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THERAPY IN PRACTICE

Management of Peripheral Edema in Patients with *MET* Exon 14-Mutated Non-small Cell Lung Cancer Treated with Small Molecule MET Inhibitors

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Abstract

Small molecule mesenchymal-epithelial transition (MET) inhibitors, such as crizotinib, capmatinib, and tepotinib, are treatment options for metastatic non-small cell lung cancer (NSCLC) in adult patients whose tumors have a mutation that leads to *MET* exon 14 skipping. In clinical trials, these MET inhibitors were associated with a high incidence of peripheral edema, although this was generally mild-to-moderate in severity. There is limited information about the mechanism involved in MET inhibitor-induced peripheral edema. Perturbation of hepatocyte growth factor (HGF)/MET signaling may disrupt the permeability balance in the vascular endothelium and thus promote edema development. Another potential mechanism is through effects on renal function, although this is unlikely to be the primary mechanism. Because edema is common in cancer patients and may not necessarily be caused by the cancer treatment, or other conditions that have similar symptoms to peripheral edema, a thorough assessment is required to ascertain the underlying cause. Before starting MET-inhibitor therapy, patients should be educated about the possibility of developing peripheral edema. Patient limb volume should be measured before initiating treatment, to aid assessment if symptoms develop. Since the exact mechanism of MET inhibitor-induced edema is unknown, management is empiric, with common approaches including compression stockings, specific exercises, massage, limb elevation, and/or diuretic treatment. Although not usually required, discontinuation of MET inhibitor treatment generally resolves peripheral edema. Early diagnosis and management, as well as patient information and education, are vital to decrease the clinical burden associated with edema, and to reinforce capmatinib treatment adherence.

Key Points

Peripheral edema (usually mild/moderate) is common in patients receiving small molecule mesenchymal-epithelial transition (MET) inhibitors.

Discerning the etiology of peripheral edema is important for optimal management.

Patient information and education are important approaches to limiting the impact of MET inhibitor-related edema. It can generally be managed using diuretics, elevation, compression stockings, exercise, and dietary changes, in addition to dose reduction or interruption in patients with persistent Grade ≥ 2 edema.

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1 Introduction

The small molecule mesenchymal-epithelial transition (MET) tyrosine kinase inhibitors capmatinib (Tabrecta®; Novartis, East Hanover, NJ, USA) and tepotinib (Tepmetco®; Merck KGaA, Darmstadt, Germany) are both approved as first-line (in the USA [1, 2]) or line-agnostic (in Japan [3, 4]) treatment of metastatic non-small cell lung cancer (NSCLC) in adult patients whose tumors have a mutation that leads to *MET* exon 14 (*METex14*) skipping. This mutation predominantly occurs in NSCLC, and is present in about 3–4% of all patients with NSCLC [5]. In Europe, tepotinib is approved in patients previously treated with immunotherapy or platinum-based chemotherapy [6], and capmatinib has received a positive opinion from the Committee for Medicinal Products for Human Use for approval in this indication [7]. Other small molecule MET inhibitors that may be used in this setting include crizotinib (Xalkori®; Pfizer, NY, USA) [8] and savolitinib (Orpathys®; HUTCHMED, China, and AstraZeneca, Cambridge, UK)

[9], although the latter agent is only approved in China. Crizotinib is a type Ia inhibitor of MET, anaplastic lymphoma kinase (ALK), and c-ros proto-oncogene 1 (ROS1), while capmatinib, tepotinib, and savolitinib are type Ib MET inhibitors that target and selectively bind to MET, including the mutant variant produced by *METex14* skipping [5, 10]. Capmatinib and tepotinib have demonstrated clinically meaningful efficacy and a good tolerability profile in adult patients with advanced NSCLC with this mutation in several clinical trials [11–15]. The National Comprehensive Cancer Network guidelines now recommend capmatinib or tepotinib as first-line therapy in patients with the *METex14* mutation, with crizotinib being considered useful in certain circumstances [8]. Prior to the approval of these small molecule MET inhibitors, first-line treatment for patients with metastatic NSCLC included platinum doublet chemotherapy with or without vascular endothelial growth factor (VEGF) signaling pathway inhibitors [16–18]. Due to the mechanism of action (i.e., anti-angiogenesis), the inhibition of the VEGF pathway can lead to vascular disturbances including hypertension and proteinuria, which can be intensified by concurrent pathologic conditions [19]. In contrast, MET inhibitors have limited effect on renal function, although reversible increases in creatinine levels were observed in 24% of patients treated with capmatinib [12] and 27% of those treated with tepotinib [14].

In clinical trials, MET inhibitors, such as crizotinib, capmatinib, and tepotinib, have been associated with a high incidence of peripheral edema [5, 10]. The incidence of cancer drug-induced peripheral edema is often difficult to ascertain. There is no specific definition of peripheral edema in the latest version of the Common Terminology Criteria for Adverse Events (CTCAE), although there is a definition of edema limb [20]. Clinical trials may not all use the same terms, or they may group several CTCAE events together, for example, as 'edema'. Furthermore, peripheral edema is common in cancer patients, and may not necessarily be drug related [21], and patients may have other conditions with symptoms similar to peripheral edema [22]. Consequently, peripheral edema may be misdiagnosed or under-recognized.

The aim of this review is to describe the incidence of peripheral edema in patients treated with small molecule MET inhibitors, the potential molecular mechanism of this toxicity, and ways in which to manage it. We also highlight the need to accurately define peripheral edema in order to initiate early management and avoid negative effects on patients' quality of life.

2 Methods

Literature searches of PubMed and SCOPUS (from January 2000 to June 2022) were performed using various relevant search terms ('peripheral edema', 'non-small cell lung cancer', 'MET inhibitor', 'capmatinib', 'tepotinib', 'crizotinib', 'savolitinib', 'supportive care', 'management' and 'adverse events') to identify English-language clinical data on the incidence, mechanism, and management of peripheral edema associated with the use of small molecule MET inhibitors. The reference lists of identified studies were screened for additional information. The data from the literature search were used to supplement the authors' clinical experience in using MET inhibitors and in managing associated peripheral edema.

3 Incidence of Peripheral Edema in Clinical Trials

The incidence of peripheral edema associated with MET inhibitors in clinical trials is summarized in Table 1. In Phase I studies of capmatinib, peripheral edema was one of the most common adverse events (AEs). In an open-label Phase I study in patients with MET-positive solid tumors, peripheral edema was one of the most commonly reported AEs with capmatinib monotherapy (expansion dose: 400 mg twice daily [tablets] or 600 mg twice daily [capsules]), occurring in 39% of patients in the dose-expansion phase, and was suspected to be treatment related in 26% of patients [23]. Similarly, the incidence of peripheral edema of any grade was 20.5% in a Japanese open-label, Phase I dose-escalation and -expansion trial of capmatinib ($n = 44$; dose range 100 mg once daily to 600 mg twice daily) in patients with advanced solid tumors (not selected based on *MET* dysregulation status) [24]. In the Phase II GEOMETRY mono-1 study in 364 patients with *MET*-dysregulated advanced NSCLC, peripheral edema was the most common AE with capmatinib (400 mg tablets, twice daily), developing in 51% of patients (treatment-related in 43%), and resulted in permanent treatment discontinuation in six patients [12]. Although the majority of cases were mild or moderate in severity, 9% of patients had Grade 3 or 4 peripheral edema [12]. In a preplanned analysis of Japanese patients enrolled in GEOMETRY mono-1 ($n = 45$), peripheral edema was the second most frequent treatment-related AE, occurring in 31% of patients [25]. More recently, real-world data from an international early access program study of capmatinib in

Table 1 Incidence of peripheral edema in clinical trials of mesenchymal-epithelial transition (MET) inhibitors

MET inhibitor	Type of adverse event	Incidence of peripheral edema
Capmatinib		
Phase I study (NCT01324479) [23]		
Dose-escalation part	Any	40%
	Treatment-related	21%
Dose-expansion part	Any	39%
	Treatment-related	26%
Phase I Japanese study (NCT01546428) [24]	Any	21%
GEOMETRY mono-1 Phase II study (NCT02414139) [12]	Any	51%
	Treatment-related	43%
GEOMETRY mono-1: Japanese patients [25]	Treatment-related	31%
Early access program [26]	Treatment-related	48%
Crizotinib		
PROFILE 1001 Phase I study (NCT00585195) [27]	Treatment-related	51%[a]
METROS Phase II study (NCT02499614) [28]	Treatment-related	31% (*MET*-deregulated) 50% (*ROS1*-rearranged)
Tepotinib		
Phase I study (NCT01014936) [29]	Treatment-related	26%
VISION Phase II study (NCT02864992) [14]	Treatment-related	63%
VISION Phase II study: Japanese patients [15]	Treatment-related	47%
Savolitinib		
Phase I study (NCT01773018) [30]	Any	31%
	Treatment-related	23%
Phase Ia/Ib study (NCT0198555) [31]	Treatment-related	21%
Phase II study (NCT02897479) [32]	Treatment-related	54%

[a]Reported as a clustered term (i.e., edema) according to the Common Terminology Criteria for Adverse Events, version 3.0

81 patients with advanced *METex14*-mutated NSCLC found that peripheral edema was the most common treatment-related AE of any grade (48%) or Grade ≥ 3 (13%) [26].

The MET inhibitor crizotinib has also been associated with peripheral edema. In the Phase I PROFILE 1001 study of crizotinib in patients with *METex14*-altered NSCLC ($n = 69$), the most common treatment-related AE was edema (51%; reported as a clustered term according to CTCAE, version 3.0) [27]. The Phase II METROS study in patients with *MET*-deregulated or *ROS1*-rearranged NSCLC also showed a high incidence of peripheral edema with crizotinib, with 31% of patients with *MET*-deregulated NSCLC having treatment-related peripheral edema [28].

Peripheral edema was the one of most common treatment-related AEs in a Phase I study of tepotinib in patients with advanced solid tumors ($n = 149$), reported in 26% of patients receiving micronized tepotinib capsules (300–1200 mg once daily for 3 weeks) [29]. In the Phase II VISION study of tepotinib in patients with *METex14* NSCLC, peripheral edema was the most common treatment-related AE, reported in 63% of patients and leading to a dose reduction or interruption in 16 and 18%, respectively [14]. In a Japanese subset analysis of the VISION study, peripheral edema was the second most common treatment-related AE, reported by 47% of patients [15]. Although common, peripheral edema was manageable and did not lead to permanent treatment discontinuation in any of these patients [15].

Early clinical trials of savolitinib have shown that this selective MET inhibitor is also associated with a high incidence of peripheral edema. Open-label, Phase I studies in patients with advanced solid tumors reported treatment-related peripheral edema in 21–23% of patients [30, 31]. In a Phase II Chinese study in patients with *METex14* skipping NSCLC ($n = 70$), peripheral edema was the most common treatment-related AE of any grade (54%) or Grade ≥ 3 (9%) with savolitinib (400 or 600 mg once daily) [32].

4 Potential Mechanisms of Edema with MET Inhibitors

Peripheral edema is the result of a perturbation in fluid homeostasis between the vascular, lymphatic, and interstitial spaces [22]. Many drugs can cause peripheral edema via different mechanisms that can combine synergistically [33]. Potential mechanisms include precapillary arteriolar vasodilation (vasodilatory edema), sodium and/or water retention (renal edema), lymphatic insufficiency (lymphedema), and increased capillary permeability (permeability edema).

Despite the high incidence of peripheral edema in patients receiving MET inhibitors, there is limited information in the literature about the mechanism involved. Mesenchymal-epithelial transition is a proto-oncogenic gene whose gene product naturally binds to hepatocyte growth factor (HGF), controlling a wide range of signaling pathways, including proliferation, motility, migration, and invasion [5]. Thus, MET dysregulation, due to an ongoing oncogenic process, is associated with the development and progression of several types of cancer, including NSCLC [5, 34, 35]. Hepatocyte growth factor is a powerful pro-angiogenic protein that also inhibits vascular permeability and inflammation and attenuates thrombin-induced endothelial permeability [35, 36]. The perturbation of the HGF/MET signaling by the inhibition of MET could disrupt the permeability balance in the vascular endothelium [36], thus, promoting edema development. A study in healthy volunteers treated with capmatinib showed that the drug was largely distributed to the peripheral tissues [37], which could contribute to the development of peripheral edema in patients treated with MET inhibitors.

Another potential mechanism by which MET inhibitors may cause edema is through effects on renal function. The Phase I dose-escalation study and the GEOMETRY mono-1 study of capmatinib [12, 23, 24] and the Phase I study and the VISION study of tepotinib [14, 29] showed elevated serum creatinine levels during treatment, an effect that seemed to be dose dependent. However, the number of participants per dose group in the capmatinib dose-escalation study was too small to draw conclusions [24].

Serum creatinine is cleared by active tubular secretion and renal transporters, such as multidrug and toxic extrusion (MATE) and organic anion transporters, in addition to renal glomerular filtration [38]. The increase in creatinine levels observed during capmatinib or tepotinib treatment could be due to the inhibition of the MATE proteins 1 and 2-K, since both agents are thought to inhibit these renal transporters [6, 12]. However, these changes in serum creatinine do not appear to be accompanied by a clinically meaningful impairment in renal function, so this is unlikely to be the primary mechanism of edema development.

There is some clinical evidence to suggest that the mechanism of MET inhibitor-induced peripheral edema is different from that of VEGF inhibitor-induced edema. In contrast to HGF-related inhibition of vascular permeability, VEGF promotes endothelial permeability [35, 39]. Therefore, although both MET inhibitors and VEGF inhibitors disrupt the homeostatic balance, VEGF inhibitors affect a wider range of the inhibitory and stimulatory factors controlling vascular permeability in the peripheral circulation [40].

5 Diagnosis and Management of MET Inhibitor-Induced Edema

A study of edema in advanced cancer revealed that patients with edema had a high symptom burden, including pain, limb swelling, heaviness, paresthesia, and concomitant overall impairment of well-being [41]. Although intervention is not always necessary, peripheral edema may become an issue if left unmanaged, especially for older and/or frail patients who are more susceptible to toxicities and are more likely to have other comorbidities. In addition, peripheral edema can necessitate cancer treatment dose interruption or reduction, and sometimes treatment discontinuation [12].

Before initiating MET inhibitor treatment, patients should be advised of the likelihood of edema development and assessed for any underlying conditions that might predispose them to developing edema [21]. Edema is common in patients with cancer [21], and may not necessarily be caused by their treatment. Thus, it is important to investigate the underlying cause, as their cancer treatment might exacerbate an existing comorbidity [21]. Physicians also need to distinguish between lymphedema (secondary lymphedema) and peripheral edema, both of which can be caused by cancer treatment [22, 42]. While peripheral edema caused by MET inhibitors is systemic, reversible, and often does not require treatment (as high-grade edema is rare) [21], lymphedema is local, chronic, and requires palliative care [43]; MET inhibitor treatment has not been associated with lymphedema [12, 14, 28, 32]. A careful history of the timing of the peripheral edema, and whether it changes with body position, is essential, and may provide clues to the underlying cause [44]. Lower extremity examination, tests for renal, hepatic, or thyroid function, or markers of heart failure, such as B-type natriuretic peptide, may also help to elucidate the underlying cause [44].

Since the exact mechanism by which MET inhibitors induce edema is unclear, management is empiric [21]. Multiple approaches may be used, including compression stockings, and lifestyle and dietary changes (Table 2). In clinical practice, diuretic therapy is administered as first-line

Table 2 Possible approaches to the management of cancer therapy-induced peripheral edema

Management [45, 46]	Comments
Compression stockings or bandaging	
Massage affected area	e.g., lymphatic massage
Limb elevation	Several times a day (while sitting) and while sleeping
Exercise	
Dietary changes: reduce salt intake, eat a balanced diet, consider consulting a dietitian (oncology certified)	
Diuretic treatment	Consider use if edema is interfering with quality of life
Cancer treatment dose reduction, interruption, or withdrawal	Consider for persistent or severe peripheral edema

Table 3 Severity grading of peripheral edema (CTCAE term: edema limb) and recommended capmatinib dosage modification

Grade[a]	CTCAE v5.0 definition [20]	Recommended dose modification [1]
1	5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	No modification
2	> 10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	No modification. If intolerable, consider stopping capmatinib treatment until edema is improved, then resume capmatinib at a reduced dose
3	> 30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL	Stop capmatinib treatment until edema is improved, then resume capmatinib at a reduced dose

[a]There is no Grade 4 category for edema limb. Adapted with permission from Goodwin et al. [45]

ADL activities of daily living, *CTCAE* Common Terminology Criteria for Adverse Events

treatment and patients are advised to raise their legs to reduce lower limb edema. If edema subsequently persists or interferes with the activities of daily life, dose adjustment or interruption of MET inhibitor therapy should be considered (Table 3). Patients should also be advised about appropriate skin and foot care to prevent secondary cellulitis [44].

In clinical trials of MET inhibitors, most cases of peripheral edema were mild-to-moderate in severity (refer to Table 3 for grading criteria). In a post hoc analysis of the GEOMETRY mono-1 study, 58% of the patients who developed peripheral edema during capmatinib treatment required additional therapy [45]. Of these, 81% were prescribed diuretics and 11% used compression stockings. A report on the experiences of two US-based institutions involved in this study found that peripheral edema sometimes occurred within the first 3 weeks of treatment, was generally mild, and was usually managed with one or a combination of the following: compression stockings, elevation, and diuretics [45]. One of these institutions (Massachusetts General Hospital) referred patients with peripheral edema to a lymphedema clinic, where symptoms were managed with lymphatic massage, stretching exercises, compression stockings (prescription grade), or a combination of these treatments. In some patients, these physiotherapeutic methods improved lower edema; in those patients for whom bilateral lower edema did not resolve, discontinuation of capmatinib resulted in a resolution of symptoms [45]. The authors' clinical experience is that such measures are often only temporarily effective, and that discontinuation of MET inhibitor therapy is frequently the only approach to completely resolving drug-induced peripheral edema.

Given the reasonably high incidence of peripheral edema in patients receiving MET inhibitors, the above-mentioned lymphedema clinic [45] recommends that limb volume is measured before initiating treatment, and again if edema symptoms develop. It further recommends that a volume change of 5–10% indicates the patient should be closely monitored, while a > 10% change indicates compression therapy should be initiated.

6 Conclusions

Small molecule MET inhibitors have proven efficacy and acceptable tolerability in the treatment of patients with *METex14*-mutant NSCLC. Despite the high incidence of

peripheral edema in patients treated with MET inhibitors, most cases are mild-to-moderate in severity, and only a small percentage of patients require treatment interruption or discontinuation. Early diagnosis and management of peripheral edema, as well as patient information and education, are vital to decrease the clinical burden associated with peripheral edema and to reinforce treatment adherence. In addition, determining the etiology of the edema is important, as MET inhibitor therapy may be only one of several potential causes of edema in a patient with cancer.

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