Effective treatment of *MET* exon 14 skipping mutation-positive non-small cell lung cancer using capmatinib following serious maculopapular rash caused by two MET inhibitors: a case report

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Background: Multi-gene panel testing and advancements in molecular targeted therapy have improved the overall survival of patients with driver mutation-positive non-small cell lung cancer (NSCLC). Mesenchymal-epithelial transition factor (*MET*) exon 14 skipping mutation-positive NSCLC, which remains untreated with MET inhibitors, shows a poorer prognosis than do cases of NSCLC without *MET* mutations. However, serious treatment-related adverse events (TRAEs) act as substantial treatment barriers.

Case Description: Herein, we report a case of advanced NSCLC in a male in his 40s with *MET* exon 14 skipping mutation. A MET-inhibitory investigational drug was administered as first-line treatment; the development of grade 3 maculopapular rash necessitated dose reduction, which resulted in disease progression. Tepotinib was then administered with dexamethasone as a third-line treatment but was discontinued owing to the re-development of the grade 3 maculopapular rash. Finally, capmatinib administration as the fifth-line treatment appeared partially effective, with no serious adverse events. The patient could successfully resume work.

Conclusions: This is the first report of *MET* exon 14 skipping mutation-positive NSCLC wherein partial response was achieved without severe TRAEs by alternating between two MET inhibitors. If no alternative treatments are available, cautious repeated re-administration of MET inhibitors after resolving serious rashes can be considered a potential approach.

Keywords: Capmatinib; tepotinib; mesenchymal-epithelial transition factor (MET); non-small cell lung cancer (NSCLC); case report

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Introduction

Background

Advanced-stage non-small cell lung cancer (NSCLC) is a highly lethal malignancy (1). However, the widespread adoption of cancer multi-gene panel testing and advancements in molecular targeted therapy have partially facilitated prolonged overall survival (OS) (2). In some cases, even with this approach, treatment-related adverse events (TRAEs), such as severe maculopapular rash, have

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been shown to potentially impede effective management of the condition.

Rationale and knowledge gap

Mesenchymal-epithelial transition factor (*MET*) exon 14 skipping mutation-positive NSCLC, which remains untreated with MET inhibitors, has a poorer prognosis compared with that of NSCLC without *MET* mutations (3). Therefore, evaluating the feasibility of using MET inhibitors following the occurrence of serious TRAEs is crucial for developing an effective treatment strategy. Despite limited reports on the re-administration of a MET inhibitor following the onset of serious TRAEs (4,5), the evidence supporting its effectiveness remains insufficient (1).

Objective

Herein, we present a case of successful management of grade 3 (G3) maculopapular rash, according to the Common Terminology Criteria for Adverse Events version 5.0, in a patient diagnosed with *MET* exon 14 skipping mutation-positive NSCLC. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-181/rc).

Highlight box

Key findings

- Re-administering mesenchymal-epithelial transition factor (MET) inhibitors, even in the second round, can effectively control treatment response and adverse events in *MET* exon 14 skipping mutation-positive non-small cell lung cancer (NSCLC) with recurrent severe maculopapular rash.

What is known and what is new?

- In a few cases, re-administration of MET inhibitors has demonstrated effectiveness in managing *MET* exon 14 skipping mutation-positive NSCLC with prior MET inhibitor-induced adverse events.
- In some *MET* exon 14 skipping mutation-positive NSCLC cases, a second round of MET inhibitor re-administration may continue to effectively manage therapeutic efficacy and adverse events.

What is the implication, and what should change now?

- Consideration of MET inhibitor re-administration after discontinuation due to ad-verse events can be among the treatment strategies for *MET* exon 14 skipping mutation-positive NSCLC.

Case presentation

A never-smoker man in his 40s with a history of progressively worsening right chest and back pain was diagnosed with *MET* exon 14 skipping mutation-positive stage IVB (cT2aN1M1c) lung adenocarcinoma with multiple intrapulmonary, pleural, and bone metastases but without brain metastases (*Table 1*), exhibiting a programmed death-ligand 1 tumor proportion score of 1–4%. The patient developed progressive disease (PD) during fourth-line pembrolizumab treatment and was referred to our department. Physical examination revealed no abnormalities except diminished breath sounds in the right lower chest area.

During the health examination, an abnormality was identified in a chest photograph three months before the initial treatment. Subsequently, a diagnosis of *MET* exon 14 skipping mutation-positive NSCLC was confirmed through trans-bronchial biopsy. The treatment history is presented in *Figure 1*. Treatment was initiated with MET-inhibitory investigational drug (full dose), as first-line therapy; however, on day 11, pruritic macules and papules developed all over the body, excluding the hands, which were diagnosed as G3 maculopapular rashes. Dexamethasone (4 mg/d) was administered, and the skin rash was resolved. Subsequently, the dose of MET-inhibitory investigational drug was reduced to 83.3%. However, the malignant pleural effusion worsened, resulting in PD within 9 months. Second-line treatments included nivolumab, ipilimumab, carboplatin, and pemetrexed. The patient experienced PD owing to bone metastasis and worsening malignant pleural effusion. Companion diagnostic (CDx) analysis of malignant pleural fluid specimens revealed no specific secondary resistance (*Table 1*).

A combination of tepotinib and dexamethasone (4 mg/d) was administered as the third-line treatment but discontinued on day 8 owing to the re-development of the G3 maculopapular rash. For the fourth-line treatment, pembrolizumab was used, but PD occurred after two courses. Nonetheless, the patient opted to continue pembrolizumab treatment and was prescribed dexamethasone (4 mg/d) and oxycodone (30 mg/d) to alleviate nausea and pain.

After visiting our department, the patient received three additional courses of pembrolizumab based on personal preference. However, the treatment was discontinued because the malignant pleural effusion and pain worsened. In line with the personal preference for re-administering

Table 1 Results of the companion diagnostic[†] analysis

Analytical results at different times	Sample	Genes	Isoform	Locus
Result before treatment	Tumor tissue			
Gene fusions		*MET-MET*	*MET-MET*.M13M15.1	chr7:116444708–chr7:116414935
Copy number variations		Not detected	Not detected	Not detected
Result before third-line tepotinib treatment	Pleural effusion			
Gene fusions		*MET-MET*	*MET-MET*.M13M15.1	chr7:116444708–chr7:116414935
Copy number variations		*FGFR3*	chr4: 1800932	0.27

[†], Oncomine Precision Assay. MET, mesenchymal-epithelial transition factor; FGFR, fibroblast growth factor receptor.

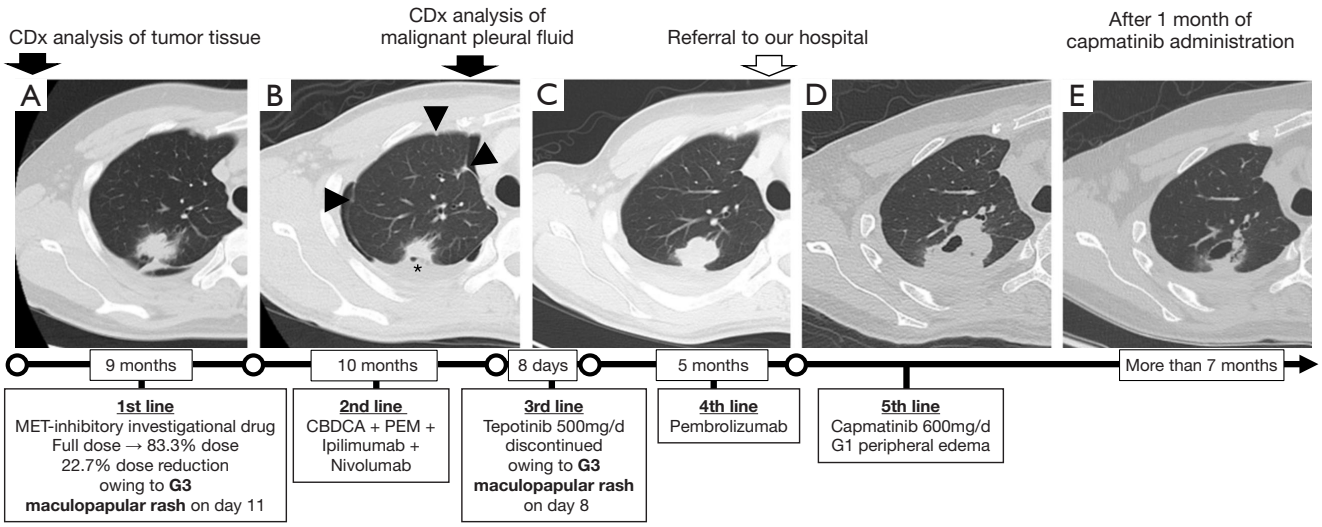

Figure 1 Clinical course of treatment. (A) Pre-treatment chest CT revealed a 31-mm diameter primary lesion with an air bronchogram and pleural indentation on the dorsal aspect of the right upper lobe. On day 11 after the MET-inhibitory investigational drug treatment, the patient developed a G3 maculopapular rash, and the MET-inhibitory investigational drug was readministered at a dose of 83.3% after a 2-week-long withdrawal. (B) However, after 9 months, the patient was diagnosed with PD owing to pleural dissemination (arrowheads) and increased malignant pleural effusion (asterisk). Second-line chemotherapy, comprising CBDCA, pemetrexed, ipilimumab, and nivolumab, was administered. Ten months after chemotherapy, cervical bone metastasis and enlargement of the primary tumor were observed, and PD was diagnosed. A second CDx assay was performed using malignant pleural fluid specimens, and no apparent secondary resistance to MET inhibitors was detected. (C) Tepotinib was introduced as a third-line therapy with dexamethasone but was discontinued after 8 d of treatment owing to the re-appearance of G3 maculopapular rash. Two courses of pembrolizumab were utilized as the fourth line of therapy, but the patient was diagnosed with PD associated with increased malignant pleural effusion. Subsequently, the patient was referred to our hospital because he preferred to continue receiving pembrolizumab treatment after PD. (D) Three more courses of pembrolizumab were administered; however, further enlargement of the primary tumor with a cavity, increased malignant pleural effusion, and worsened cancer-related pain were detected. (E) The patient agreed to receive capmatinib as the fifth-line therapy, and treatment was initiated; the pain decreased within 1 week, and a chest CT 1 month after treatment revealed a partial response. MET, mesenchymal-epithelial transition factor; CDx, companion diagnostic; CBDCA, 1-cyclobutanedicarboxylatodiamine platinum; PEM, pemetrexed; G, grade; CT, computed tomography; PD, progressive disease.

a MET inhibitor, capmatinib was utilized as the fifth-line therapy. Considering the history of TRAEs, the dexamethasone dosage was increased to 8 mg/d, and the initial daily dose of capmatinib was set at 600 mg. After 1 month of capmatinib treatment, chest computed tomography revealed rapid tumor regression and reduced symptoms. Consequently, dexamethasone and oxycodone were reduced to 4 and 5 mg/d, respectively, and no TRAEs were detected except for G1 peripheral edema. The performance status of the patient was reported to be 1, and his appetite and level of activities improved to approximately 70% of their pre-NSCLC levels. The patient could successfully resume work. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Key findings

We present, to our knowledge, the first documented case of a severe maculopapular rash associated with the MET-inhibitory investigational drug and tepotinib, which led to a switch to treatment with capmatinib and the successful alleviation of symptoms.

Comparison with similar research

Although the pathophysiology of maculopapular rash has not been fully elucidated, it is considered a hypersensitivity reaction and is reported in patients with rearranged during transfection (*RET*) fusion-positive NSCLC and prior exposure to immune checkpoint inhibitors used predominantly for their treatment (2). Skin rash (grade ≥3) has been reported in 0.6% of patients with *RET* fusion-positive NSCLC treated with selpercatinib (2). The combination of corticosteroids and a reduced selpercatinib dose successfully achieved a re-challenge rate of 86% in *RET* fusion-positive NSCLC (2).

The VISION study reported a case (0.7%) of maculopapular rash in *MET*-mutant NSCLC (6), whereas no such cases were reported in the GEOMETRY mono-1 study (7). In a recent real-world study by Paik *et al.*, less than 20% of the patients discontinued treatment, and among them, 90% were attributed solely to PD (8). These data indicate a considerably low probability of treatment discontinuation caused by the appearance of skin rash in *MET*-mutant NSCLC. To our knowledge, no cases of repeated re-administration of MET inhibitors after resolving severe TRAEs have been reported.

Explanations of findings

In our case, the association of maculopapular rash, a grade ≥3 TRAE, with the MET-inhibitory investigational drug and tepotinib rather than capmatinib remains unclear; several reasons can be considered. A severe maculopapular rash following tepotinib, combined with dexamethasone, can be attributed to the prior usage of nivolumab and ipilimumab. As the one-step dose reduction dosage of tepotinib is a 50% dose reduction, administration of tepotinib without dose reduction may have also caused the maculopapular rash. In contrast, capmatinib was applied only after pembrolizumab treatment, a 25% dose reduction, and an increased dose of dexamethasone may have avoided serious TRAEs. Recent studies have reported alterations in metabolic pathways induced by CYP3A (9) and the ability of capmatinib and tepotinib to access lysosomes (10), but none of these features for the MET-inhibitory investigational drug; these differences may also have influenced TRAEs. In addition, the tumor progressed after the first-line MET inhibitor treatment but responded to capmatinib. The reason is also unclear but may be attributed to the anticancer drugs administered between the three MET inhibitors (11), as well as slight differences in the mechanism of action among these MET inhibitors (12). While these factors partially explain this fact, the lack of concrete evidence to explain the specific phenomenon is noticeable.

Strengths and limitations

In this case, MET-inhibitory investigational drug treatment resulted in the development of PD, and severe maculopapular rash reappeared despite the administration of a combination of tepotinib and dexamethasone, whereas capmatinib was attempted to be administered. There are no clinical guidelines that recommend re-administrating MET inhibitors after disease progression or when experiencing a grade ≥3 TRAE with MET inhibitors.

Conclusions

In situations with limited alternative treatment options, the cautious repeated re-administration of a different MET inhibitor may offer potential benefits to prolong OS for certain patients with a history of severe maculopapular rash caused by MET inhibitors. Further research and careful analyses are warranted to confirm this inference.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-181/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-23-181/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-181/coif). 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 this study were in accordance with the ethical standards of the institutional and/or national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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