Capmatinib successfully overcomes tepotinib-induced intolerable peripheral edema

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Abstract
In May 2020 and February 2021, capmatinib and tepotinib, respectively were approved by the Food and Drug Administration (FDA) for the treatment of metastatic non-small cell lung carcinoma harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. Herein, we present a case of intolerable peripheral edema caused by tepotinib, in which MET inhibitor could be continued by switching to capmatinib. Peripheral edema has been identified as one of the most common adverse events in capmatinib and tepotinib; however, there is no unified management for this adverse event. This is the first report that two MET inhibitors have different effects on the development of peripheral edema, and that the MET inhibitors can be continued by switching these drugs.

KEYWORDS
capmatinib, MET ex.14 skipping, peripheral edema, tepotinib

INTRODUCTION
The mesenchymal–epithelial transition (MET) is a tyrosine kinase receptor that is mostly expressed in epithelial cells. A mutation that results in loss of exon 14 in the MET gene leads to dysregulation and inappropriate signaling that is associated with increased responsiveness to MET tyrosine kinase inhibitors (TKIs). In May 2020 and February 2021, capmatinib and tepotinib, respectively were approved by the Food and Drug Administration (FDA) for the treatment of metastatic non-small cell lung carcinoma (NSCLC) harboring MET exon 14 skipping alterations. Capmatinib should be administered at 400 mg twice daily under fasting, for a total dose of 800 mg. Moreover, tepotinib should be administered at a dose of 500 mg once daily after meals. Peripheral edema is the characteristic toxicity of these drugs. It frequently occurs in approximately 50% of all grades and 7%–11% of grades 3 or higher. Herein, we present a case of intolerable peripheral edema caused by tepotinib, in which MET inhibitor could be continued by switching to capmatinib.

CASE REPORT
A 72-year-old man who had never smoked with a history of hypertension and diabetes mellitus had undergone left lower lobectomy 4 years previously and was diagnosed with lung adenocarcinoma, pathological T2aN2M0. He received adjuvant chemotherapy. EGFR mutation, ALK, and ROS1 fusions were not detected, and PD-L1 tumor proportion score (TPS) was 60%. After one and a half years, multiple brain and lung metastases recurred. He was treated with systemic chemotherapy as follows; first-line pembrolizumab, second-line combination treatment of cisplatin, pemetrexed and bevacizumab, and third-line combination treatment of docetaxel and ramucirumab. At this point, MET c.3028+2 T > C mutation in the splicing acceptor site was detected in the surgical specimen by FoundationOne® CDx, and the same mutation was confirmed by the ArcherMET assay. Initially, tepotinib was started at 500 mg; however, within 2 weeks, grade 3 based on CTCAE v.5.0 edema developed in the extremities (Figure 1). Despite the administration of diuretics, edema from the thigh to the dorsum of the foot was severe, the range of motion of the ankle joint was
severely limited, and gait disturbance also occurred (Figure 2a). After a 2-week recovery, the edema improved and treatment was resumed at 250 mg; however, grade 3 edema developed again. Onycholysis of fingers was also observed (Figure 2a). Although 250 mg was administered every other day, the edema continued to worsen. He requested that tepotinib was discontinued, resulting in the decision being made to switch him to capmatinib 151 days after tepotinib administration. The dose of capmatinib was reduced and started at 400 mg; however, there was no exacerbation of edema. The dose was increased to 600 mg, resulting in a grade 2 increase in serum creatinine. Thereafter, the dose was reduced to 400 mg. He continued capmatinib at 400 mg for approximately 100 days without exacerbation of edema (Figure 2b), and his tumor was well controlled (Figure 3).

**DISCUSSION**

Peripheral edema induced by capmatinib and tepotinib is probably caused by inhibition of the MET signaling pathway. The same adverse events of peripheral edema have been reported with antibody drugs as well as tyrosine kinase inhibitors, which inhibit the MET pathway. In clinical trials with rilotumumab and onartuzumab, both of which are humanized monoclonal antibodies specific for an epitope in the hepatocyte growth factor (HGF) binding domain of the MET receptor, adverse events of peripheral edema have been frequently observed. Drug-induced peripheral edema has been described as noninflammatory edema and has four mechanisms: precapillary arteriolar vasodilation (vasodilatory edema), sodium/water retention (renal edema), lymphatic insufficiency (lymphedema) and increased capillary permeability (permeability edema). The etiology of MET inhibitor-induced edema is still unclear, but may be attributable to an attenuation of HGF-mediated signaling in the peripheral vascular endothelium. Physiological conditions, HGF in the vascular endothelium helps to protect against VEGF-induced endothelial hyperpermeability. Perturbation of HGF/MET signaling could disrupt this balance resulting in endothelial leak. The only treatment for edema is the use of diuretics or the discontinuation of the causative agent, but as shown in this case, the use of diuretics may not be effective. Permeability edema occurs mainly in the lower legs. In the case reported here, the patient was unable to wear shoes due to edema and unable to ride a bicycle due to dorsiflexion. This was a major hindrance to his daily life. Therefore, the MET TKI had to be discontinued.

Capmatinib and tepotinib are novel, ATP-competitive inhibitors of MET with IC50 of 0.13 and 4 nM, respectively in a cell free assay. In the present case, peripheral edema occurred even at a low dose of tepotinib, suggesting that 50% inhibition concentration of MET kinase activity is not necessarily related to the development of edema. Capmatinib is metabolized mainly by CYP3A, which is not involved in the metabolism of tepotinib. CYP3A polymorphisms specifically involved in the
metabolism of capmatinib have not been identified, but it is possible that these differences have produced differences in serum concentration of each drug in individual cases and may have influenced adverse events.

In conclusion, MET TKIs are a promising treatment for NSCLC patients harboring MET ex.14 skipping mutations, but peripheral edema associated with these agents is a common and sometimes difficult to control adverse event. At present, the existence of two MET TKIs available in clinical practice may have a significant aspect in continuing MET TKIs when intolerable edema occurs, as shown in this case.

CONFLICT OF INTEREST
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