Review Article

Comprehensive management of MET tyrosine kinase inhibitor-induced peripheral edema in patients with *MET*-altered non-small-cell lung cancer: a narrative review

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Background and Objective: The mesenchymal-epithelial transition factor (MET) proto-oncogene plays an important role in the development of non-small cell lung cancer (NSCLC). MET tyrosine kinase inhibitors (TKIs) have shown promising antitumor activity in patients with NSCLC harboring MET alterations. Peripheral edema (PE), the most common adverse event of MET TKIs, has received increasing attention from clinicians. The aim of this review is to describe the incidence, potential molecular mechanisms, diagnosis, and management of MET TKI-induced PE, to increase the recognition and standardize the management of PE.

Methods: We conducted a comprehensive literature search across PubMed, Wanfang Med Online, China National Knowledge Infrastructure (CNKI), and the oncology conferences websites for related studies published between 2000 and 2023. Of the 491 titles screened, we identified 80 research articles fitting the inclusion criteria and a comprehensive literature review was conducted. The review incorporated patient conditions, comprehensive examinations, and clinical experiences to propose a standardized management framework.

Key Content and Findings: The review focused on the incidence of MET TKI-induced PE, its potential molecular mechanisms, diagnostic criteria, and management strategies. The etiology of edema is complex in cancer patients; however, it may involve treatment-related increases in vascular permeability, impacts on renal function, and hypoalbuminemia. Based on the literature review, a diagnostic and comprehensive management approach for MET TKI-induced PE is proposed, which includes prevention strategies, non-pharmacological treatments, pharmacological interventions, and dosage adjustments related to MET TKIs.

Conclusions: In this review, we propose a diagnostic and comprehensive management approach for MET TKI-induced PE. By standardizing management, clinicians can enhance patient care for those treated with MET TKIs, facilitating earlier detection of PE, reducing patient suffering, and improving treatment adherence and outcomes.

Keywords: Non-small cell lung cancer (NSCLC); MET tyrosine kinase inhibitor (MET TKI); adverse event (AE); peripheral edema (PE); safety management

Submitted Sep 24, 2024. Accepted for publication Jan 24, 2025. Published online Apr 17, 2025.
doi: 10.21037/tlcr-24-866
View this article at: https://dx.doi.org/10.21037/tlcr-24-866

Introduction

Mesenchymal-epithelial transition factor (*MET*), also known as c-*MET*, is a proto-oncogene located on chromosome 7q21-q31 that encodes transmembrane receptor tyrosine kinase normally expressed on epithelial cells. The hepatocyte growth factor (HGF)/c-MET pathway is essential in several cell vital processes, including carcinogenesis and tumor progression. In non-small cell lung cancer (NSCLC), multiple *MET* alterations have been discovered, among which *MET* exon 14 skipping (*MET*ex14), *MET*-amplified (*MET*amp) and MET protein overexpression after epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance have attracted increased attention. These alterations may aberrantly activate MET oncogenic signaling pathway and promote tumor development (1). MET TKI has demonstrated the dramatic efficacy in patients with *MET*-altered NSCLCs (1).

MET TKIs are classified into three types: type I inhibitors compete with adenosine 5'-triphosphate (ATP) for the ATP binding pocket of the active form of MET, which can be further subdivided into non-selective type Ia inhibitors (e.g., crizotinib) and selective type Ib inhibitors (e.g., capmatinib, tepotinib, savolitinib, vebreltinib and glumetinib); type II inhibitors (e.g., cabozantinib), also ATP competitors, bind to the inactive conformation of MET; type III inhibitors are non-ATP competitors. Currently, only type Ib MET TKIs are approved for advanced NSCLC (aNSCLC) patients with *MET*ex14 (2).

Since the approval of tepotinib in Japan in March 2020, multiple MET TKIs have been approved worldwide, especially in China, where four MET TKIs have been approved. As MET TKI become widely used in clinical practice, peripheral edema (PE), one of the most common adverse events (AEs) reported in clinical trials, has attracted growing attention from clinicians and patients (3). Because PE is common in cancer patients and not necessarily caused by antitumor drugs, antitumor drug-related PE is usually difficult to define and is highly susceptible to misdiagnosis or under-recognition. In this review, by summarizing the relevant literature, we describe the incidence, potential pathophysiological mechanism, diagnosis, and comprehensive management of MET TKI-induced PE to improve recognition and standardize the management of PE. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-866/rc).

Methods

Literature search was conducted on PubMed, Wanfang Med Online, China National Knowledge Infrastructure (CNKI), and the official website of American Society of Clinical Oncology (ASCO), World Conference on Lung Cancer (WCLC), American Association for Cancer Research (AACR), Chinese Society of Clinical Oncology (CSCO) and European Society for Medical Oncology (ESMO) for publications from January 1, 2000, to December 31, 2023. Various relevant search terms were used, including non-small cell lung cancer, MET inhibitor, crizotinib, capmatinib, INC280, savolitinib, volitinib, AZD6094, HMPL-504, tepotinib, gumarontinib, glumetinib, SCC244, bozitinib, vebreltinib, APL-101, PLB-1001, CBT-101, supportive care, treatment, management, AEs and edema. The literature was limited to systematic reviews, meta-analysis, clinical studies and conference abstracts. The reference lists of identified studies were screened and reviewed (*Table 1*, *Figure 1*). Based on the evidence from published studies and the authors' clinical experience, we performed this literature review of the comprehensive management MET TKI-induced PE in patients with *MET*-altered NSCLC.

Incidence of PE in clinical trials

The exploration of MET TKI in *MET*-altered NSCLC mainly involves patients receiving MET TKI monotherapy or combination therapy with EGFR TKI. The results of the MET TKI monotherapy trials demonstrate that PE is one of the most common AEs, with an incidence of 10–74%, mostly mild-to-moderate (grade 1/2). Severe PE (grade ≥3) can occur in up to 13% of patients. The incidence of PE caused by type Ia inhibitors is relatively low, but type Ia inhibitors have not yet been approved globally for treating *MET*-altered NSCLC. Among patients treated with MET TKI plus EGFR TKI, the incidence of PE is 16% to 63.3% (*Table 2*). Interestingly, the incidence of PE in patients receiving tepotinib combined with EGFR TKI was lower than that in patients receiving tepotinib monotherapy, which may be related to the younger age of patients enrolled in the combination group (42), but the exact reasons need to be further explored.

MET TKI monotherapy

In the phase I dose-escalation trial of tepotinib, PE was

Table 1 The search strategy summary

Items	Specification
Date of search	January 5, 2024 to March 10, 2024
Databases and other sources searched	PubMed, Wanfang Med Online, CNKI, ASCO, WCLC, AACR, CSCO and ESMO
Search terms used	Non-small cell lung cancer, MET inhibitor, crizotinib, capmatinib, INC280, savolitinib, volitinib, AZD6094, HMPL-504, tepotinib, gumarontinib, glumetinib, SCC244, bozitinib, vebreltinib, APL-101, PLB-1001, CBT-101, supportive care, treatment, management, adverse events and edema
Timeframe	January 1, 2000 to December 31, 2023
Inclusion and exclusion criteria	The literature was limited to systematic reviews, meta-analysis, clinical studies, and conference abstracts. There was no restriction on the language
Selection process	The databases were searched by an experienced researcher (S.Y.M.L.). Two authors (J.X.L. and H.S.) individually screened the available studies. Following this, full texts of the selected articles were retrieved and assessed for eligibility. Any differences of opinion were settled by consensus or referral to other review author (Y.L.W.)

AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology; CNKI, China National Knowledge Infrastructure; ESMO, European Society for Medical Oncology; WCLC, World Conference on Lung Cancer.

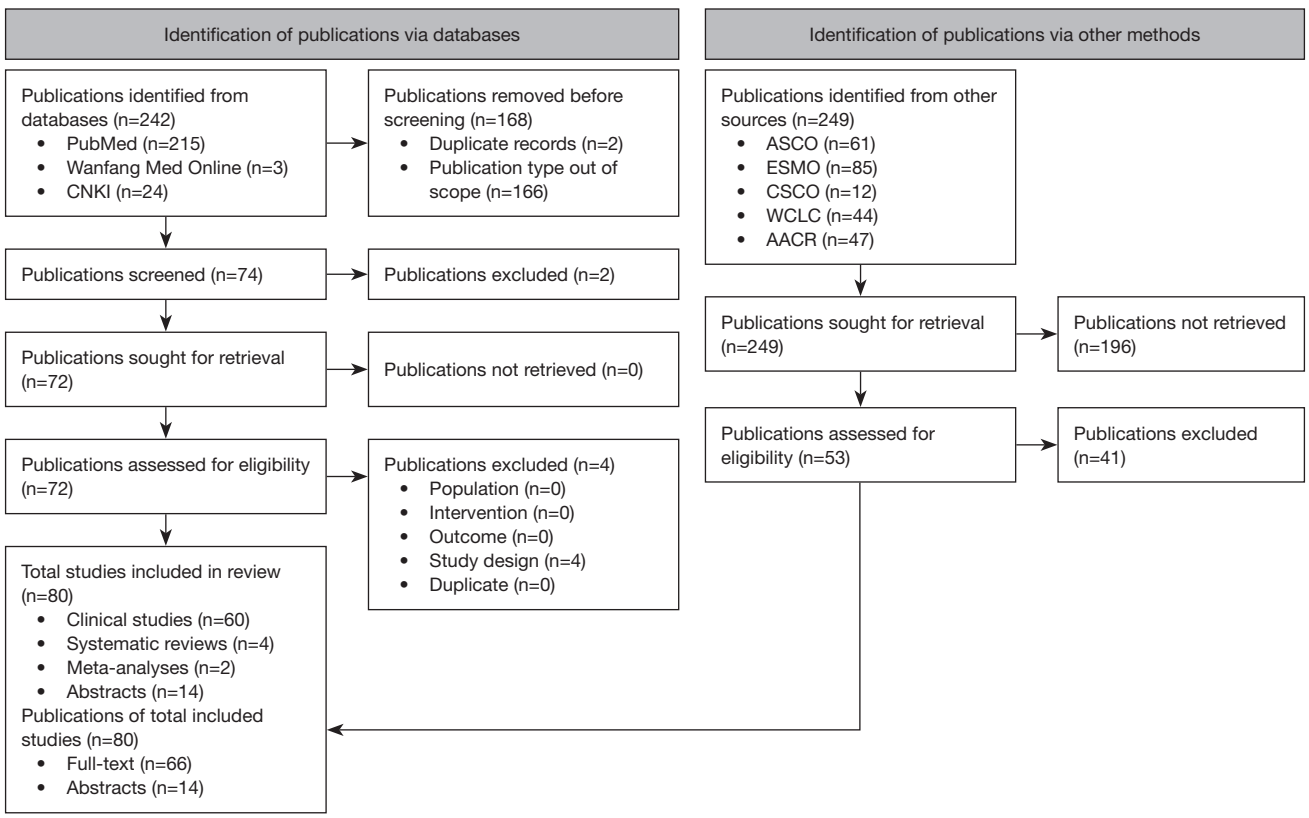

Figure 1 Diagram of literature searches conducted in January 2024. AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; CSCO, Chinese Society of Clinical Oncology; CNKI, China National Knowledge Infrastructure; ESMO, European Society for Medical Oncology; WCLC, World Conference on Lung Cancer.

Table 2 Incidence of MET TKI-induced PE in patients with NSCLC

Regimen	Trial name or number	Phase	Population	Sample size	CTCAE	Any grade, n (%)	Grade ≥3, n (%)
MET TKI monotherapy							
Tepotinib	NCT01014936 (4)	I	*MET*amp, *MET* overexpression	42[§]	CTCAE 4.0	11 (26.2)	1 (2.4)
	VISION (cohort A + C) (5)	II	*MET*ex14	313	CTCAE 4.03	210 (67.1)	35 (11.2)
	VISION (cohort B) (6)	II	*MET*amp	24	CTCAE 4.03	12 (50.0)	2 (8.3)
	VISION (Asian patients) (7)	II	*MET*ex14	106	CTCAE 4.03	66 (62.3)	8 (7.5)
	VISION (Chinese subset) (8)	II	*MET*ex14	30	CTCAE 4.03	21 (70.0)	1 (3.3)
	VISION (Japanese subset) (9)	II	*MET*ex14	19	CTCAE 4.03	9 (47.4)	1 (5.3)
Capmatinib	NCT01324479 (10)	I (dose escalation)	*MET*amp, *MET* overexpression	38[#]	CTCAE 4.0	8 (21.1)	1 (2.6)
	NCT01324479 (11)	I (NSCLC expansion cohort)	*MET*ex14, *MET*amp, *MET* overexpression	55	CTCAE 4.0	18 (32.7)	2 (3.6)
	NCT01546428 (12)	I	*MET*amp, *MET* overexpression, *MET* mutation	44[£]	CTCAE 4.0	9 (20.5)	1 (2.3)
	GEOMETRY mono-1 (13)	II	*MET*ex14, *MET*amp	373	CTCAE 4.03	172 (46.1)	34 (9.1)
	GEOMETRY mono-1 (Japanese subset) (14)	II	*MET*ex14, *MET*amp	45	CTCAE 4.03	14 (31.1)	3 (6.7)
	GeoMETry-C (15)	II	*MET*ex14	15	CTCAE 5.0	4 (26.7)	0
	GeoMETry-III (16)	III	*MET*ex14	15[ƒ]	CTCAE 5.0	7 (46.7)	0
	RECAP (17)	RWS	*MET*ex14	81	CTCAE 5.0	39 (48.1)	11 (13.6)
	IFCT-2104 CapmMATU (18)	RWS	*MET*ex14	146	–	–	12 (8.2)
Savolitinib	NCT01773018 (19)	I	*MET* unknown, *MET*amp	48[†]	CTCAE 3.0	11 (22.9)	4 (8.3)
	NCT0198555 (20)	Ia/Ib	*MET* unknown, *MET*ex14, *MET*amp, *MET* overexpression	85[‡]	CTCAE 4.3.1	18 (21.2)	0
	NCT02897479 (21)	II	*MET*ex14	70	CTCAE 4.03	39 (55.7)	6 (8.6)
	NCT04923945 (22)	IIIb	*MET*ex14	87	–	52 (59.8)	6 (6.9)
Glumetinib	GLORY (23)	II	*MET*ex14	84	CTCAE 5.0	62 (73.8)	–
Vebreltinib	NCT02896231 (24)	I	*MET*ex14, *MET*amp, *MET* overexpression	37	–	12 (32.4)	–
	NCT03175224 (25)	I/II	*MET*ex14, *MET*amp, *MET* overexpression	17*	CTCAE 4.03	4 (23.5)	0
	KUNPENG (26)	II	*MET*ex14, *MET*amp	113		64 (56.6)	8 (7.1)
Crizotinib	PROFILE 1001 (27,28)	I	*MET*ex14	69	CTCAE 3.0	35 (50.7)[¶]	1 (1.4)[¶]
		I	*MET*amp	38	CTCAE 3.0	12 (31.6)[¶]	0[¶]
	METROS (29)	II	*MET*ex14, *MET*amp	26	CTCAE 4.0	8 (30.8)	0
	AcSé (30)	II	*MET* mutation, *MET*amp[&]	53	CTCAE 4.0	38 (71.7)[¶]	3 (5.7)[¶]
Ensartinib	ChiCTR2100045803 (31)	II	*MET*ex14	29	CTCAE 5.0	3 (10.3)	0

Table 2 (*continued*)

Table 2 (*continued*)

Regimen	Trial name or number	Phase	Population	Sample size	CTCAE	Any grade, n (%)	Grade ≥3, n (%)
MET TKI + EGFR TKI							
Tepotinib + gefitinib	INSIGHT (32)	Ib/II	*MET*amp, *MET* overexpression	31	CTCAE 4.0	9 (29.0)	2 (6.5)
Tepotinib + osimertinib	INSIGHT2 (33)	II	*MET*amp	128	CTCAE 5.0	52 (40.6)	6 (4.7)
Capmatinib + gefitinib	NCT01610336 (34)	Ib/II	*MET*amp, *MET* overexpression	161	CTCAE 4.0	36 (22.4)	–
Capmatinib + erlotinib	NCT01911507 (35)	I/II	*MET*ex14, *MET*amp, *MET* overexpression	35	CTCAE 4.0	13 (37.1)	2 (5.7)
Savolitinib + gefitinib	NCT02374645 (36)	I	Not tested, *MET*amp	57	CTCAE 4.03	9 (15.8)	0
Savolitinib + osimertinib	TATTON cohort B (37)	Ib	*MET*amp, *MET* overexpression	138	CTCAE 4.0	49 (35.5)	–
	TATTON cohort D (37)	Ib	*MET*amp, *MET* overexpression	42	CTCAE 4.0	13 (31.0)	–
	TATTON cohort C (38)	Ib	*MET*amp, *MET* overexpression	12	CTCAE 4.0	4 (33.3)	0
	SAVANNAH (39)	II	*MET*amp, *MET* overexpression	196	CTCAE 5.0	–	–
	ORCHARD (40)	II	*MET*amp, *MET*ex14	20	CTCAE 5.0	–	0
Glumetinib + osimertinib	NCT04338243 (41)	Ib/II	*MET*amp, *MET* overexpression	30	–	19 (63.3)[¶]	3 (10.0)[¶]

[§], patients with solid tumors treated with 500 mg tepotinib once daily; [#], including 1 patient with NSCLC; [£], including 15 patients with NSCLC; [ʃ], 22 patients were enrolled and 15 patients received capmatinib, 7 patients received docetaxel; [†], the total number of patients, including 3 NSCLC patients; [‡], a total of 85 patients were enrolled in this phase Ia/Ib study, of which 21 patients in the dose-escalation phase had undetectable *MET* and 65 patients in the dose-expansion phase had *MET*-altered, including 25 patients with NSCLC; *, the study enrolled 17 patients with solid tumors with *MET*-altered, including 8 patients with *MET*amp, 7 had c-*MET* overexpression, 1 had non-lung cancer c-*MET*ex14 and 1 had a c-*MET* kinase domain mutation (H1094Y); [¶], the incidence of edema, not PE; [&], including 25 patients with *MET*amp and 28 patients with MET mutations, including 25 patients with *MET*ex14. CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition factor; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; PE, peripheral edema; RWS, real world study; TKI, tyrosine kinase inhibitor.

one of most common treatment-related AEs (TRAEs) in patients with advanced solid tumors. Among 42 patients who received tepotinib with a recommended phase II dose (RP2D), 26.2% and 2.4% had any grade and grade ≥3 PE, respectively (4). In VISION trial of tepotinib in patients with *MET*-altered NSCLC, PE was the most common TRAE, reported in 67.1% of patients with *MET*ex14, and 11.2% of patients had grade ≥3 PE (5). In a pool analysis of 228 patients with advanced solid tumors treated with tepotinib, including 81 Asian patients, PE occurred in 33.8% of patients overall and in 24.7% of Asian patients (grade ≥3: 3.5% and 0%, respectively) (43). PE was mostly grade 1/2 and the incidence was essentially the same irrespective of patient characteristics (44).

PE was the most frequently reported AE in phase I clinical trials of capmatinib (also known as INC280) for advanced solid tumors (10-12). This result was replicated in GEOMETRY mono-1 study and GeoMETry-III trial (13,16). In the real-world RECAP study of capmatinib, PE was also the most common TRAE in patients with *MET*ex14 aNSCLC, 13% of patients had grade 3/4 PE and led to dose reduction in 23 patients (28%), treatment interruption in 10 patients (12%), and treatment discontinuation in 6 patients (7%) (17). In another real-world IFCT-2104 CapmATU

study of capmatinib for *MET*ex14 NSCLC patients, PE was the most common TRAE of grade ≥3, occurring in 8.2% of patients, and 18 patients were discontinued due to toxicity, with edema accounting for 66.7% of the patients (18).

In two phase I trials of savolitinib (also known as volitinib, AZD6094 or HMPL-504) in patients with advanced solid tumors, treatment-related PE (TRPE) was reported in 23% and 21% of patients (19,20). In the phase II and phase IIIb confirmatory trials of savolitinib for *MET*ex14 aNSCLC, PE occurred in 56% and 59.8% of patients respectively (21,22). In the pivotal phase II global trial of glumetinib (also known as gumarontinib or SCC244) in patients with *MET*ex14 aNSCLC, the most common TRAE was edema (80%), with 62 (74%) patients having PE (23). In two studies of vebreltinib (also known as bozitinib, APL-101, PLB-1001 or CBT-101) for *MET*-altered aNSCLC and solid tumors, TRPE was observed in 32.4% and 24% of patients (24,25). KUNPENG trial was a pivotal phase II study of vebreltinib in patients with *MET*-altered aNSCLC, and PE was the most common TRAE of any grade (56.6%) and grade ≥3 (7.1%) (26).

For crizotinib and ensartinib, only preliminary explorations have been conducted. In PROFILE 1001 trial for *MET*ex14 NSCLCs (27,28), METROS trial for *MET*ex14 or *MET*amp patients (29), edema occurred in 31% of patients, and AcSé trial for *MET*amp or *MET*-mutated patients demonstrated the similar safety profile of crizotinib (30). In the study of ensartinib for *MET*ex14 NSCLC, 10% of patients had TRPE (31).

MET TKI combined with EGFR TKI

*MET*amp is an important mechanism of EGFR TKI resistance in *EGFR* mutation (*EGFR*m) NSCLC. MET TKI plus EGFR TKI is an effective therapy to overcoming MET mediated resistance.

The efficacy and safety of tepotinib plus gefitinib or osimertinib of *EGFR*m NSCLC patients with *MET*amp were explored in INSIGHT (32) and INSIGHT2 studies (33). PE was one of the most common TRAEs in both studies, occurring in 29% and 40.6% of the patients respectively (grade ≥3: 6.5% and 4.7%).

In a phase Ib/II study of capmatinib plus gefitinib in patients with *EGFR*m, *MET*amp NSCLC after progression on EGFR TKIs, the incidence of TRPE was 22% (34). In another study of capmatinib plus erlotinib for *MET*-altered aNSCLC, the incidence of TRPE was 37% (35).

Currently, several studies on savolitinib plus EGFR TKI have been published. In a phase Ib study of savolitinib plus gefitinib, TRPE occurred in 16% of the patients (36). The efficacy and safety of savolitinib in combination with osimertinib in patients with aNSCLC have been explored in the TATTON, SAVANNAH, and ORCHARD trials. In cohort B, cohort C, and cohort D of the TATTON study, the incidence of TRPE was similar (31–36%) and rarely for grade ≥3 (0–3%) (37,38). This result was subsequently validated in the SAVANNAH study (39) and ORCHARD study (40). Interestingly, in cohort B and cohort D of the TATTON study, five patients experienced osimertinib-related PEs, but these AEs were not reported in the previous AURA3 study (45), FLAURA study (46), and ADAURA study (47). Therefore, the role of osimertinib in the development of PE is unclear. So far, only a phase Ib/II study of glumetinib plus osimertinib has been published, where edema was the most common TRAE, with a high incidence of grade ≥3 of 10% of patients (41).

Factors and potential mechanisms of MET TKI-induced edema

PE is the result of a perturbation in fluid homeostasis among the vascular, lymphatic, and interstitial spaces. Many drugs can cause PE via multiple synergistic mechanisms, the main ones being: increased capillary permeability (permeability edema), sodium/water retention (renal edema), lymphatic insufficiency (lymphedema) and precapillary arteriolar vasodilation (vasodilatory edema) (48). Despite the high incidence of MET TKI-induced PE, the exact mechanism has not been elucidated, and may be related to the following mechanisms.

Increased capillary permeability

MET TKI-induced edema is most likely due to increased vascular permeability. In physiological conditions, HGF in the vascular endothelium helps to protect vascular endothelial cells from vascular endothelial growth factor (VEGF)-induced endothelial cell hyper-permeability. MET TKI action on the HGF/MET signaling pathway may disrupt this balance, leading to increased endothelial cell permeability, as well as promoting edema development (48). A study in healthy volunteers treated with capmatinib demonstrated that the drug was largely distributed to the peripheral tissues, which could contribute to the development of PE (49). Alao MET inhibition could reduce the proteasomal degradation of VEGFR2 and increases its

expression, leading to increased permeability (44,50).

Effect on renal function

Another potential mechanism of MET TKI-induced edema is through effects on renal function. Elevated serum creatinine levels during treatment have been observed in several clinical trials of MET TKIs, and the effect appears to be dose-dependent (3,5). However, serum creatinine level is influenced by a number of factors, in addition to glomerular filtration, and it can also be affected by active renal tubular secretion and clearance of renal transport proteins, such as multidrug and toxic extrusion (MATE) transporter proteins and organic anion transporter (51). The increase in creatinine observed during capmatinib or tepotinib treatment could be due to the inhibition of the MATE proteins 1 and 2-K (3,52). Therefore, elevated serum creatinine is not necessarily a marker of impaired renal function, and data from several studies also demonstrated that MET TKI-induced elevated serum creatinine does not seem to be accompanied by clinically meaningful renal impairment (53,54). In the GLORY study of glumetinib, 13 patients with elevated serum creatinine developed edema, yet 81% of patients with edema did not have elevated serum creatinine, suggesting that elevated serum creatinine may not be the primary mechanism of edema, but the effects on renal function may exacerbated the development of edema in some patients (23).

Hypoalbuminemia

Hypoalbuminemia is another common AE during MET TKI treatment and may be an independent risk factor for edema pathogenesis (55). The mechanism of MET TKI-related hypoalbuminemia is not fully understood but may be due to that MET TKI blocks the HGF pathway in albumin production in hepatocyte (23). To date, there is no clear evidence that MET TKI-induced hypoalbuminemia is secondary to hepatic or renal impairment. Studies have demonstrated that the serum albumin level is correlated with the risk and severity of edema, and there is also a significant positive trend between the magnitude of serum albumin decline and the severity of edema, with more severe edema observed in patients with the greatest reduction in serum albumin (55).

The exact mechanism of MET TKI-induced PE is not well defined and may be related to one or more potential mechanisms. In cancer patients, the mechanisms of edema are more complex and may be the result of synergistic effect of multiple etiologies and mechanisms.

Clinical manifestations and diagnosis of MET TKI-induced PE

Clinical manifestations

MET TKI-induced edema is predominantly PE, which can manifest as edema of peripheral tissues, such as the face and extremities. Swollen extremities are the most bothersome symptom for patients, followed by pain and weight gain, and some patients may also have sensory abnormalities and skin infections. Patients with severe PE are more likely to have pain and skin lesions than those with mild-to-moderate PE (56).

MET TKI-induced edema may not be immediately symptomatic, and the time to onset and time to remission may differ across agents. In the GEOMETRY mono-1 study of capmatinib, the median time to first grade ≥2 PE was 3.5 months, and the median time to first grade 3/4 PE was 5.0 months (57). Crizotinib-induced edema occurred at approximately 2 months, and the median time from therapy initiation to the onset of edema with savolitinib was 50 days (58,59). For tepotinib, the median time to first onset of edema was 7.9 weeks and 18.9 weeks for grade 3 edema (44). The median time from the first dose of glumetinib to the onset of edema was 42 days, and the median time to the onset of grade 3 edema was 75 days (23). When patients were treated with tepotinib combined with EGFR TKI, the median time to onset of PE of any grade was 12.1 weeks in the INSIGHT study and 9.9 weeks in the INSIGHT2 study (42).

MET TKI-induced edema was more common in elderly. In the GEOMETRY mono-1 trial, 84% of patients with *MET*ex14 NSCLC who developed PE were older than 65 years (52). This phenomenon may be related to the fact that *MET*ex14 is more common in older patients (60). Advanced age was an independent risk factor for the development of edema in patients treated with tepotinib and was not associated with drug exposure (55). In the VISION study, the incidence of edema was higher in patients aged ≥65 years than in those aged <65 years, and also the incidence was higher in patients aged ≥75 years than in those aged <75 years (44). White patients, a high body mass index (BMI), low mobility and time on treatment were also reported as common risk factors for PE (44,56).

Diagnosis

The etiology of edema is complex, a comprehensive medical history should be taken when PE appears in order to facilitate diagnosis, and that includes: the timing of PE, unilateral or bilateral, whether PE changed with body position and accompanied by other systemic disease, and patient medication history. Acute edema is commonly associated with deep venous thrombosis (DVT), cellulitis, and acute compartment syndrome from trauma, whereas the chronic generalized edema is due to the onset or exacerbation of chronic systemic conditions, such as congestive heart failure (CHF), renal disease, or hepatic disease. Edema caused by venous insufficiency is more likely to be found in low-hanging parts of the body and can vary with position. Unilateral edema is often caused by impaired venous or lymphatic drainage, commonly due to DVT, venous insufficiency, venous or lymphatic obstruction secondary to the tumor or filariasis. Bilateral or generalized swelling usually suggests a systemic cause (61) (*Figure 2A*).

MET TKI-induced PE should be considered in patients who develop or experience a significantly worsening of PE during MET TKI treatment. Therefore, the diagnosis of MET TKI-induced PE should include a clear history of MET TKI administration and PE-related clinical symptoms temporally associated with therapy (3,59). At the same time, relevant laboratory tests and examinations should be performed to exclude other diseases, such as cardiac disease, renal disease, hepatic disease, endocrine disease, and DVT (61) (*Figure 2A*). PE should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (*Table 3*).

Comprehensive management of MET TKI-induced PE

Although not life-threatening, MET TKI-induced edema can negatively impact quality of life (QoL) and treatment adherence, and once edema develops, it is long-lasting and difficult to relieve (44). Real-world experience has shown that the resolution time for PE is up to 3 months in patients with mild-to-moderate PE and up to 6 months in patients with severe PE (56). Therefore, it is crucial to manage PE comprehensively, which includes prevention, early recognition and timely intervention. PE can be prevented or alleviated by lifestyle intervention or physical therapy before onset or for grade 1/2; for grade 3 PE, pharmacological intervention may be required by the clinical judgment (59) (*Figure 2A*).

Prevention

Before initiating MET TKI treatment, patients and their families should be informed of the possible risk of edema. PE can be monitored at the beginning and in the course of MET TKI treatment by proactively measuring body weight, limb circumference, and detecting whether limb swelling or skin erosions is present, which is conducive in reducing clinical symptoms due to PE exacerbation, such as pain, paresthesia, and skin infections.

Non-pharmacological treatment

Non-pharmacological interventions, including lifestyle intervention or physical therapy, such as low-salt and light diet, moderate exercises, raising the limb swelling, wearing elastic stockings, lymphatic massage, are recommended for patients with mild-to-moderate PE to alleviate symptoms, one or more interventions may be used based on the grade of PE (3,59).

Pharmacological treatment

When patients develop severe edema, diuretics can be used according to clinical judgment. Severe PE can lead to hypovolemia and special attention must be paid when using diuretics to avoid excessive diuresis, worsening of renal hypoperfusion and acute renal injury. Therefore, it is recommended that daily weight loss should be ≤0.5 kg, especially in elderly patients. In patients who already have renal insufficiency, potassium-sparing diuretics and osmotic diuretics should be used with caution. When the estimated glomerular filtration rate is less than 30 mL/min, the diuretic effect of thiazide diuretics is poor, and loop diuretics are recommended. For patients with PE combined with hyponatremia, tolvaptan can be considered, but currently there is a lack of evidence-based medical proof from large sample studies. During the application of diuretics, attention should be given to maintaining the electrolyte and acid–base balance, alerting to AEs such as hyponatremia, hypokalemia and hypotension, and the dosage should be adjusted timely (59). Pain is an important symptom of PE, especially for severe PE, and appropriate analgesic drugs can be used according to the patient conditions (56). Pharmacological treatment can only temporarily alleviate the symptoms, and if PE is to be eliminated, it is necessary

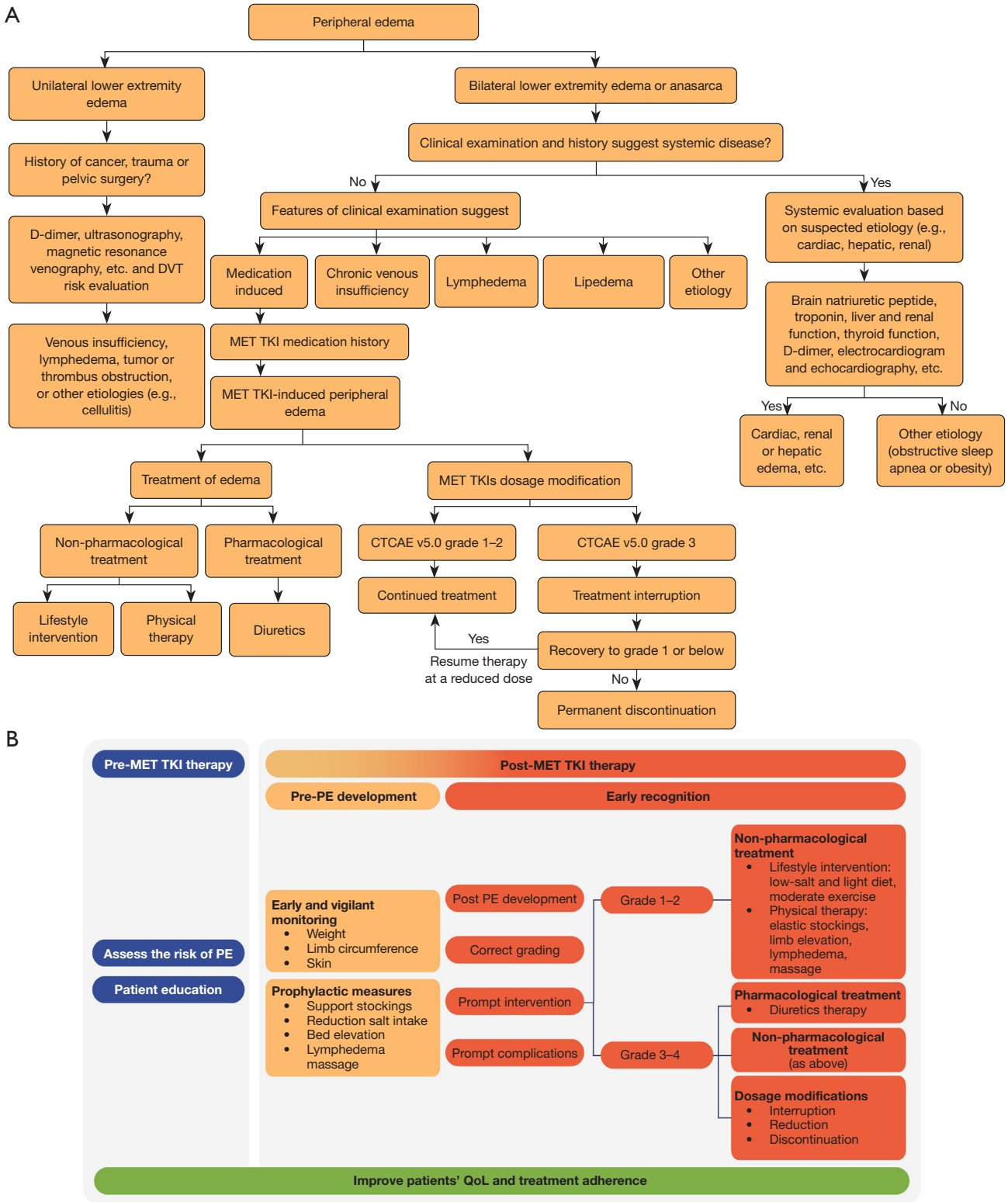

Figure 2 Comprehensive management of MET TKI-induced peripheral edema. Algorithm for the differential diagnosis (A) and clinical management of MET TKI-induced peripheral edema (B). CTCAE, Common Terminology Criteria for Adverse Events; DVT, deep venous thrombosis; MET, mesenchymal-epithelial transition factor; PE, peripheral edema; TKI, tyrosine kinase inhibitor.

Table 3 Grading criteria for PE (CTCAE v5.0) and treatment principle

Grades	Description	Treatment principle (3,59)
1	5–10% inter-limb discrepancy in volume or circumference at the point of greatest visible difference; physical examination showing mild edema or swelling	No dosage modification, and can be alleviated by lifestyle intervention or physical therapy
2	>10–30% inter-limb discrepancy in volume or circumference at the point of greatest visible difference; physical examination showing obvious edema or swelling, affecting instrumental activities of daily living[†]	
3	>30% inter-limb discrepancy in volume or circumference at the point of greatest visible difference; physical examination showing significant edema or swelling, affecting the basic activities of daily living of individuals[‡]	Withhold treatment until recovery to grade 1, then resume treatment at a reduced dose; otherwise discontinue permanently; pharmacologic treatment can be used according to clinical judgment

[†], activities of daily living using devices: using telephone, shopping, food cooking, housekeeping, and traveling; [‡], basic activities of daily living of individuals: using the toilet, eating, dressing, making up, bathing, and walking. CTCAE, Common Terminology Criteria for Adverse Events; PE, peripheral edema.

Table 4 Dose reduction regimens for commonly used MET TKIs

Regimens	Dose reduction
Crizotinib	Starting dose of 250 mg bid, first reduction to 200 mg bid, second reduction to 250 mg qd, permanent discontinuation if 250 mg qd is still not tolerated
Capmatinib	Starting dose of 400 mg bid, first reduction to 300 mg bid, second reduction to 200 mg bid, permanent discontinuation if still not tolerated
Tepotinib	The starting dose is 450 mg qd, which may be reduced to 225 mg qd if needed due to adverse effects, or permanently discontinued if 225 mg qd is still not tolerated
Savolitinib	Body weight ≥50 kg: the starting dose is 600 mg qd, the first dose is reduced to 400 mg qd, the second dose is reduced to 300 mg qd, and the third dose is reduced to 200 mg qd Body weight <50 kg: the starting dose is 400 mg qd, the first dose is reduced to 300 mg qd, and the second dose is reduced to 200 mg qd
Vebreltinib	Starting dose 200 mg bid, first reduction to 150 mg bid, second reduction to 100 mg bid
Glumetinib	Starting dose of 300 mg qd, first reduction to 250 mg qd, second reduction to 200 mg qd, third reduction to 150mg qd

MET, mesenchymal-epithelial transition facto; TKIs, tyrosine kinase inhibitors; mg, milligram; bid, *bis in die; qd*, *quaque die*; kg, kilogram.

to rely on the dose adjustment of MET TKI, such as dosage reduction and temporary interruption of treatment.

Dosage modifications for MET TKI

Among patients treated with MET TKI, the majority of patients had mild-to-moderate PE, and only a small proportion required treatment interruption or discontinuation. Patients with grade 1/2 PE can continue therapy, whereas treatment for patients with grade 3 PE should be interrupted until edema recovers to grade 1 or below, therapy is then resumed at a reduced dose. If PE failed to recover to grade 1 or below, permanent discontinuation of the therapy is needed (3,59) (*Table 3*). The dose adjustments for different MET TKIs are presented in *Table 4*. When patients are treated with MET TKI in combination with other regimen (e.g., EGFR TKI), MET TKIs are similarly modified in the following regimens.

Since PE is a class effect, changing to another MET inhibitor is unlikely to be beneficial. Reducing the dose and/or interrupting treatment, including taking frequent short breaks, seems to be the most effective approach for managing edema and should be initiated early to minimize its severity (44). A temporary pause in treatment, as opposed to reducing the dosage, might be a more effective strategy for addressing edema (55). When MET TKI-induced PE occurs, patients should be managed according to clinical symptoms and the grade of PE as soon as possible.

Future directions

Patients receiving MET TKIs often face PE as an adverse reaction, with its high incidence becoming an issue of significant concern in clinical practice. The present review provides comprehensive insights into MET TKI-induced PE, including its potential molecular mechanisms, diagnostic criteria, and management strategies. Further research into the molecular mechanisms and the management strategies is necessary to enhance the treatment of MET TKI-induced PE. This includes preclinical studies on mechanisms and clinical studies on innovative management approaches. A survey reveals two primary challenges in the management of MET TKI-induced PE: firstly, the lack of effective treatment strategies; secondly, the inadequate understanding of the complex interaction mechanisms between PE and MET TKIs (56). Addressing these unmet needs, future directions in the management of MET TKI-induced PE may involve exploration and innovation across multiple frontier areas.

Firstly, researchers will embark on an in-depth exploration of the molecular mechanisms underlying PE. They will utilize molecular biology tools to elucidate the key molecules and signaling pathways involved in PE. This process not only expands the boundaries of basic science but also establishes a robust theoretical foundation for the development of novel and precise therapeutic agents. Simultaneously, continued enhancements in the chemical composition of MET TKIs by pharmaceutical companies, or the finding of efficacious practical therapeutic observed in clinical practice, will result in a comprehensive solution to MET TKI-induced PE. Finally, enhancing patient education is recognized as a pivotal measure to elevate the management of MET TKI-induced PE. To address gaps in patient awareness in this area, some educational resources may aid patients in developing accurate understanding. Additionally, with the development of telemedicine and digital health technologies, the management tools may undergo revolutionary changes, such as mobile applications, will provide real-time feedback and foster close interaction between patients and physicians.

Conclusions

MET TKIs provide a new treatment option for patients with MET-altered NSCLC (62). PE, a common adverse event of MET TKI, has a high incidence but is generally mild-to-moderate in most patients. However, if PE is not treated in a timely manner and develops into severe PE, the duration time will be prolonged, and become difficult to manage, which is likely to have a negative impact on patients' QoL and treatment adherence. Therefore, once MET TKI-induced edema occurs, we should actively perform a comprehensive management including non-pharmacological treatment, pharmacological treatment and dosage modifications (*Figure 2B*), which are essential for alleviating patients suffering and reinforcing treatment adherence.

Acknowledgments

Medical writing assistance and figure processing for this manuscript was provided by Yafang Zhang, of Merck Serono Co., Ltd., Beijing, China, an affiliate of Merck KGaA.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-866/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-866/prf

Funding: This work was funded by the National Natural Science Foundation of China (No. 82202997 to S.Y.M.L.) and Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (No. 2017B030314120 to Y.L.W.).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-866/coif). Y.L.W. reports the grants from AstraZeneca, BMS, and Pfizer and speaker fees from Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Sanofi, MSD, Hengrui, Pfizer, and BMS. The other 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.

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Cite this article as: Lin JX, Sun H, Peng YL, Xie Z, Liu SYM, Wu YL. Comprehensive management of MET tyrosine kinase inhibitor-induced peripheral edema in patients with *MET*-altered non-small-cell lung cancer: a narrative review. Transl Lung Cancer Res 2025;14(4):1482-1495. doi: 10.21037/tlcr-24-866

