Case Report

Effectiveness of crizotinib in a patient with mesenchymal-epithelial transition overexpression/fluorescence in situ hybridization-negative/next-generation sequencing-negative advanced lung adenocarcinoma: a case report

Peng Song[1], Li Liu[2], Yutao Liu[3], Tao Zhang[4], Lei Guo[2], Weihua Li[2], Jianming Ying[2], Lin Yang[2], Shugeng Gao[1]

[1]Department of Thoracic Surgery, [2]Department of Pathology, [3]Department of Medical Oncology, [4]Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Correspondence to: Shugeng Gao. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Panjiayuan Nanli 17#, Beijing 100021, China; Lin Yang. Department of Pathology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Panjiayuan Nanli 17#, Beijing 100021, China. Email: shugenggao@126.com; linyang0616@yahoo.com.

Abstract: Crizotinib, an oral ATP-competitive tyrosine kinase inhibitor (TKI), has shown significant activity against advanced non-small cell lung cancer (NSCLC) tumors harboring mesenchymal-epithelial transition (MET) amplification or exon 14 mutation. Methods to detect MET alteration includes immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), next-generation sequencing (NGS) and reverse transcription polymerase chain reaction (RT-PCR). Despite multiple methods for detecting MET alteration, the response to crizotinib in advanced NSCLC patients according to the results of MET IHC staining is still unknown. This case showed effectiveness of crizotinib in a pretreated patient with advanced lung adenocarcinoma detected as MET overexpression/FISH-negative/NGS-negative. MET overexpression might be a biomarker for predicting efficacy of crizotinib.

Keywords: Lung adenocarcinoma; crizotinib; immunohistochemistry (IHC); fluorescence in situ hybridization (FISH); next-generation sequencing (NGS)

Submitted Nov 29, 2018. Accepted for publication Mar 08, 2019.
doi: 10.21037/tcr.2019.03.14
View this article at: http://dx.doi.org/10.21037/tcr.2019.03.14

Introduction

In recent years, the tyrosine kinase receptor mesenchymal-epithelial transition (MET) has become a target in non-small cell lung cancer (NSCLC). Crizotinib, a potent tyrosine kinase inhibitor (TKI) of anaplastic lymphoma kinase (ALK) and ROS1, has demonstrated its remarkable therapeutic effect in patients with *MET* amplified or *MET* exon 14 skipping mutated advanced-stage non-small-cell lung cancer in several previous reports (1-5). Methods to detect *MET* alteration includes immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), next-generation sequencing (NGS) and reverse transcription polymerase chain reaction (RT-PCR). Few cases reported response to crizotinib in advanced NSCLC patients according to the results of MET IHC staining. In this article, we report a case of crizotinib effectiveness in a pretreated patient with advanced lung adenocarcinoma detected as MET overexpression/FISH-negative/NGS-negative.

Case presentation

A 53-year-old male smoker visited our hospital with the chief complaint of causing cough and fever on March 12, 2018. Physical examination revealed enlarged lymph nodes in the left supraclavicular region. The patient underwent computed tomography (CT) scanning, which showed space-occupying lesions in the right lung and multiple enlarged lymph nodes in the mediastinum that were preliminarily determined to be lung adenocarcinoma by bronchoscopic examination and no distant metastatic lesions was detected (*Figure 1A*,*B*). Aspiration biopsy of the left supraclavicular lymph node was performed and histological examination revealed a lymph node invaded by adenocarcinoma cells which originated from primary adenocarcinoma of lung confirmed by IHC (*Figure 1C*,*D*). In addition, IHC revealed that the metastatic tumor expressed MET protein which was strong positive (score 3+ with SP44 from Ventana Medical Systems, USA) (*Figure 1E*). FISH analysis showed neither *MET* amplification nor *ALK* or *ROS1* rearrangements (*MET*: Vysis MET SpectrumRed/CEP7 SpectrumGreen, Abbott Molecular, USA; *ALK*: Vysis ALK Dual Color, Abbott Molecular, USA; *ROS1*: Vysis ROS1 Dual color, Abbott Molecular, USA) (*Figure 1F*). We performed targeted NGS using biopsy tissue from left supraclavicular lymph node. Genomic DNA was profiled by using a capture-based targeted sequencing panel (Burning Rock Biotech, Guangzhou, China), including all exons in 56 genes and selected introns in *MET*, *ALK*, *ROS1*, *RET*, *NTRK1*, *FGFR3* and *FGFR1*. Detailed procedure was reported in our previous study (6). The results of sequencing showed that no mutation was detected in *MET* gene (*Figure 1G*). The patient was treated with pemetrexed-carboplatin doublet chemotherapy initially on March 23, 2018. After two cycles of chemotherapy, the primary lesion maintained as stable disease (*Figure 1H*), but a metastatic tumor occurred in the right adrenal gland (*Figure 1I*). Considering strong positive staining of MET, we finally decided to administrate crizotinib 250 mg twice daily after multidisciplinary discussion on May 10, 2018. After one month of crizotinib treatment, the primary lesion and the metastatic tumor in the right adrenal gland both achieved a marked partial response (PR) (*Figure 1J*,*K*). The patient continued to receive crizotinib with no significant cancer progression as of December 2018.

Discussion

While crizotinib is recommended in advanced-stage NSCLC patients with *MET* amplification or *MET* exon 14 skipping mutation by NCCN guidelines, we report its effectiveness in an advanced lung adenocarcinoma considered MET IHC-positive/FISH-negative/NGS-negative.

As for detection of *MET* alteration, no gold standard method is widely accepted to determine appropriate patients with NSCLC who can benefit from crizotinib. The need for accurate detection of *MET* alteration has become much more important. Previous studies have described the correlation between *MET* amplification and MET protein expression, and revealed that almost all patients who displayed amplification of the *MET* gene also were positive for MET protein expression, while only half of the IHC positive patients had amplification (7,8). Therefore, for detection of *MET* alteration, many centers routinely applied IHC as initially screening tool due to its rapid and inexpensive advantage, and those with moderate or intense staining indicative of *MET* gene expression are then tested by FISH for confirmation of *MET* amplification.

Few studies reported the treatment efficacy of crizotinib in NSCLC patients with MET overexpression/FISH-negative. Li *et al.* demonstrated that 11 advanced NSCLC patients with de-novo overexpression of MET achieved PR to crizotinib, of which 3 patients showed MET IHC strong positive without *MET* amplification and *ALK* or *ROS1* rearrangements (9). Our case also achieved PR to crizotinib based on MET IHC staining. However, the 3 patients in Li *et al.*'s study did not undergo gene sequencing to determine the *MET* exon 14 mutational status, and hence the effective treatment of crizotinib in these 3 patients may be attributed to the presence of *MET* exon 14 mutation. In view of the above-mentioned uncertainty, NGS was applied into our case and no *MET* exon 14 mutation was found, in addition to negative finding for *MET* amplification and *ALK* or *ROS1* rearrangements.

We herein infer from this case that MET overexpression could be a biomarker for predicting efficacy of crizotinib. Further studies awaiting to be done for collecting more patients with MET overexpression for evaluating efficacy of crizotinib.

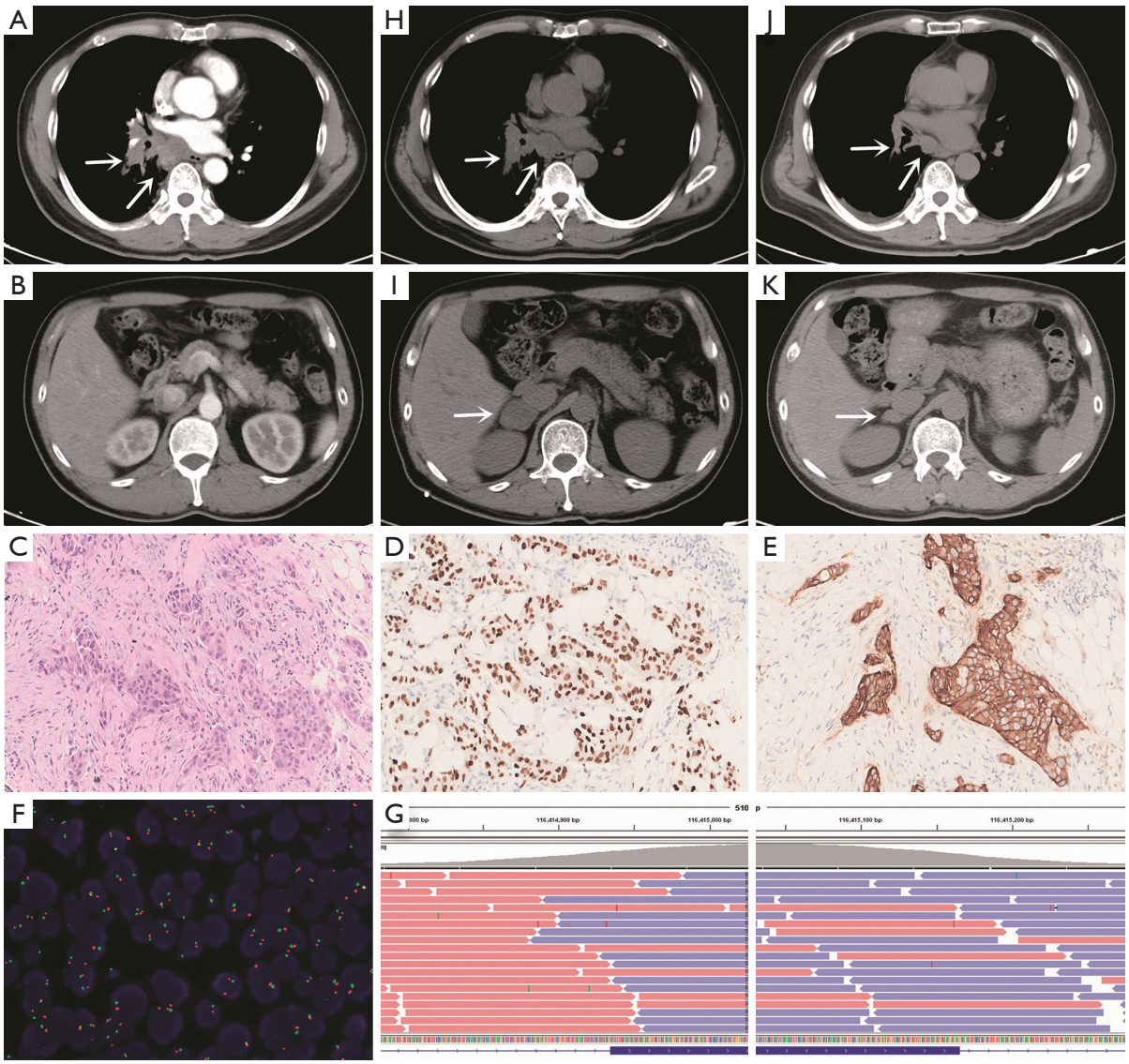

Figure 1 Illustration of the computed tomography images, histopathological, immunohistochemical, fluorescence in situ hybridization and next-generation sequencing results. (A) CT scan of thorax and mediastinal lymph nodes at diagnosis. A lung mass localized in the right lower lobe with an enlarged lymph node in the mediastinum (arrows indicate primary tumor and lymph node); (B) abdominal CT scan at diagnosis. No adrenal lesions were observed; (C) hematoxylin-eosin staining of the patient's aspiration biopsy sample. Picture magnification: 20×; (D) TTF-1 immunohistochemistry using the SP141 monoclonal antibody. Picture magnification: 20×; (E) C-Met immunohistochemistry using the SP44 monoclonal antibody. We observed a diffuse and intense c-Met immunostaining in tumor cells (score 3+). Picture magnification: 20×; (F) MET FISH using Vysis LSI MET SpectrumRed/CEP7 SpectrumGreen probe. We observed a negative result of MET amplification with MET to CEP7 ratio <2. Picture magnification: 60×; (G) next-generation sequencing analysis of MET exon 14 mutation. We observed no mutation in MET exon 14; (H) CT scan of thorax and mediastinal lymph nodes after two cycles of chemotherapy. The dominant mass and the enlarged mediastinal lymph node maintained stable (arrows indicate primary tumor and lymph node); (I) abdominal CT scan after two cycles of chemotherapy. A right adrenal lesion was observed (arrow indicates adrenal gland); (J) CT scan of thorax and mediastinal lymph nodes after one month of crizotinib treatment. A marked response to therapy with significant decrease of the dominant mass and lymph node was observed (arrows indicate primary tumor and lymph node); (K) abdominal CT scan after one month of crizotinib treatment. A significant decrease in the size of right adrenal lesion was observed (arrow indicates adrenal gland). CT, computed tomography; TTF-1, thyroid transcription factor-1; MET, mesenchymal-epithelial transition; FISH, fluorescence in situ hybridization.

Acknowledgments

The authors thank Jiali Mu and Ruomei Dong for their technical assistance.

Funding: This work was supported by Beijing Municipal Science & Technology Commission No. LC2015A13 and National Key R&D Program of China (2017YFC1308700).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.03.14). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

References

1. Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-6.
2. Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32:abstr 8001.
3. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015;5:850-9.
4. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov 2015;5:842-9.
5. Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpression. J Clin Oncol 2016;34:721-30.
6. Li W, Zhang J, Guo L, et al. Combinational analysis of FISH and immunohistochemistry reveals rare genomic events in ALK fusion patterns in NSCLC that responds to crizotinib treatment. J Thorac Oncol 2017;12:94-101.
7. Duan J, Yang X, Zhao J, et al. Correlation among genetic variations of c-MET in Chinese patients with non-small cell lung cancer. Oncotarget 2017;9:2660-7.
8. Park S, Koh J, Kim DW, et al. MET amplification, protein expression, and mutations in pulmonary adenocarcinoma. Lung Cancer 2015;90:381-7.
9. Li AN, Yang JJ, Zhang XC, et al. Crizotinib in advanced non-small-cell lung cancer with de novo c-Met overexpression. J Clin Oncol 2015;15:abstr 8090.

Cite this article as: Song P, Liu L, Liu Y, Zhang T, Guo L, Li W, Ying J, Yang L, Gao S. Effectiveness of crizotinib in a patient with mesenchymal-epithelial transition overexpression/fluorescence in situ hybridization-negative/next-generation sequencing-negative advanced lung adenocarcinoma: a case report. Transl Cancer Res 2019;8(2):705-708. doi: 10.21037/tcr.2019.03.14

