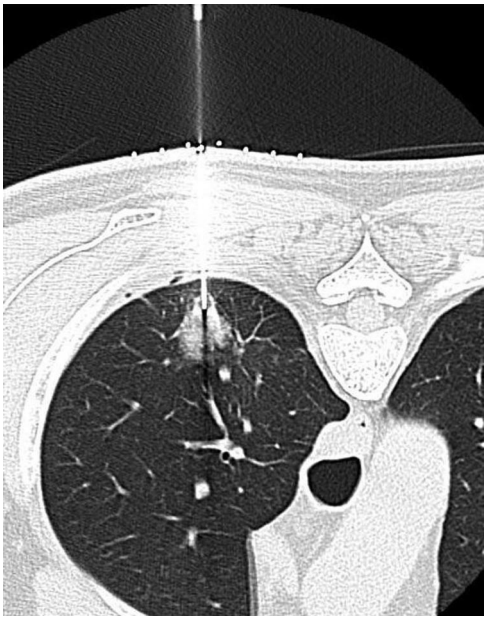

FIGURE 1. Computed tomography-guided lung biopsy performed on the tumor harboring complex mutations with G719S and L858R.

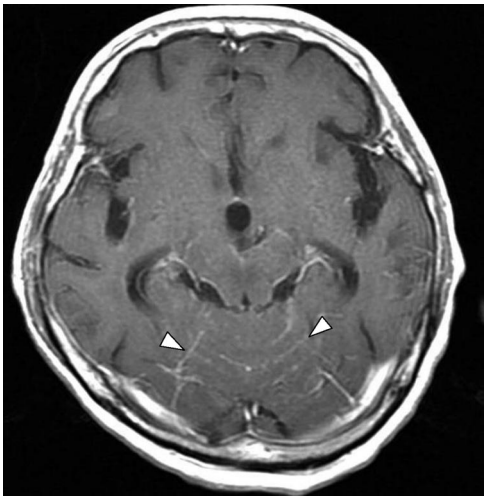

FIGURE 2. The magnetic resonance image shows findings of leptomeningeal metastases (arrow heads).

has not yet received EGFR-tyrosine kinase inhibitor (TKI) therapy.

Case 2 was a 66-year-old woman. She was diagnosed with lung adenocarcinoma and underwent surgery as the initial therapy. *EGFR* mutational analysis in the surgical tissue revealed complex mutations consisting of a deletional mutation in exon 19 (Del-19) and L858R. After recurrence, she underwent multiple chemotherapies including EGFR-TKIs. In the course of treatment, she complained of gait disturbance and neck stiffness. Brain magnetic resonance imaging showed leptomeningeal metastases (Figure 2), and a lumbar puncture was performed. Unexpectedly, Del-19 disappeared, and only L858R was detected by *EGFR* mutational analysis of malignant cells in the cerebral spinal fluid. Rechallenge treatment with erlotinib was administered, and the clinical benefit has continued for 4 months.

Case 3 was an 81-year-old man. He was initially diagnosed with lung adenocarcinoma with pleural disseminations. *EGFR* mutational analysis of the primary tumor showed complex mutations consisting of Del-19 and L858R. Considering the patient's age, gefitinib was chosen as the first-line treatment. Primary tumor and pleural disseminations markedly responded to gefitinib for approximately 20 months. However, the right pleural effusion has recently increased (Figure 3), and the cytology of pleural effusion revealed adenocarcinoma cells. Similarly, Del-19 disappeared, and both L858R and a point mutation in exon 20 (T790M) were detected by *EGFR* mutational analysis of the pleural effusion. Chest tube drainage has been carried out.

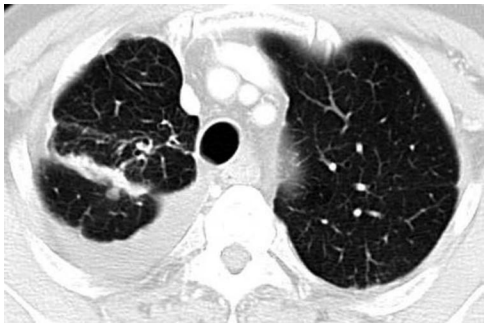

FIGURE 3. Right pleural effusion containing adenocarcinoma cells harboring complex mutations with Del-19 and L858R, and pleural disseminations are shown.

Case 1 implies the existence of heterogeneous *EGFR* mutations in a single tumor: cytological fluid cells harboring only L858R and histological tissue cells harboring both G719S and L858R simultaneously existed in a single tumor. The intratumoral heterogeneity of *EGFR* mutation has been previously reported; both *EGFR* mutated and wild-type malignant cells were confirmed in a single tumor tissue in the report.[2] In cases 2 and 3, although complex mutations consisting of Del-19 and L858R were detected at the initial *EGFR* mutational analysis, Del-19 has disappeared and L858R remained after EGFR-TKI treatments. Higher sensitivity to EGFR-TKIs in patients with Del-19 than L858R has been demonstrated in several reports.[3] If Del-19 and L858R cells had existed separately, Del-19 cells would have responded to EGFR-TKIs better than L858R cells, and L858R cells might have remained.

Our present cases exhibiting these complex mutations suggest the intratumoral heterogeneity of *EGFR* mutations. Considering intratumoral heterogeneity consisting of *EGFR*-sensitive-mutated cells and wild-type or *EGFR*-resistant-mutated cells, the detection of *EGFR* mutations using a highly sensitive polymerase chain reaction method from small biopsies may not always reflect whole tumor sensitivity to EGFR-TKIs.[4] However, our data were taken from only a few cases, and further research is needed. The clinical significance of intratumoral heterogeneity warrants future studies.

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Evaluation of *ALK* Gene Status in Primary Lung Adenocarcinoma and Matched Metastases

To the Editor:

On March 2010, because of a worsening in his breathing ability, a heavy smoking (>40 pack/yr) 54-year-old man performed a chest computed tomography, which showed a left-sided pleural effusion. A thoracoscopy showed multiple pleural nodules, which were biopsied. The diagnosis was pleural metastases from lung adenocarcinoma. The percentage of tumor cells in the pleural bioptical specimen was 60. The tumor did not harbor neither the epidermal growth factor receptor nor K-*ras* mutations. Six cycles of cisplatin plus pemetrexed were administered with a partial response. On November 2010, he received a laparoscopy diagnosing peritoneal metastases from lung adenocarcinoma. The percentage of tumor cells in the peritoneal bioptical specimen was 70. Sanger bidirectional sequencing did not show epidermal growth factor receptor and K-*ras* mutations. Two cycles of gemcitabine plus docetaxel were administered with a progressive disease. On December 2010, the presence of *EML4-ALK* gene fusion was investigated. The fluorescent in situ hybridization test was performed on formalin-fixed and paraffin-embedded tissue samples by using a break-apart probe to ALK (ALK Dual Color Probe of Vysis, Inc., Downers Grove, IL). According to the score proposed by Kwak et al.,[1] the test was considered negative in the pleural biopsy (4% of the neoplastic cells with split of the 5′ and 3′ probe signals), whereas it was positive in the peritoneal sample (>15% of the scored tumor cells had split of the 5′ and 3′ probe signals or had isolated 3′ signals). Unfortunately, because of a rapid deterioration of the clinical conditions, the patient was unable to receive any further therapy and died on January 2011.

The *EML4-ALK* fusion gene possesses a potent oncogenic activity both in vitro and in vivo and is detected in approximately 3 to 5% of non-small cell lung cancer, predominantly in patients with adenocarcinoma and no or minimal smoking history.[1,2] These patients were also found to be less responsive to platinum-based chemotherapy and to have a lower overall survival.[3] Crizotinib, an inhibitor of the tyrosine kinase activity of both ALK and the met proto-oncogene, demonstrated high activity in these patients.[1] To the best of our knowledge, this is the first report concerning a discrepancy of the *EML4-ALK* gene detection between primary and corresponding metastases. The molecular basis for this disparity is not known, but the evidence of tumultuous growth in disease evolution might be related to a rapid change in tumor biology. In our case, the *EML4-ALK* fluorescent in situ hybridization positivity was detected in a heavy smoker, not a frequently characteristic, and the onset of peritoneal metastasis, positive for the *EML4-ALK* fusion gene, corresponded to a worsening of prognosis as expected. These observations may have important clinical implications for the molecular testing of targeted therapies, calling for a much better selection of patients and for the availability of metastatic tissue for the detection of the presence of specific target to better address the treatment.

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