Tepotinib Improves Prognosis in an Elderly Patient with Poor Performance Status and *MET* Exon 14 Skipping Mutation-positive Non-small Cell Lung Cancer

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Several target therapies for driver gene mutations related with lung cancer growth are clinically effective in patients with advanced non-small cell lung cancer. Gefitinib and alectinib have been reported as being effective and safe even in those with poor performance status (PS), but little is known about efficacy and tolerability of other TKIs. An 84-year-old man was diagnosed with non-small cell lung cancer (cT3N2M1c stage IVB). During the initial treatment with carboplatin and nab-paclitaxel, his Eastern Cooperative Oncology Group PS increased to 3. He was found to be positive for the mesenchymal-epithelial transition factor (*MET*) exon 14 skipping mutation, and tepotinib, a c-Met inhibitor, was started. His PS improved to 0–1 and partial response was maintained for 12 months or more. The *MET* exon 14 skipping mutation is common in the elderly, and TKI treatment may improve prognosis, even in patients with reduced PS.

Key words: Mesenchymal-epithelial transition factor, Non-small cell lung cancer, Tyrosine kinase inhibitor, Performance status

INTRODUCTION

Chemotherapy for non-small cell lung cancer (NSCLC) has progressed remarkably in recent years. In addition to treatment decisions based on the histological subtypes of cancer, personalized therapies based on driver gene mutations and protein expression have improved the prognosis. Even in patients with poor performance status (PS), it has been well established that targeted drugs like gefitinib for epidermal growth factor receptor (*EGFR*) gene mutation-positive cancer and alectinib for anaplastic lymphoma kinase (*ALK*) fusion gene-positive tumors are effective and safe [1, 2].

The mesenchymal-epithelial transition factor (*MET*) exon 14 skipping mutation is a rare genetic mutation found in approximately 2.8% of Japanese patients with NSCLC [3]. It is often found in smokers (64%) and more common in elderly patients with a median age of 72.5 years compared with *EGFR* mutation (61 years) or *KRAS* mutations (65 years) [4]. In addition, multivariate analysis has shown that positivity for *MET* mutations, such as *MET* exon 14 skipping mutation and MET gene amplification, is an independent factor for poor prognosis with conventional treatments [5]. Recently, two MET tyrosine kinase inhibitors (TKIs), tepotinib and capmatinib, showed efficacy in treating NSCLC with the *MET* exon 14 skipping mutation in the VISION and GEOMETRY mono-1 trials, respectively [6, 7]. However, data on TKIs for MET mutations are limited for patients with an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 and absent for those with poor PS.

Herein, we report a case of an elderly NSCLC patient with ECOG PS 3 who demonstrated good prognosis with tepotinib treatment.

CASE REPORT

An 84-year-old man with a 62-pack-year history of smoking, diabetes mellitus, and dyslipidemia was referred to our hospital because of generalized pain and abnormal chest shadows. Blood tests revealed an elevated peripheral blood leukocyte count (19,700 /μl), mild anemia, a high serum C-reactive protein (17.49 mg/dL), hypoalbuminemia (2.7 g/dL), hyperglycemia (503 mg/dL), and a high hemoglobin A1c level (11.1%), but no elevation of tumor markers. A chest radiograph showed a mass 5 cm in diameter in the right hilum, multiple nodules in the left lung, and a fracture of the left fifth rib (Fig. 1A). Computed tomography (CT) of the body showed a mass with irregular margins extending from the upper lobe of the right lung to the right hilum, multiple nodules in the left lung, enlarged mediastinal lymph nodes (Fig. 1B), and a mass in the pelvis.

Bronchoscopy revealed mucosal irregularity, mucosal redness, and swelling of the upper right lobe bronchi. Hematoxylin eosin staining of transbronchial biopsy specimens showed proliferation of atypical cells with enlarged nuclei in the absence of glandular structures, suggesting a poorly differentiated malignant

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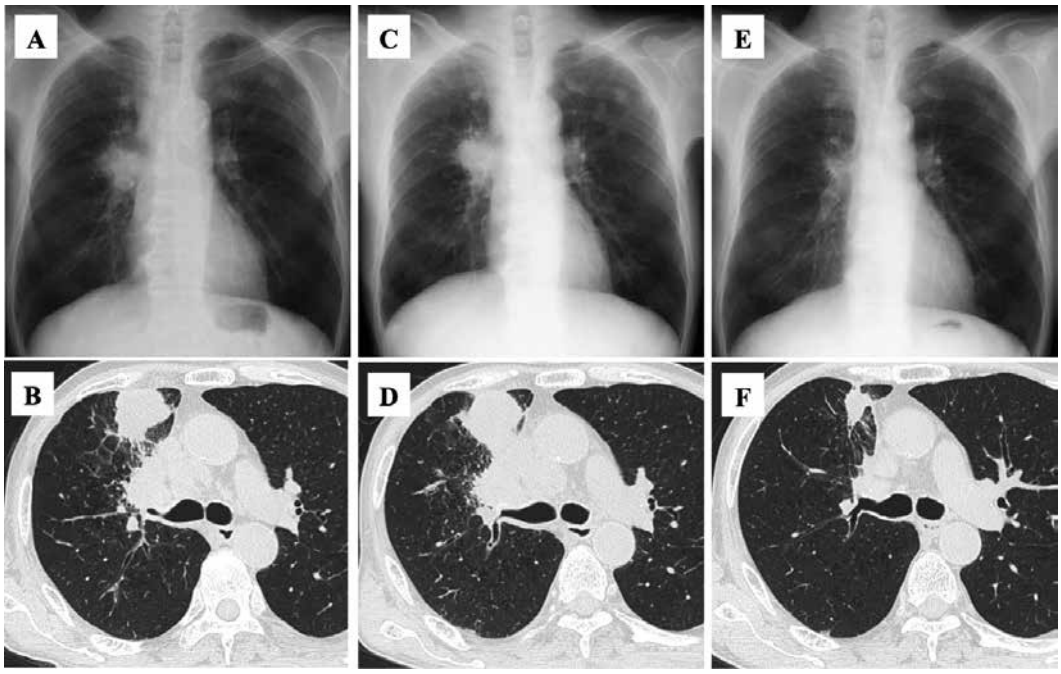

Fig. 1 Chest radiographs and computed tomography (CT) scans before and during the treatment course
Chest radiograph (A) and CT (B) at the first visit showed a mass in the right upper lobe of the lung and the hilum, and multiple nodules in the left lung. One week after cytotoxic chemotherapy, the tumor grew further (C, D), and tepotinib was initiated. Three months later (E, F), the tumor had shrunk and maintained a partial response for more than 12 months.

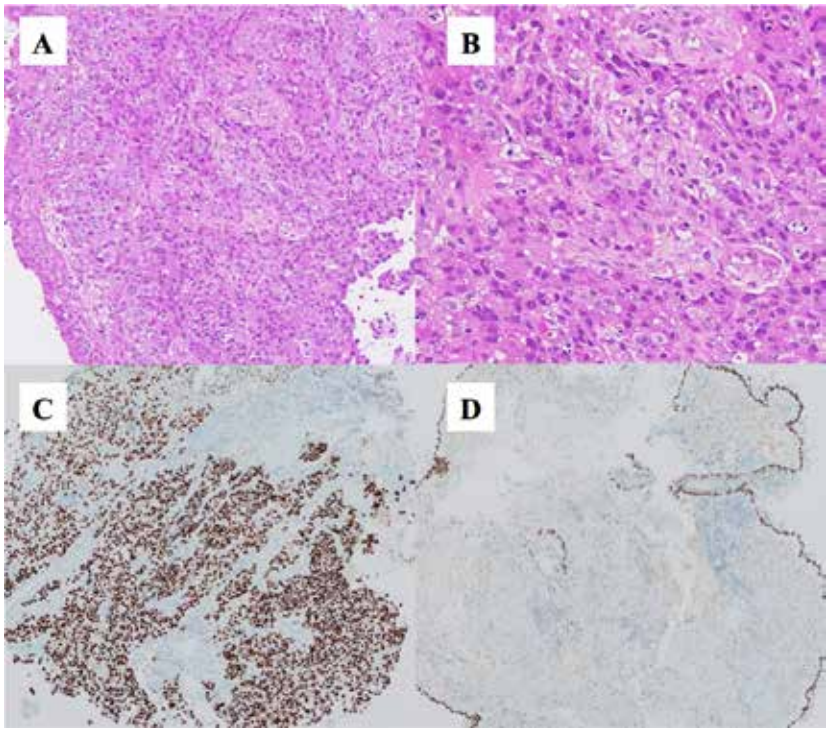

Fig. 2 Pathological findings of a mass in the right lung
Hematoxylin eosin (HE) staining of transbronchial biopsy specimens showed proliferation of atypical cells with enlarged nuclei (A: 100x, B: 400x). Immunohistochemical analysis demonstrated positive staining for thyroid transcription factor-1 (C), but negative staining for p40 (D).

tumor (Fig. 2A, B). Immunohistochemical staining was positive for thyroid transcription factor-1 (Fig. 2C), negative for p40 (Fig. 2D), and 70% and 90% positive for Ki-67 and programmed death-ligand 1, respectively. Based on the above results, we diagnosed the patient with NSCLC (cT3N2M1c stage IVB). Since he was negative for *EGFR, ALK*, and c-ros oncogene 1 gene mutations, first-line chemotherapy with carboplatin and nab-paclitaxel was started, but the tumor grew further (Fig. 1C, D) and ECOG PS worsened from 1 to 3.

At this time, the patient was found to be positive for the *MET* exon 14 skipping mutation with ArcherMET. A written consent was obtained from the patient after being informed that the evidence of efficacy and safety of tepotinib had been limited for the patients with poor PS, and then, treatment with tepotinib (500 mg/day) was started. After the start of tepotinib administration, his PS improved to 0–1 after 1 week, and the partial response was maintained for more than 12 months (Fig. 1E, F). No serious side effects other than mild lower leg edema were observed.

DISCUSSION

We report a case of NSCLC in an 84-year-old patient with poor PS caused by disease progression and the side effects of cytotoxic anticancer drugs. The patient tolerated tepotinib treatment well and showed improvement after administration. This report shows that targeted treatment of the *MET* exon 14 skipping mutation may be beneficial, even for elderly patients with poor PS.

Since TKIs are generally less toxic than cytotoxic anticancer drugs, they are expected to be relatively safe, even in the elderly. In a phase II study of gefitinib monotherapy in *EGFR* mutation-positive NSCLC patients over 75 years of age (NEJ003 study), the overall response rate was 74% and the median progression-free survival was 12.3 months, showing similar efficacy and safety to those of treatment in younger patients [8]. The efficacy of elrotinib monotherapy was equivalent in patients aged >75 years and <75 years in a phase II study (JO22903) [9]. Although there are no data on rare mutations, including *MET* gene mutations in subgroups of patients aged 75 years or older, the VISION study for tepotinib (median age, 74 years) and the GEOMETRY mono-1 study for capmatinib (median age, 71 years) both showed consistent efficacy in the elderly [6, 7]. Similar to EGFR-TKIs, MET-TKIs are considered effective for the treatment of *MET* exon 14 skipping mutation-positive NSCLC, even in patients older than 75 years.

However, evidence on the efficacy and safety of TKIs in patients in a poor condition (ECOG PS 3–4) is limited to that for gefitinib and alectinib [1, 2]. Both the VISION and GEOMETRY mono-1 studies only included patients with PS 0 or 1, and no data were available for cases with PS 2 or higher [6, 7]. The present case demonstrates that MET inhibitors may be tolerable in patients with poor PS. Ninomaru *et al.* also reported that a 77-year-old woman with leptomeningeal metastasis of *MET* exon 14 skipping mutation-positive NSCLC demonstrated remarkable improvement in neurologic symptoms and PS in response to tepotinib treatment [10]. Although the frequency and profile of adverse events vary among TKIs and some drugs require withdrawal or dose reduction even in patients in a good condition, tepotinib can be a choice for the treatment of patients with poor PS due to advanced diseases and should be studied further as a first-line targeted therapy.

CONCLUSION

Tepotinib may improve the prognosis of patients with *MET* exon 14 skipping mutation-positive NSCLC, including patients with low PS who are considered difficult to treat with cytotoxic agents.

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