CASE REPORT

What’s your treatment option in a patient with impending respiratory failure due to disseminated lung cancer?

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Summary
Diffuse bronchiolo-alveolar cell carcinoma (BAC) with endolymphatic tumor emboli involving whole lung fields was found in a 25-year-old male. He had a history of 6 pack years of smoking. After a thoracoscopic lung biopsy, his condition was aggravated leading to imminent respiratory failure. Although gefitinib is not usually recommended as a first-line chemotherapeutic drug, we decided to use it considering that the added toxicity of conventional drugs would be fatal to him. Surprisingly, the patient showed the dramatic improvement and was able to exercise 1 week after the treatment. The immunostainings for p-Akt and E-cadherin were strongly positive. A deletion mutation (delE746–750) was detected in exon 19 by sequencing. The fluorescent in situ hybridization (FISH) was negative as low trisomy suggesting that the epidermal growth factor receptor (EGFR) mutation is a more reliable finding for prediction of the response to this novel drug, even in a patient with unfavorable clinical characteristics such as male gender and smoker. An EGFR–tyrosine kinase inhibitor (EGFR-TKI), either alone or combined with other chemotherapeutic drugs, should be considered an initial therapeutic option in patients with disseminated lung cancer requiring urgent treatment.

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Introduction

Gefitinib, an orally active epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR–TKI), has shown favorable anti-tumor activity and good tolerability in lung cancer patients. A favorable response to this drug has been more frequently observed in female, non-smoker, ethnic Asians and adenocarcinoma (especially, bronchiolo-alveolar cell carcinoma (BAC)).\(^1^,\(^2\) Responses have often led to prompt improvement of symptoms and the disease itself. The immediate patient response to this treatment suggests that it might be most useful in life-threatening situations. We report an impressive response in a young male patient with a smoking history and lung cancer.

Case report

A previously healthy 25-year-old male was referred to our hospital in June 2007 for the management of BAC that was diagnosed by a thoracoscopic biopsy at a local hospital. He visited that hospital 2 weeks previously for cough and dyspnea of 2 months’ duration. He had a history of 6 pack years of smoking. An initial chest PA showed a mass-like opacity adjacent to the right side of the cardiac border with disseminated small nodules in both lung fields (Figure 1A). His dyspnea was aggravated after the biopsy due to the progression of the lung cancer (Figure 1B). The dyspnea was so severe that it was difficult for him to stand up out of bed and to eat. The PaO\(_2\) was 66.3 mmHg in oxygen supplied at 10 L/min by mask. The respiratory rate was over 30/min suggesting that respiratory failure was imminent. BAC was confirmed by the pathological examination of the obtained lung specimen. In addition, endolymphatic tumor emboli were found, which might explain the widespread nature of the disease. Surprisingly, his symptoms started improving just 3 days after treatment with gefitinib. The patient could exercise 1 week after the start of treatment. The chest PA taken 1 week later showed that the disseminated lung lesions were remarkably improved (Figure 1C). This dramatic response was also demonstrated on the chest CT performed 3 weeks later (Figure 2). The immunostainings for p-Akt and E-cadherin were strongly positive (Figure 3A and B). The analysis for EGFR–TK mutations (exon 18–21) by sequencing revealed a deletion mutation (delE746–750) in exon 19 (Figure 3C) while the fluorescent in situ hybridization (FISH) was negative as low trisomy (Figure 3D).

Discussion

The current guidelines for non-small cell lung cancer treatment recommend that the EGFR–TKI should be used after cytotoxic chemotherapy in unselected patients with advanced stage disease. However, several reports showed that treatment with gefitinib could achieve a high response rate in chemotherapy-naïve patients with favorable clinical characteristics for a response\(^3\) or EGFR mutations\(^4\,^5\) although the exact role of gefitinib, as a first-line drug, should be clarified through randomized trials comparing cytotoxic agents. Some reports demonstrated that gefitinib could rapidly control intractable symptoms such as bronchorrhea and dyspnea.\(^6\,^7\)

**Figure 1** (A) A chest radiograph showing a mass-like opacity adjacent to the right side of the cardiac border with disseminated small nodules in both lung fields. (B) Aggravated lung lesions after the thoracoscopic biopsy. (C) Markedly improved diffuse BAC 1 week after the treatment with gefitinib.
In some cases, such as the one reported here with imminent respiratory failure due to disseminated lung cancer, emergency intervention is required. Under these circumstances, the added toxicity of chemotherapeutic agents could increase the morbidity and mortality of patients. Consideration of EGFR–TKI as an initial agent seems to be reasonable due to the reported prompt and dramatic responses.

Many studies including some prospective reports showed that EGFR mutations, especially the exon 19 deletion, are closely related to the clinical response to EGFR–TKI. In addition, several studies have suggested that the EGFR gene copy number by FISH is a possible predictor of sensitivity to EGFR–TKI. Although our patient had the unfavorable clinical characteristics such as male gender and smoker, with regard to response to EGFR–TKI, his remarkable response could be explained by the EGFR deletion mutation at exon 19 and positive immunohistochemical stainings for p-Akt and E-cadherin. However, the gene amplification by FISH was negative; this suggests that the EGFR mutation may be a more reliable factor for prediction of response to EGFR–TKI treatment, consistent with the report by Sone et al. EGFR–TKI, either alone or in combination with other chemotherapeutic drugs, should be considered as an initial therapeutic option in patients with disseminated lung cancer requiring urgent management.

Figure 2 (A) Airspace opacities of the RLL and the RML with diffuse fine nodules, ground glass opacities in both lungs suggesting diffuse-type BAC. (B) Lung cancer presenting airspace opacities of the RLL and the RML with diffuse pulmonary metastasis remarkably improved on chest CT taken 3 weeks later.

Figure 3 (A) The immunohistochemical staining for p-Akt revealed diffuse nuclear and cytoplasm positive reaction (Cell Signaling, 1:200). (B) The strong cytoplasm membrane positivity was found with the immunohistochemical staining for E-cadherin (DAKO, 1:50). (C) The deletion mutation (delE746–750) in exon 19 was detected by sequencing for EGFR. (D) Dual color FISH with EGFR (orange signal) and chromosome 7 (CEP7, green signal) probes showed FISH negative as low trisomy.
Conflict of interest statement

None declared.

References

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