Successful Long-Term Treatment With Pemetrexed of NSCLC Associated With EML4-ALK and Low Thymidylate Synthase Expression

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Clinical Practice Points

- The discovery of an EML4-ALK rearrangement led to a new direction in research for molecular targeted therapy in non–small-cell lung cancer (NSCLC).
- Recent retrospective studies have suggested that EML4-ALK–positive patients may have a superior progression-free survival (PFS) with treatment using pemetrexed-based therapies; however, the underlying biological mechanism is unclear.
- We report a patient with NSCLC positive for the EML4-ALK fusion gene who benefited from treatment with pemetrexed plus carboplatin over a period of 15 months.
- Immunohistochemical analysis revealed a low level of intratumoral thymidylate synthase (TS) expression, suggesting that such a low expression level for this target of pemetrexed may have contributed to the long-term response to pemetrexed-based chemotherapy.
- Further studies are warranted to investigate predictive values of intratumoral TS levels in EML4-ALK–positive patients.

Introduction

Fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) genes has recently been identified in non–small cell lung cancer (NSCLC). The dual MET-ALK inhibitor crizotinib has shown promising activity in patients whose tumors harbor this oncogene,1 but it has remained unclear whether such patients manifest similar sensitivity to cytotoxic chemotherapy. Two recent retrospective studies have suggested that EML4-ALK–positive patients may have a superior progression-free survival (PFS) with treatment using pemetrexed-based therapies.2,3

We now report a case of EML4-ALK–positive NSCLC that showed long-term benefit from treatment with pemetrexed plus carboplatin.

A 62-year-old woman, an asymptomatic nonsmoker, was admitted to our hospital after the detection of an abnormal shadow on a chest roentgenogram. A chest computed tomographic scan revealed a solitary spiculated lesion in the right upper lung lobe associated with pleural effusion suggestive of pleural dissemination (Figure 1A). A biopsy specimen obtained by video-assisted thoracoscopic surgery yielded a pathologic diagnosis of pleural dissemination of a signet-ring adenocarcinoma (Figure 1C). Mutation analysis showed that the tumor was wild type for the epidermal growth factor receptor (EGFR) gene. Fluorescence in situ hybridization (FISH) analysis with break-apart probes for ALK revealed the presence of an ALK rearrangement (Figure 1D), and subsequent reverse transcription and polymerase chain reaction (PCR) analysis confirmed the presence of EML4-ALK fusion transcript variant 1 (Figure 1E). As a first-line treatment, pemetrexed plus carboplatin were chosen for the following reasons. Pemetrexed is active in the nonsquamous NSCLC histologic type, and carboplatin-based regimens have been preferred over cisplatin regimens because they are less toxic and more convenient to administer in the outpatient treatment setting. The treat-ment consisted of pemetrexed 500 mg/m² and carboplatin area under the curve (AUC) 6 every 21 days for 4 cycles followed by maintenance pemetrexed 500 mg/m² on day 1 of a 21-day cycle. A computed tomographic scan revealed 33% shrinkage of tumor, which was categorized as a partial response according to Response

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Evaluation Criteria in Solid Tumors (RECIST) 1.1. A total of 20 treatment cycles (16 maintenance cycles) had been administered over 15 months at the time of this writing, with no evidence of severe adverse events or disease progression (Figure 1B).

Discussion
The EML4-ALK fusion gene has recently been identified in a subset of NSCLC tumors, being detected most often in never-smokers and associated with distinct pathologic features such as signet-ring cell adenocarcinoma. ALK inhibitors have shown marked clinical efficacy in NSCLC patients harboring EML4-ALK, but it has remained unclear whether such patients will manifest similar sensitivity to platinum-based combination chemotherapy compared with patients whose tumors are negative for EML4-ALK.

Preliminary data from a small number of patients who were retrospectively identified as harboring EML4-ALK suggest that EML4-ALK–positive tumors treated with platinum-based chemotherapy show a response similar to that of tumors without EML4-ALK or EGFR mutations. However, 2 recent studies have suggested that EML4-ALK–positive patients may have a superior PFS when treated with pemetrexed-based therapies compared with patients with other molecularly defined subtypes of NSCLC, although the reason for this difference is not known. A semiquantitative immunohistochemical analysis of the expression of thymidylate synthase (TS), a target...
enzyme of pemetrexed, in tumor biopsy specimens from 24 consecutive patients with NSCLC treated with pemetrexed combined with platinum agents revealed that patients with a low level of TS expression had a significantly longer PFS than did those with a high level of TS expression. Additional analysis has now revealed that EML4-ALK (the 2 most common variants, variant 1 and variant 3a) was present in 2 of these 24 patients, including the present case (Figure 2). Moreover the lowest level of TS expression was observed in our patient, who harbored the EML4-ALK variant 1. Given the importance of a low level of TS expression for increased sensitivity to pemetrexed-based regimens, the low TS expression level of the proband may have contributed to the long-term efficacy of pemetrexed. The other patient harboring EML4-ALK (variant 3a) manifested a moderate level of TS expression but had early disease progression after 1 cycle of treatment. Whether a low level of TS expression is associated with EML4-ALK–positive NSCLC and confers an improved response to TS-targeting agents such as pemetrexed in such patients remains to be determined. TS-targeting agents such as pemetrexed may offer new ways of increasing antitumor potency in EML4-ALK–positive NSCLC patients. Further investigations are thus warranted concerning the role of TS in EML4-ALK-positive patients.

**Conclusion**

We report the successful long-term treatment with pemetrexed and carboplatin in a patient with EML4-ALK–positive NSCLC. The low TS expression level of the tumor may have contributed to the beneficial outcome of pemetrexed-based chemotherapy.

**Disclosure**

The authors report that they have no relevant relationships to disclose.

**References**