OncoTargets and Therapy

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CASE REPORT

Successful long-term treatment of non–small cell lung cancer positive for *RET* rearrangement with pemetrexed

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: The discovery of *RET* rearrangement in non–small cell lung cancer (NSCLC) has prompted development of molecularly targeted therapy for such tumors, with several clinical trials being under way to evaluate the therapeutic effects of multitargeted tyrosine kinase inhibitors. The sensitivity of *RET* fusion–positive NSCLC to cytotoxic chemotherapy has remained unclear, however. We here report a case of NSCLC positive for the *CCDC6-RET* fusion gene that benefited from treatment with pemetrexed over a period of 30 months, suggesting that thymidylate synthase–targeted drugs such as pemetrexed may show efficacy for NSCLC harboring *RET* fusions.

Keywords: CCDC6-RET, non–small cell lung cancer, pemetrexed, predictive marker

Introduction

RET fusion genes such as *KIF5B-RET* and *CCDC6-RET* have recently been identified in non–small cell lung cancer (NSCLC).[1,2] Several clinical trials are already under way to evaluate the therapeutic effects of tyrosine kinase inhibitors whose targets include RET—such as vandetanib, cabozantinib, and alectinib—in individuals with *RET* fusion–positive NSCLC, with some patients having shown marked treatment responses.[3,4] However, no selective RET inhibitor has yet been approved specifically for RET-driven lung cancer, and it has remained unclear whether such patients manifest a sensitivity to cytotoxic chemotherapy similar to that of other NSCLC patients. We here report a case of *RET* fusion–positive NSCLC that showed long-term benefit from treatment with pemetrexed.

Case report

A 63-year-old female never-smoker with stage IV lung adenocarcinoma was enrolled in an ongoing observational study to evaluate the feasibility of the application of next-generation sequencing to mutation analysis of lung cancer specimens at Kindai University.[5] The multiplex genetic testing identified a *CCDC6-RET* fusion gene in tissue specimens obtained from the patient for lung cancer diagnosis (Figure 1A). We verified this chromosomal inversion by fluorescence in situ hybridization with probes that flank the *RET* translocation site identified in tumors positive for the *CCDC6-RET* fusion (Figure 1B). The patient was treated with several lines of therapy, including platinum-based chemotherapy, docetaxel plus an experimental multikinase inhibitor, erlotinib plus an investigational drug, and an investigational antiangiogenic agent. Pemetrexed at a dose

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http://doi.org/10.2147/OTT.S211582

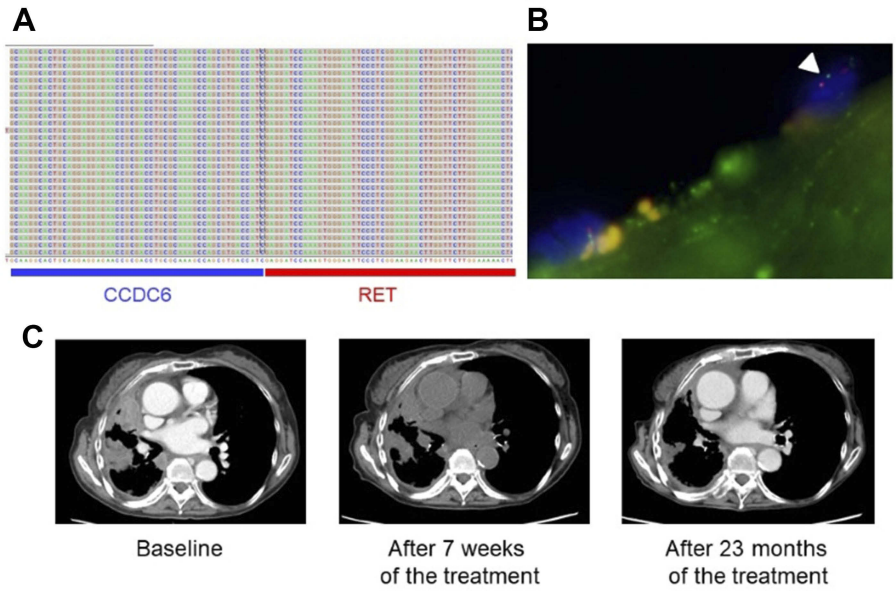

Figure 1 (**A**) Junction reads for *CCDC6-RET* fusion transcripts as determined by next-generation sequencing of tumor cDNA from the patient. (**B**) Fluorescence in situ hybridization analysis of tumor tissue from the patient with break-apart probes for *RET* (5′ probe, green; 3′ probe, red). The *RET* rearrangement is indicated by the presence of a single isolated red signal (arrowhead). (**C**) Chest computed tomography scans of the patient before, 7 weeks after, and 23 months after initiation of treatment with pemetrexed and carboplatin.

of 500 mg/m^2 every 3 weeks was then initiated as a fifth-line therapy. After 7 weeks of pemetrexed administration, computed tomography revealed shrinkage of the primary lung lesion (Figure 1C), which was ultimately categorized as a partial response. The serum carcinoembryonic antigen (CEA) level had decreased markedly by this time and remained low thereafter throughout the period of tumor regression (Figure 2). Anemia of grade 3 and an aspartate aminotransferase elevation of grade 3 occurred during the first treatment cycle, but no severe adverse events were subsequently noted after the pemetrexed dose was reduced to 400 mg/m^2. A total of 40 treatment cycles for pemetrexed was administered over 30 months until disease progression.

Discussion

RET fusion genes have recently been identified in a subset of NSCLC tumors, being detected most often in patients who are never-smokers, are of a younger age, and have tumors with an adenocarcinoma histology. Multikinase inhibitors with activity against RET have shown marked clinical efficacy in NSCLC patients harboring *RET* fusions,[3,4] but it has remained unclear whether such patients might receive benefit from cytotoxic chemotherapy. The present case shows long-term efficacy of pemetrexed for >2 years in the fifth-line setting. Preliminary data from a phase III study (PROFILE 1007) comparing crizotinib with pemetrexed or docetaxel chemotherapy after failure of one prior platinum-based chemotherapy regimen

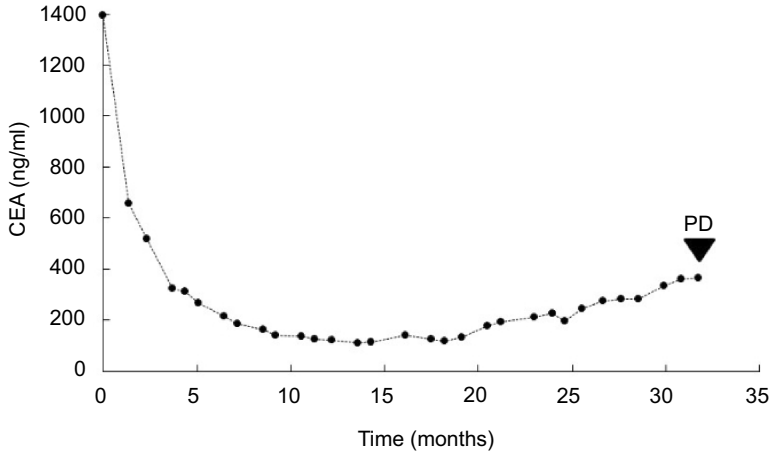

Figure 2 Time course of serum CEA level for the patient after initiation of pemetrexed treatment at time zero.
Abbreviations: CEA, carcinoembryonic antigen; PD, progressive disease.

have shown that pemetrexed treatment produced a better outcome compared with docetaxel in patients with *ALK* fusion–positive NSCLC.[6] Moreover, two retrospective studies have suggested that *EML4-ALK*–positive patients may have a superior progression-free survival when treated with pemetrexed-based therapies compared with patients with other molecularly defined subtypes of NSCLC.[7,8] Given the importance of a low level of thymidylate synthase (TS) expression for sensitivity to pemetrexed-based regimens,[9] a low TS expression level of the proband may have contributed to the long-term efficacy of pemetrexed.[10] Similar to lung tumors positive for *ALK* rearrangement, a recent study also showed that *RET* fusion–positive lung cancers were sensitive to pemetrexed-based therapies, although data for TS expression were not available.[11] TS-targeting agents such as pemetrexed and S-1 may thus offer promising treatment options for patients with *RET* fusion–positive NSCLC.

In conclusion, we report the successful long-term treatment of a *RET* fusion–positive NSCLC patient with pemetrexed. Given the insufficient data regarding pemetrexed sensitivity and *RET* fusion, further investigations are warranted to investigate these biological mechanisms.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images before the patient received chemotherapy. Institutional approval was not necessary to publish a case report.

Disclosure

Dr Masayuki Takeda reports personal fees from Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., and Chugai, outside the submitted work. Dr Kazuko Sakai received lecture fees from Roche Diagnostics, Bio-Rad Laboratories, SRL, AstraZeneca, Thermo Fisher Scientific, and Becton, Dickinson and Company, outside the submitted work. Professor Kazuto Nishio reports grants from Korea Otsuka Pharmaceutical Co., Ltd., Life Technologies Japan Ltd., Astellas Pharma Inc., Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., and Ignyta, Inc., and received lecture fees from Sumitomo Bakelite Co., Ltd., Daiichi Sankyo Co., Ltd., Chugai Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., AstraZeneca K.K., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical, Sanofi, Solasia Pharma, Taiho Pharmaceutical Co. Ltd, Eli Lilly Japan K.K., Pfizer Inc., Bristol Myers Squibb, Life Technologies Japan Ltd., Novartis Japan, and SymBio Pharmaceuticals, outside the submitted work. Professor Kazuhiko Nakagawa reports grants and personal fees from MSD K.K., Eli Lilly Japan K.K., Bristol Myers Squibb Company, Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., AstraZeneca K.K., Astellas Pharma Inc., Novartis Pharma K.K., Nippon Boehringer Ingelheim Co., Ltd., and Pfizer Japan Inc., during the conduct of the study. He also received grants and personal fees from CON Japan K.K., Takeda Pharmaceutical Co., Ltd., PAREXEL International Corp., IQVIA Services Japan K.K., A2 Healthcare Corp., AbbVie Inc., SymBio Pharmaceuticals Limited., EP-CRSU Co. Ltd., Linical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., EPS International Co., Ltd., Quintiles Inc., CMIC Shift Zero K.K., Eisai Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd, EPS Corporation., Daiichi Sankyo Co., Ltd., Bayer Yakuhin Ltd, inVentiv Health Japan, Gritsone Oncology Inc, GlaxoSmithKline K.K., Yakult Honsha Co., Ltd., Covance Inc., Kyorin Pharmaceutical Co., Ltd., CareNet, Inc, Nichi-Iko Pharmaceutical Co., Ltd., Hisamitsu Pharmaceutical Co., Inc., Nikkei Business Publications, Inc., Thermo Fisher Scientific K.K., Nanzando Co., Ltd, Medical Review Co., Ltd., Yomiuri Telecasting Corp., and Reno Medical K.K., outside the submitted work. The authors report no other conflicts of interest in this work.

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