Case Report

Tepotinib in a Patient With Advanced Non-Small Cell Lung Cancer Harboring *MET* Exon 14 Skipping Undergoing Concomitant Hemodialysis for Renal Failure: A Case Report

Moritz Kleemiss,[1] Christa E. Müller,[2] Marion Schneider,[2] Rainer Strotmann,[3] Katrin Orlowski,[4] Kosalaram Goteti,[5] Mert Yanik,[4] Peter Brossart,[1] Franz-Georg Bauernfeind[1]

Clinical Practice Points

- Tepotinib, a potent, highly selective, once-daily, oral MET tyrosine kinase inhibitor, is approved in multiple countries for the treatment of advanced/metastatic *MET*ex14 skipping NSCLC and can be used in patients with mild-moderate renal impairment without dose adjustment. However, data in severe renal impairment are lacking.
- We report the feasibility of using the standard dose of tepotinib (500 mg; 450 mg active moiety) in a patient with advanced *MET*ex14 skipping NSCLC with end-stage renal disease undergoing hemodialysis, who attained disease control, with only mild adverse events that did not necessitate dose adjustment.
- Use of the standard dose was supported by tepotinib plasma concentration measurements, which fell within the expected range for a typical patient with NSCLC predicted using a population pharmacokinetic model and indicated no clinically relevant drug loss during dialysis.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide,[1] with non-small cell lung cancer (NSCLC) accounting for >80–85% of cases.[2] In patients with lung cancer, renal impairment is a common comorbidity estimated to affect 28% of patients, with severe renal impairment in 2%.[3] Furthermore, a ~1.5-fold increase in lung cancer risk has been reported after kidney transplant.[4] Chronic kidney disease (CKD) and end-stage renal disease (ESRD) requiring hemodialysis are poor prognostic factors in lung cancer.[5,6] However, these patients are typically excluded from clinical trials of anti-cancer agents,[7,8] partly due to the potential impact of renal dysfunction on efficacy and/or safety related to changes in pharmacokinetics, which are observed with many chemotherapeutic drugs.[9,10] For example, decreased renal excretion can increase drug exposure and thereby impact on safety, while drug losses during hemodialysis can decrease exposure and thereby compromise efficacy.[10,11] Due to their frequent exclusion from trials, patients with renal insufficiency have fewer anti-cancer treatment options.

Several oncogenic driver alterations have been identified in NSCLC and a better understanding of their role in tumor biology has allowed the development of new targeted therapies that have changed the treatment landscape.[12] Mesenchymal–epithelial transition factor (*MET*) exon 14 (*MET*ex14) skipping is a primary oncogenic driver reported in 3%-4% of patients with NSCLC,

Abbreviations: CLcr, creatinine clearance; CKD, chronic, kidney disease; ESRD, end-stage renal disease; MET, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14 skipping; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PAD, peripheral arterial disease; PopPK, population pharmacokinetics; QD, once daily; SD, standard deviation; TKI, tyrosine kinase inhibitor.

[1]Department of internal Medicine III, University Hospital Bonn, Bonn, Germany
[2]PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical & Medicinal Chemistry, University of Bonn
[3]Qualitative Pharmacology, the healthcare business of Merck KGaA, Darmstadt, Germany
[4]Merck Healthcare Germany GmbH, Weiterstadt, Germany, an affiliate of Merck KGaA, Darmstadt, Germany
[5]Quantitative Pharmacology, EMD Serono, Rockland, MA

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Address for correspondence: Moritz Kleemiss, Staatsexamen, Department of internal Medicine III, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany
E-mail contact: moritz.kleemiss@ukbonn.de

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most of whom are elderly.[13] Although *MET*ex14 skipping confers a poor prognosis with standard-of-care therapy,[14] it also sensitizes tumors to MET tyrosine kinase inhibitors (TKIs).[15-18] Tepotinib, a potent, highly selective, once-daily, oral MET TKI,[19] is approved in multiple countries for the treatment of advanced/metastatic *MET*ex14 skipping NSCLC,[20] based on the VISION study.[16,21,22] Clinical practice guidelines, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®), American Society of Clinical Oncology and Ontario Health (Cancer Care Ontario) joint guidelines, and European Society for Medical Oncology guidelines, recommend MET TKIs, including tepotinib and capmatinib, for eligible patients with *MET*ex14 skipping.[23-25]

Tepotinib can be used without dose adjustment in patients with mild-moderate renal impairment.[26] This practice is based on population pharmacokinetic (PopPK) modelling of data from the VISION trial, which showed no clinically meaningful effect of mild-moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min) on tepotinib exposure.[26,27] Tepotinib has not been studied in patients with severe renal impairment (CLcr <30 mL/min).[20,26] However, given its predominantly biliary elimination,[28] any impact of severe renal impairment on tepotinib pharmacokinetics is expected to be minimal.[10,11] Furthermore, despite its relatively low molecular weight, tepotinib may be protected from removal during hemodialysis by its high protein binding and large volume of distribution.[10,11,28] Nonetheless, clinical evidence in patients with severe renal impairment is needed.

We report on the efficacy, safety, and pharmacokinetics of tepotinib in a patient with *MET*ex14 skipping NSCLC with comorbid ESRD (residual estimated glomerular filtration rate of <15 mL/min), who was undergoing hemodialysis.

Case Report

A 73-year-old Caucasian female with a 40 pack-year smoking history was diagnosed with squamous NSCLC in January 2021. The medical history included: ESRD due to polycystic kidney disease, for which hemodialysis had been conducted three times a week (since 2005); kidney transplant (in 2014), which had been followed by graft failure and transplant nephrectomy; squamous cell carcinoma of the skin (completely resected in December 2020); hypertension; and peripheral arterial disease (PAD), for which an aortobifemoral Y-prosthesis had been implanted (in 2012). Residual estimated glomerular filtration rate was <15 mL/min, associated metabolic alterations such as hyperphosphatemia and acid–base imbalances were well controlled with medication, and hepatic function was normal.

At NSCLC diagnosis, the patient had clinical stage IVB disease (cT4 cN0 cM1c) with bone, pleural and lung metastasis, and Eastern Cooperative Oncology Group performance status of 1. Next-generation sequencing analysis of a tissue biopsy (QIASEQ® Targeted DNA Custom Panel, Qiagen, Venlo, The Netherlands) revealed a *MET*ex14 skipping mutation (c.3017-3028+26del) with concomitant intermediate-level *MET* amplification (gene copy number 4.95). The programmed death ligand-1 tumor proportion score was 90% by immunohistochemistry (PD-L1 IHC 22C3 pharmDx assay, Agilent Technologies, Santa Clara, CA, USA). First-line therapy with pembrolizumab (200 mg, every 3 weeks) was initiated in January 2021 and continued without significant adverse events until disease progression in May 2021. The patient also received palliative radiation (39 Gy, 13 fractions) to the thoracic vertebrae (T4-T6) for pain from osteolytic bone metastasis.

Based on the *MET*ex14 skipping alteration, second-line therapy with tepotinib was initiated through a compassionate use program in Germany in July 2021, at which time tepotinib was not yet approved in the European Union. Tepotinib was administered at the standard dose of 500 mg (450 mg active moiety), orally, once daily in the morning with food, under conditions of careful safety and pharmacokinetic monitoring to confirm the appropriateness of the dose in this patient receiving hemodialysis for ESRD. The first response assessment showed shrinkage of the primary tumor (from 6.1 × 4.3 cm to 4.6 × 3.0 cm) and lung metastases, with a reduction in sum of lesion diameters <30%. The best overall response to tepotinib was stable disease, and the patient reported improvements in mobility, physical function, and pain. Grade 1 fatigue and Grade 2 peripheral edema were observed but did not necessitate dose adjustment. Tepotinib was continued for a total of 5.5 months until December 2021, when the patient died due to PAD with concurrent cerebral hemorrhage. Prior to death, a second tumor assessment had shown maintenance of the primary tumor shrinkage with further reductions in the lung metastases, indicating that the NSCLC was well controlled.

During tepotinib treatment, hemodialysis was performed 3 times per week using a Gambro D396 machine (Gambro Lundia AB, Deerfield, IL, USA) with an ELISIO®19H dialyzer (Nipro, Mechelen, Belgium), at a blood flow of 300 mL/min, over 4 hours and 10 minutes. The first sessions were conducted on treatment Days 5, 7, and 9, approximately 3–4 hours after tepotinib administration. Tepotinib was taken at the same time of day on dialysis and non-dialysis days. Plasma samples were collected pre- and post-dialysis, approximately 1 hour and 8 hours and 25 minutes after tepotinib administration, respectively. Tepotinib was assayed in plasma samples by liquid chromatography–tandem mass spectrometry at the Department of Pharmaceutical and Medicinal Chemistry, University of Bonn (Germany), with 4 technical bioanalysis replicates per sample.

While variability between technical replicates was within the acceptable range, there was some between-day variability in the predialysis concentrations of tepotinib (Figure 1). Based on nominal sampling times, all observed tepotinib plasma concentrations were close to the expected median plasma concentrations, as predicted by the PopPK model for a typical patient with NSCLC receiving this tepotinib dose-regimen.[27] The observed post-dialysis plasma concentrations of tepotinib were 16.8–24.2% lower than the predialysis plasma concentrations but fell within the 90% prediction interval for patients receiving tepotinib without dialysis.

Discussion

Tepotinib is approved to treat advanced/metastatic *MET*ex14 skipping NSCLC and can be used in patients with mild-moderate renal impairment without dose adjustment; however, data in severe renal impairment have been lacking.[20,26,27] The present case demonstrates, for the first time, the successful use of tepotinib in

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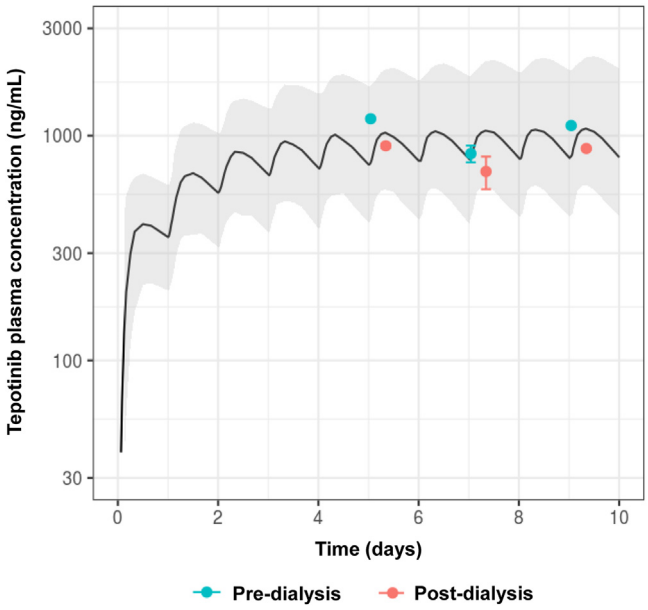
Figure 1 Mean plasma concentration of tepotinib at Days 5, 7, and 9, recorded pre- and post-dialysis and plotted alongside the median and 90% prediction interval for the tepotinib concentration–time profile for typical patients treated with 500 mg tepotinib QD as predicted from the tepotinib PopPK model. Data points indicate the mean and SD of 4 technical replicates. PopPK, population pharmacokinetic; QD, once daily; SD, standard deviation.



a patient with ESRD undergoing hemodialysis. With the standard tepotinib dose (500 mg), the patient attained disease control lasting >5 months, with only mild adverse events, which was accompanied by improvements in mobility, physical function, and pain and, therefore, quality of life. The patient ultimately died from an NSCLC-unrelated cause without disease progression.

In patients with ESRD managed with hemodialysis, anti-cancer drug exposure can either be increased due to impaired renal elimination or decreased due to enhanced systemic clearance resulting from drug loss during hemodialysis.[10] In the present case, the first hemodialysis was conducted on treatment Day 5, at which time tepotinib should almost have reached steady state (given its terminal elimination half-life of 32 hours).[26,28] The pre-dialysis tepotinib concentration on this day was in line with expectations for a typical patient without ESRD, indicating no substantial increase in tepotinib exposure secondary to renal impairment. The limited impact of severe renal impairment on tepotinib clearance is consistent with the minimal contribution of renal excretion to the total elimination of tepotinib, with 85% of tepotinib excreted in feces and only 13.6% in urine.[26,28] Furthermore, on Days 5, 7, and 9, pre- and post-dialysis concentrations showed no clinically relevant loss of tepotinib during hemodialysis, which was likely protected from removal by its high plasma protein binding (98%) and large volume of distribution (574 L after an intravenous tracer microdose).[28] Overall, observed plasma concentrations were within the 90% prediction interval for patients receiving tepotinib without dialysis, thereby suggesting the patient achieved efficacious exposure (Figure 1). The pharmacokinetic data provide a rationale for the observed efficacy and tolerability of tepotinib, which did not require dose adjustments to manage adverse events, and provided disease control.

Conclusion

This case report illustrates the feasibility of using the standard dose of tepotinib in a patient with advanced *MET*ex14 skipping NSCLC with ESRD undergoing hemodialysis, and provides plasma concentration data supporting its use without dose adjustment in this setting. These data may be applicable to other patients with severe renal impairment.

Consent

The patient gave written informed consent for de-identified data to be disclosed and published in any scientific journal for educational purposes.

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Disclosure

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CRediT authorship contribution statement

Moritz Kleemiss: Formal analysis, Investigation, Methodology, Writing – review & editing. **Christa E. Müller:** Investigation, Writing – review & editing. **Marion Schneider:** Investigation, Writing – review & editing. **Rainer Strotmann:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Katrin Orlowski:** Conceptualization, Formal analysis, Writing – review & editing. **Kosalaram Goteti:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Mert Yanik:** Conceptualization, Formal analysis, Writing – review & editing. **Peter Brossart:** Investigation, Writing – review & editing. **Franz-Georg Bauernfeind:** Investigation, Writing – review & editing.

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