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Correspondence

MET inhibitors as salvage therapy for MET-amplified gastric cancer with pulmonary lymphangitis

Xiufeng Zheng,[1,2,‡] Mo Cheng,[2,‡] Wenke Li,[2] Ming Liu[2,*]

[1]Department of Radiation Oncology, The Second Affiliated Hospital of Guangxi Medical University, Nanning 530007, China
[2]Gastric Cancer Center, Division of Medical Oncology, West China Hospital, Sichuan University, Chengdu 610041, China
*Corresponding author. Ming Liu, liuming629@wchscu.cn
‡Xiufeng Zheng and Mo Cheng contributed equally to this work.

Dear Editor,

Approximately 4%–10% of upper gastrointestinal (GI) tumors harbor mesenchymal–epithelial transforming factor (MET) amplification, while 50% of individuals with advanced gastric cancer (GC) exhibit MET protein overexpression [1]. Activated MET signaling promotes cancer cell proliferation, survival, and invasion, correlating with poor prognosis in GI malignancies. Pulmonary lymphangitic carcinomatosis (PLC) is a specific type of pulmonary metastasis, marked by extensive tumor cell infiltration in lymphatic capillaries. PLC occurs in ∼10% of gastric cancer patients, with a very poor prognosis, showing a median survival of <3 months [2]. A recent study identified MET amplification as a molecular event enriched in gastric cancer with PLC, which represents a distinct subtype responsive to molecular-targeted therapy [3]. Savolitinib, the inaugural MET kinase inhibitor to be approved in China, is indicated for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) exhibiting MET exon 14 skipping, whose disease has progressed following platinum-based chemotherapy or who are intolerant to it [4]. This paper presents a discussion of the clinicopathological features and prognosis of 5 gastric cancer patients with PLC and MET amplification, with the objective of determining the therapeutic effect of savoltinib.

At the West China Hospital of Sichuan University, 8 gastric cancer patients with MET amplification were screened from 2018 to 2023, of whom 5 (62.5%) developed PLC. MET amplification was identified through genetic testing using targeted-capture sequencing instead of fluorescence in situ hybridization (FISH). All patients received first-line fluorouracil-based chemotherapy, but were readmitted due to progressive dyspnoea. Patient 1, a 45-year-old man with a MET copy number (CN) of 2.7, experienced disease progression after 2 months of second-line treatment and ultimately died of respiratory failure, with an overall survival (OS) of 12 months. Patient 2, a 37-year-old woman with a MET CN of 5.5 and a PD-L1 CPS of 5, showed rapid symptom improvement with savolitinib and achieved a progression-free survival (PFS) of 5.3 months; however, she died of PLC 1 month later with an OS of 7.5 months. Patient 3, a 47-year-old woman with a MET CN of 1.5 and PD-L1 CPS of 2, showed significant improvement with savolitinib and survived for >12 months. Patient 4, a 34-year-old woman with a MET CN of 5.9, also experienced symptomatic improvement after savolitinib treatment and survived >14 months. Patient 5, a 51-year-old man with a MET CN of 5.6, received no further treatment after first-line chemotherapy and survived 1.5 months before dying of PLC.

All 5 patients were HER2 and EBER negative by immunohistochemistry and exhibited pMMR. NGS sequencing revealed a mean MET amplification CN of 4.24, all associated with TP53 mutations. Occasional ETV5 rearrangements, MYC amplification, CDK6 mutations, GATA3 mutations, and CDKN2A deletions were noted, without EGFR mutations (Fig. 1A). Notably, ECOG scores increased rapidly from 0–1 to 3–4 during carcinomatous lymphangitis. Figure 1B shows improvements in lung texture post-treatment, Figure 1C illustrates the treatment and outcomes, while Fig. 1D presents the MET amplification numbers and PFS for the 5 patients after second-line treatment.

When lung tumor cells invade the lymphatic system, they can lead to inflammation and lymphatic expansion, resulting in PLC, which is primarily associated with advanced-stage lung, breast, bowel, and stomach cancers. It carries a poor prognosis, with about half of patients dying within 2 months of initial respiratory symptoms [2]. Patients with advanced GC, especially those with PLC, often have poor performance status, high chemotherapy resistance, severe side effects, and a limited treatment window [4].

The MET gene encodes the receptor tyrosine kinase MET, which interacts with hepatocyte growth factor (HGF) [1]. Numerous solid tumors, including lung, colorectal, and gastric cancers, have aberrant activation of the MET pathway through non-HGF-dependent mechanisms such as MET exon 14 skipping mutations, amplifications, rearrangements, and protein overexpression. This has led to increased interest in the role of MET in NSCLC [4]. Higher MET expression in gastric cancer indicates a more aggressive and metastatic tumor. Chaudhary *et al*. found that MET FISH positivity was linked to worse physical PS status and poor tumor differentiation, and MET FISH amplification or IHC3+ predicted poor prognosis in metastatic GC [5]. MET amplification copy number is considered to correlate with therapeutic efficacy. However, in a cohort of MET-amplified NSCLC patients treated with capmatinib, there was no significant difference in PFS between patients with gene copy numbers <4 and those with copy numbers >10 [6]. Additionally, studies examining the correlation between MET amplification detected by NGS and the efficacy of MET inhibitors have shown that using a gene copy number of 5 as the cutoff value, MET

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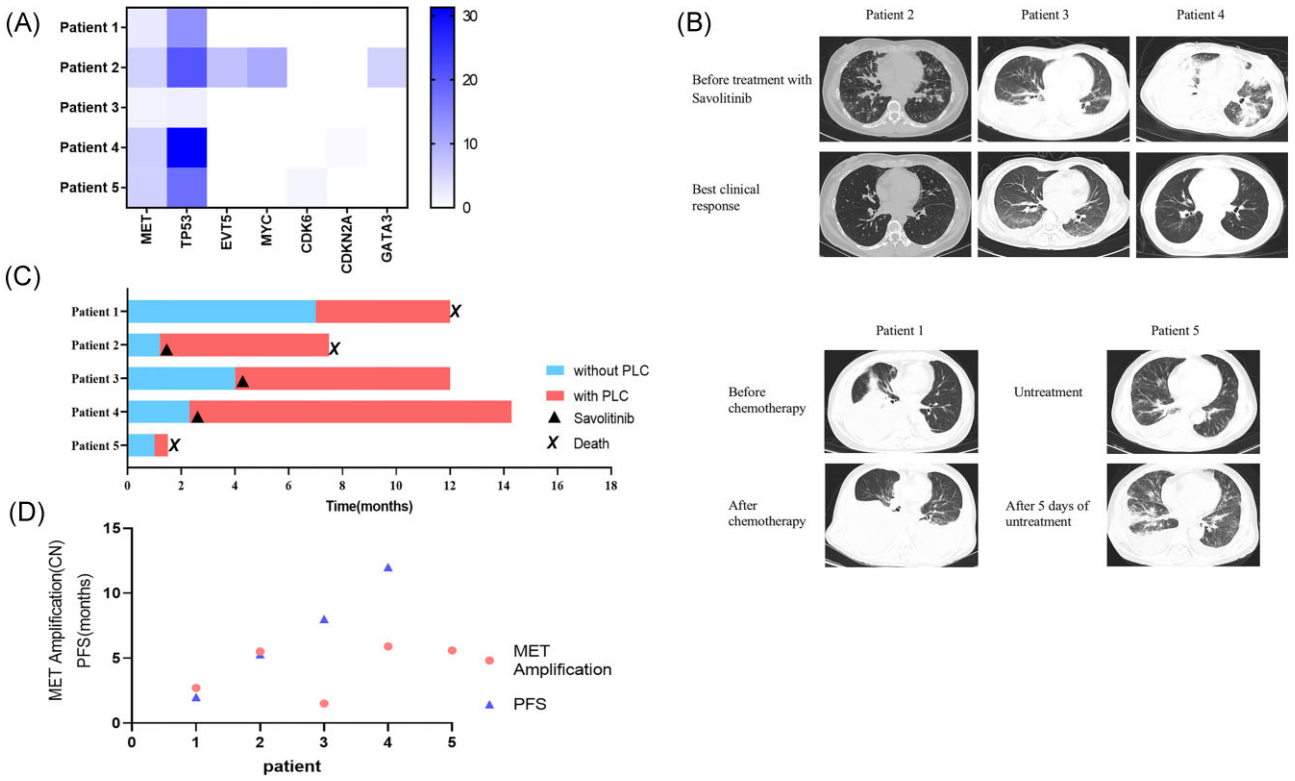

Figure 1. Summary of the diagnosis and treatment of 5 patients. (**A**) NGS sequencing results of 5 patients. (**B**) CT comparison of patients before and after treatment. (**C**) Treatment and outcomes of the patients. (**D**) MET amplification number and PFS of the 5 patients after second-line treatment.

amplification identified by NGS failed to significantly distinguish clinical outcomes [7]. Currently, the treatment of advanced GC patients with MET amplification consists mainly of palliative chemotherapy, with fluorouracil analogs as the cornerstone of single-agent and most combination regimens, with no other agents approved to date [4]. Therapeutic strategies targeting the MET pathway include small molecule TKIs, large molecule drugs, and monoclonal antibodies. A phase III study by Shah *et al.* found that in patients with MET-positive metastatic HER2-negative G/GEJ cancer, median PFS was 5.95 months with onartuzumab plus mFOLFOX6 versus 6.80 months with placebo (HR, 1.38; $P = 0.45$), and median OS was 8.51 versus 8.48 months (HR, 1.12; $P = 0.80$) [8]. In the AMG337 study by Van Cutsem E *et al.*, 54 patients with MET amplification after multiple lines of therapy, showed a median (95%CI) PFS of 3.4 (2.2–5.0) and OS of 7.9 (4.8–10.9) months, respectively [9]. In addition, tinvatinib and foretinib also did not provide significant benefit in MET-positive GC [10]. Patients with MET-amplified GC and lymphangitis are often excluded from clinical studies due to ECOG/PS scores, leaving the real-world efficacy of tinvatinib and foretinib unknown. Recent research shows that MET TKIs are effective in this population. Compared to GC without PLC, GC with PLC is more prevalent in women (42.9% versus 10.8%, $P = 0.010$), is diagnosed at a younger median age (44 versus 56 years, $P = 0.002$), and has a higher baseline ECOG PS (≥2 points, 46.2% versus 17.8%, $P = 0.016$). MET amplification is more concentrated in patients with PLC, where anti-MET therapy yields a high response rate [3].

In conclusion, precise target selection and optimal patient management tailored to the indications and molecular characteristics are the critical issues regarding the treatment of advanced GC. For GC patients with MET amplification and PLC, MET inhibitors may be considered as salvage treatment when chemotherapy and immunotherapy fail.

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Author contributions

Xiufeng Zheng (Data curation, Formal analysis, Investigation, Writing—original draft), Mo Cheng (Data curation, Formal analysis, Writing—original draft), Wenke Li (Data curation), and Ming Liu (Funding acquisition, Supervision)

Conflict of interest

None declared.

Ethics

The study was approved by the Hospital Ethics Committee of West China Hospital, Sichuan University, and the need for written informed consent was waived.

References

1. Mo MH, Liu P. Targeting *MET* in cancer therapy. *Chronic Dis Transl Med* 2017;**3**:148–53. https://doi.org/10.1016/j.cdtm.2017.06.002
2. Klimek M. Pulmonary lymphangitis carcinomatosis: systematic review and meta-analysis of case reports, 1970-2018. *Postgrad Med* 2019;**131**:309–18. https://doi.org/10.1080/00325481.2019.1595982.

3. Zhang Z, Yu Y, Xie T *et al.* Pulmonary lymphangitis carcinomatosis: A peculiar presentation clustering in MET-amplified gastric cancer. *Cancer Med* 2023;**12**:19583–94. https://doi.org/10.1002/cam4.6575.
4. Yu Y, Guo Q, Zhang Y *et al.* Savolitinib in patients in China with locally advanced or metastatic treatment-naive non-small-cell lung cancer harbouring MET exon 14 skipping mutations: results from a single-arm, multicohort, multicentre, open-label, phase 3b confirmatory study. *The Lancet Respiratory Medicine* 2024;**12**:958–66. https://doi.org/10.1016/S2213-2600(24)00211-X.
5. Chaudhary SP, Kwak EL, Hwang KL *et al.* Revisiting MET: clinical characteristics and treatment outcomes of patients with locally advanced or metastatic, MET-amplified esophagogastric cancers. *Oncologist* 2020;**25**:e1691–700. https://doi.org/10.1634/theoncologist.2020-0274.
6. Wolf J, Seto T, Han J-Y *et al.* Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020;**383**:944–57. https://doi.org/10.1056/NEJMoa2002787.
7. Peng L-X, Jie G-L, Li A-N *et al.* MET amplification identified by next-generation sequencing and its clinical relevance for MET inhibitors. *Experimental Hematology & Oncology* 2021;**10**:52. https://doi.org/10.1186/s40164-021-00245-y.
8. Shah MA, Cho J-Y, Tan IB *et al.* A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal junction. *Oncologist* 2016;**21**:1085–90. https://doi.org/10.1634/theoncologist.2016-0038.
9. Van Cutsem E, Karaszewska B, Kang YK *et al.* A multicenter phase II study of AMG 337 in patients with MET-amplified gastric/gastroesophageal junction/esophageal adenocarcinoma and other MET-amplified solid tumors. *Clin Cancer Res* 2019;**25**:2414–23. https://doi.org/10.1158/1078-0432.CCR-18-1337.
10. Zhang YF, Shen L, Peng Z. Advances in MET tyrosine kinase inhibitors in gastric cancer. *Cancer Biol Med* 2024;**21**:484–98. https://doi.org/10.20892/j.issn.2095-3941.2024.0044

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