LETTER TO THE EDITOR

Marked response to both S-1 and pemetrexed in a patient with echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase-positive lung adenocarcinoma

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To the Editor,

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 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 studies have suggested that ALK rearrangements may be a predictor of efficacy for the thymidylate synthase (TS)-targeted agent pemetrexed in terms of both response rate and progression-free survival in NSCLC [2,3]. S-1 also targets TS and has shown promising results in a phase III trial as a first-line treatment for patients with advanced NSCLC [4]. We now report a dramatic response to both S-1 and pemetrexed in a patient with EML4-ALK-positive NSCLC.

Case presentation

A 39-year-old man presented with a two-month history of productive cough. A computed tomography (CT)-scan of the chest showed a mass in the right lower lobe of the lung with bilateral hilar, multiple mediastinal, and supraclavicular lymphadenopathy as well as bone metastases. Sputum cytology and supraclavicular lymph node biopsy yielded a diagnosis of adenocarcinoma of the lung. Activating mutations of the epidermal growth factor receptor gene were not detected in tumor biopsy specimens. Fluorescence in situ hybridization (FISH) analysis with break-apart probes for the anaplastic lymphoma kinase gene (ALK) revealed the presence of an ALK rearrangement (Figure 1A), and reverse transcription and polymerase chain reaction analysis confirmed the presence of EML4-ALK fusion transcript variant 3a (Figure 1B). Physical examination of the patient and routine blood tests revealed no relevant findings. The patient was treated with six cycles of first-line chemotherapy with carboplatin (area under the curve, 6) and S-1 (60 mg twice daily), resulting in a partial response. The patient continued on maintenance chemotherapy with S-1 for six more cycles, with no evidence of disease progression at 15 months after diagnosis. Disease progression with multiple distant metastases in bone, liver, and the contralateral lung was documented during maintenance therapy (Figure 2), and the patient commenced second-line treatment with pemetrexed (500 mg/m²) every three weeks. Positron emission tomography (PET)-CT after two cycles of pemetrexed chemotherapy revealed a pronounced decrease in both size and activity for the primary and all metastatic lesions (Figure 2), with the patient developing a second partial response of ∼90% that persisted for eight months. Pemetrexed treatment appeared safe for the patient, who did not show deterioration in performance status even though more than 10 cycles of the chemotherapy were administered. The patient subsequently progressed and was then treated with docetaxel, erlotinib, and a combination of gemcitabine and vinorelbine and was...
rechallenged with pemetrexed. However, his symptoms worsened and he is currently receiving treatment with an ALK inhibitor in a clinical trial. After only two weeks of treatment, he again developed a partial response.

Discussion

We report a pronounced response to pemetrexed in a patient with EML4-ALK-positive lung cancer. Two recent studies have suggested that ALK rearrangements may be a predictor of pemetrexed efficacy with regard to both response rate and progression-free survival in NSCLC [2,3]. Why pemetrexed had such a marked and rapid effect in the present case is unclear. We previously found that a low level of thymidylate synthase (TS) expression in NSCLC tumors is associated with a favorable tumor response and progression-free survival in patients treated with pemetrexed [5], indicating that treatment outcome for pemetrexed may be related to the expression level of TS, one of the molecular targets of pemetrexed. The antitumor effect of first-line treatment with S-1 in the present case is also of interest. S-1 is an oral fluoropyrimidine agent that consists of tegafur (a 5-fluorouracil prodrug), 5-chloro-2,4-dihydroxypyridine, and potassium oxonate [6]. The antitumor activity of 5-fluorouracil is largely due to inhibition of TS. We also previously found that a low expression level of TS was associated with response to S-1-containing treatment regimens in patients with advanced NSCLC [7]. Given that pemetrexed and S-1 are both cytotoxic agents that inhibit TS, the present patient might be expected to have a low TS expression level, although this was not measured. Whether a low expression level of TS 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.

In conclusion, we report a dramatic response to TS-targeted agents including both S-1 and pemetrexed in a patient with EML4-ALK-positive NSCLC. Further investigations are warranted concerning the relation between pemetrexed and S-1 efficacies and the role of TS in EML4-ALK-positive NSCLC patients.

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References


