Successful management of a lung cancer patient harbouring both EGFR mutation and EML4-ALK fusion gene with disseminated intravascular coagulation

Kohei Fujita a, *, Megumi Naka b, Takanori Ito b, Osamu Kanai a, Koichi Maekawa b, Koichi Nakatani a, Tadashi Mio a

a Division of Respiratory Medicine, Center for Respiratory Diseases, National Hospital Organisation Kyoto Medical Center, 1-1 Fukakusa-Mukaihata, Fushimi-Ku, Kyoto, Japan
b Department of Respiratory Medicine, Ijinkai Takeda General Hospital, Kyoto, Japan
* Corresponding author.
E-mail address: kfujita.acd@gmail.com (K. Fujita).

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transfusion of erythrocytes and platelets twice. Furthermore, enhanced computed tomography images revealed an asymptomatic pulmonary thromboembolism. Therefore, we started administration of heparin. Additionally, we performed a repeat bronchoscopy to obtain a larger specimen and to check exhaustive driver oncogene alterations. The mediastinal lymph node specimen obtained by endobronchial ultrasound-guided transbronchial needle aspiration demonstrated adenocarcinoma (Fig. 1F) with EGFR mutation (L858R point mutation) and ALK rearrangement (Fig. 1G). These driver oncogene alterations were confirmed by the Oncomine Dx Target Test. On the 14th day after initial admission, she started receiving osimertinib (80 mg/day). After administration of osimertinib, anaemia and platelet depletion stopped, and malaise gradually improved. She recovered from DIC on the 20th day. Three weeks after osimertinib induction, enhanced chest computed tomography images revealed tumour regression (Fig. 2A and B). She was switched to ambulatory follow-up care on the 30th day. Ten weeks later, we confirmed that osimertinib maintained significant reduction (>30% reduction) of her tumour. We evaluated the efficacy of Osimertinib as a partial response.

3. Discussion

We encountered an exceptionally rare case of a patient with severe lung adenocarcinoma harbouring both EGFR mutations and EML4-ALK rearrangements with DIC. EGFR mutations and EML4-ALK rearrangements have a mutually exclusive relationship [3]. Concomitant existence of these gene alterations is very rare. In previous reports, only 0.9%–1.3% of EGFR mutation-positive NSCLC patients showed both EGFR mutation and EML4-ALK rearrangement [1,2]. EGFR-TKIs and ALK-TKIs are theoretically effective for patients harbouring both EGFR mutation and EML4-ALK rearrangement. However, no study has compared which drug clinicians should use initially. Some case reports reported favourable response to first- or second-generation EGFR-TKIs [4,5]. On the other hand, other case reports reported resistance to these EGFR-TKIs and changed their treatment from EGFR-TKI to ALK-TKI [1,5,7]. The EGFR and ALK signalling systems are closely related. EML4-ALK signalling can involve resistance to EGFR-TKI and vice versa [1,7,8]. We speculate that there are two possible mechanisms as to why osimertinib successfully reduced the tumour in this case. First, there may a heterogeneous distribution of EGFR-positive and ALK-positive cells. If EGFR-positive adenocarcinoma occupies the majority of the tumour, osimertinib can reduce the majority of the tumour and any remaining

Fig. 1. Computed tomography shows right upper nodule (A) and balky mediastinal lymphadenopathy (B). Bone scintigraphy (C) and brain magnetic resonance imaging (D, E) show multiple bone and brain metastases. Histopathology of a lymph node revealed adenocarcinoma (F, ×200 haematoxylin and eosin). Immunohistochemistry shows positive staining of ALK fusion gene (G, ×100).
tumour may consist of ALK-positive adenocarcinoma. Second, a recent study suggested that osimertinib can inhibit the phosphorylation activity of both EGFR and ALK in a human adenocarcinoma cell line with EML4-ALK under experimental conditions [9]. This phenomenon may partially explain the favourable clinical response in our case. Furthermore, that study [9] and another case report [10] also suggest that the combined use of EGFR-TKI and ALK-TKI can favourably manage lung adenocarcinoma harbouring both EGFR mutations and ALK rearrangements.

Our case had two notable points. First, Osimertinib, a third-generation EGFR-TKI, showed a favourable tumour response. Despite the controversy regarding the use of EGFR-TKI as first-line treatment, our patient benefitted from its use. Second, osimertinib could quickly overcome severe conditions as represented by the DIC in this patient. In general, clinicians often hesitate to induce cytotoxic chemotherapy for lung cancer patients with severe DIC because these patients are thought to have no tolerance. Molecular targeting agents such as EGFR-TKIs and ALK-TKIs are good choices for patients with severe clinical conditions.

In conclusion, we encountered a patient with severe lung adenocarcinoma harbouring both EGFR mutations and EML4-ALK rearrangements. Even in severe conditions, third-generation EGFR-TKIs may be indicated for patients with multiple sensitive driver oncogene alterations.

Author contributions

KF, MN, TI, OK, KN, and KM cared for the patient. TM supervised the patient’s care. KF drafted this case report. MN, OK, KM, and KN, and TM supervised the manuscript. All authors approved this case report.

Declaration of competing interest

All authors have no conflict of interest to declare.

References

[1] J.K. Lee, T.M. Kim, Y. Koh, et al., Differential sensitivities to tyrosine kinase inhibitors in NSCLC harboring EGFR mutation and ALK translocation, Lung Canc. 77 (2) (2012) 460–463.
[2] J.J. Yang, X.C. Zhang, J. Su, et al., Lung cancers with concomitant EGFR mutations and ALK rearrangements: diverse responses to EGFR-TKI and crizotinib in relation to diverse receptors phosphorylation, Clin.Cancer Res. 20 (5) (2014) 1383–1392.
[3] K. Inamura, K. Takeuchi, Y. Togashi, et al., EML4-ALK fusion is linked to histological characteristics in a subset of lung cancers, J. Thorac. Oncol. 3 (1) (2008) 13–17.
[4] Y.W. Ruo, S.G. Wu, C.C. Ho, et al., Good response to gefitinib in lung adenocarcinoma harboring coexisting EML4-ALK fusion gene and EGFR mutation, J. Thorac. Oncol. 5 (12) (2010 Dec) 2039–2040.
[5] R. Chiari, S. Duranti, V. Ludovini, et al., Long-term response to gefitinib and crizotinib in lung adenocarcinoma harboring both epidermal growth factor receptor mutation and EML4-ALK fusion gene, J. Clin. Oncol. 32 (9) (2014 Mar 20) e30–e32.
[6] Y. Inada, K. Yanagihara, K. Iwasaki, et al., A case of pulmonary adenocarcinoma with concomitant EGFR gene mutation and EML4-ALK fusion gene, Nihon Kokyuki Gakkai Zasshi 6 (5) (2017) 327–331.
[7] X. Chen, J. Zhang, Q. Hu, et al., A case of lung adenocarcinoma harboring exon 19 EGFR deletion and EML4-ALK fusion gene, Lung Canc. 81 (2) (2013) 308–310.
[8] A. Miyazaki, K. Shimizu, R. Noro, et al., Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation, BMC Canc. 13 (262) (2013) 2407–2413, 262.
[9] S. Arai, S. Takeuchi, K. Fukuda, et al., Osimertinib overcomes alectinib resistance caused by amphiregulin in a leptomeningeal carcinomatosis model of ALK-rearranged lung cancer, J. Thorac. Oncol. 15 (5) (2020 May) 752–765.
[10] U. Batra, M. Sharma, B.P. Amrith, et al., EML4-ALK fusion as a resistance mechanism to osimertinib and its successful management with osimertinib and alectinib: case report and review of the literature, Clin. Lung Canc. 21 (6) (2020 Nov) e597–e600.