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# Safety of Enfortumab Vedotin Plus Pembrolizumab in Hemodialysis Patients With Metastatic Urothelial Carcinoma: Case Report

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## Abstract

*Background/Aim:* Enfortumab vedotin plus pembrolizumab (EVP) is a first-line treatment for metastatic urothelial carcinoma (mUC) based on the EV302 trial; however, patients receiving hemodialysis were excluded from this study. Therefore, evidence regarding the safety and efficacy of this combination therapy in patients undergoing hemodialysis is insufficient. We present a case of mUC in a patient undergoing hemodialysis treated with EVP.

*Case Report:* A 72-year-old man underwent total urinary tract extirpation for high-grade UC and subsequently required hemodialysis. Four years later, he developed right ischial metastasis. First-line systemic therapy with enfortumab vedotin (EV) 1.25 mg/kg plus pembrolizumab (200 mg) was initiated, with infusions scheduled on nonhemodialysis days. The patient completed three cycles without any dose reduction. Treatment-related adverse events were limited to grade 2 pruritus and grade 1 fatigue, with no grade ≥3 adverse events. Restaging computed tomography after three cycles revealed enlargement of the ischial lesion, indicating progressive disease, and systemic therapy was discontinued.

*Conclusion:* A standard dose of EVP can be safely administered to patients on hemodialysis, with manageable toxicities comparable to those observed in nonhemodialysis patients. Although its antitumor efficacy was not confirmed, our experience suggests that EVP may remain a therapeutic option for selected dialysis patients with mUC.

**Keywords:** Enfortumab vedotin plus pembrolizumab, hemodialysis, urothelial carcinoma.

## Introduction

Enfortumab vedotin (EV), an antibody–drug conjugate that delivers the microtubule-disrupting agent monomethyl auristatin E to Nectin-4–expressing cells, has become a standard option for metastatic urothelial carcinoma (mUC) progression after platinum chemotherapy and immune checkpoint inhibitors, improving overall survival compared

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to chemotherapy in the EV-301 trial (1). A phase III EV-302 trial confirmed the high efficacy and acceptable safety of first-line enfortumab vedotin plus pembrolizumab (EVP), prompting its approval in Japan in September 2024 as an initial therapy for mUC (2). Notably, approximately 40% of EV-302 participants had moderate renal impairment (creatinine clearance=30-60 ml/min), and the regimen retained high efficacy and an acceptable safety profile. However, patients undergoing maintenance hemodialysis were excluded; therefore, the efficacy and safety in this subgroup remain unclear. We report a case of EVP therapy in a patient with mUC undergoing hemodialysis.

## Case Report

A 72-year-old man, with a medical history of stage 3 chronic kidney disease and type 2 diabetes mellitus, was diagnosed with a bladder tumor following abdominal ultrasound. The patient was referred to our department for further evaluation. A bladder tumor was diagnosed using cystoscopy, and the patient underwent transurethral resection of the bladder tumor (TUR-Bt) in April 2017. Pathological analysis revealed high-grade UC (pT1) with lymphatic invasion (ly1) and the absence of vascular invasion (v0). In June 2017, a second TUR-Bt was performed, and pathological analysis showed no malignancy. Subsequently, he completed a full course of intravesical Bacillus Calmette-Guérin therapy in September 2017.

In November 2018, cystoscopy revealed evidence of recurrence and TUR-Bt was performed in January 2019. Histopathological examination revealed a high-grade carcinoma in situ (CIS). At the patient's insistence, active surveillance was performed without initiating further treatment. Follow-up urine cytology in February 2020 revealed class V findings, and cystoscopy indicated recurrence. In May 2020, the patient underwent TUR-Bt and bilateral retrograde pyelography. The pathological findings confirmed CIS in the bladder and revealed cytological abnormalities in the ureters (right, class V; left, class IIIb).

Thereafter, the patient underwent total urinary tract extirpation and lymph node dissection. The pathological diagnosis was high-grade UC in the bladder and bilateral ureters, the region surrounding the right lower ureteral region, and the left upper ureter, without lymph node metastasis. Postoperative hemodialysis was initiated.

In July 2024, a follow-up computed tomography (CT) scan revealed metastasis to the right ischium, which was further confirmed using magnetic resonance imaging (MRI) (Figure 1A and B). External beam radiotherapy at a dose of 24 Gy in two daily fractions was administered to the metastatic site, and systemic therapy with EV (1.25 mg/kg) plus pembrolizumab (200 mg) was initiated in December 2024. The dosing schedule was the same as that used in the EV302 study (2), and the drug was administered on nondialysis days. The Eastern Cooperative Oncology Group performance status score was 1. During treatment, the patient experienced grade 2 pruritus and grade 1 fatigue but no other severe adverse events and completed three cycles without EV dose reduction.

However, a CT scan and MRI performed after three cycles of EVP to assess the response showed an increase in the size of the ischial metastasis, leading to progressive disease according to the Response Evaluation Criteria in Solid Tumours version 1.1 (3) (Figure 2A and B). Following extensive discussions with the patient and his wife, a transition to supportive care was initiated.

## Discussion

In the present case, EVP was administered to a patient undergoing hemodialysis for mUC. Although its efficacy was not confirmed, the patient safely completed three cycles of EVP therapy without serious complications. To the best of our knowledge, this is the first report of its use in hemodialysis patients.

In 2017, the KEYNOTE-045 trial demonstrated the efficacy and safety of pembrolizumab as second-line therapy for advanced UC (4). Pembrolizumab has a molecular weight of 149 kDa and is filtered through the

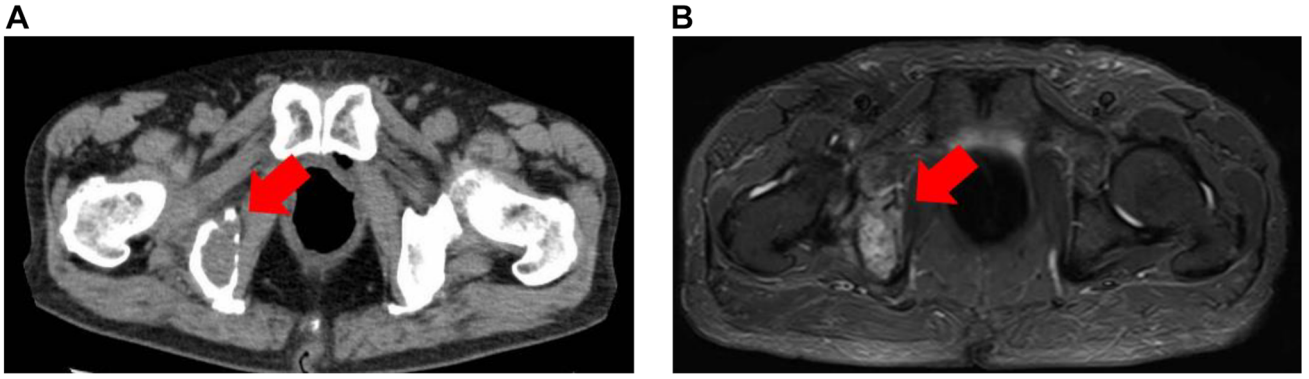


Figure 1. *Plain computed tomography (A) and T1-weighted magnetic resonance imaging (B) showing a right ischial metastasis.*

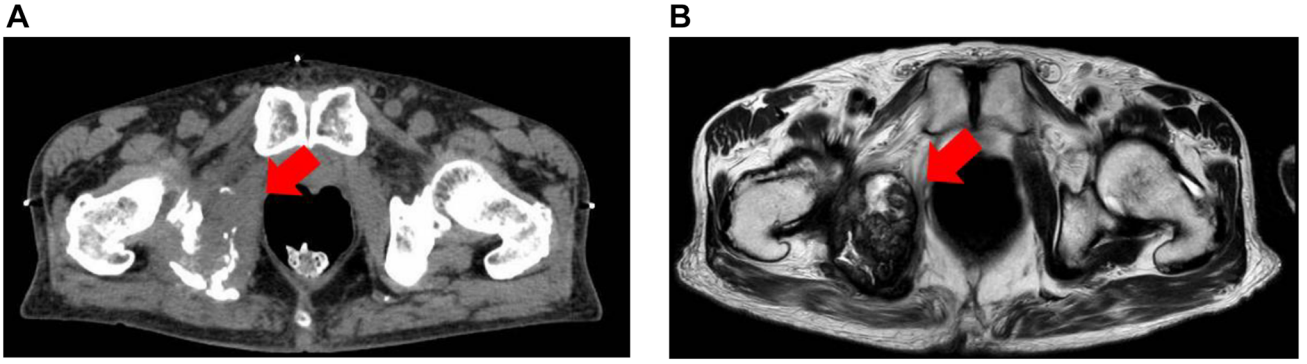


Figure 2. *Plain computed tomography (A) and T1-weighted magnetic resonance imaging (B) after three cycles of enfortumab vedotin plus pembrolizumab therapy showing enlargement of the right ischial metastasis.*

glomerulus of the kidney, preventing it from being excreted in the urine. Therefore, from a pharmacological perspective, pembrolizumab does not affect renal function. However, this trial excluded patients with end-stage renal disease. Vitorino *et al.* reported the case of a 72-year-old hemodialysis patient with mUC who, after progressing on platinum chemotherapy, received second-line pembrolizumab and achieved a durable complete response (5).

Tang *et al.* demonstrated that systemic exposure to EV and its free monomethyl auristatin E payload remains essentially unchanged across normal, mild, moderate, and severe renal impairments, indicating that no dose adjustment is necessary for patients with reduced kidney function who are not receiving dialysis (6). However, patients on dialysis were excluded from the EV301 trial; therefore, their efficacy and safety remain unknown (1). Furubayashi *et al.* retrospectively analyzed 58 patients with advanced UC who received EV and found no significant change in serum creatinine levels before and after treatment, concluding that EV did not worsen renal function (7). Several case reports have described EV monotherapy for mUC in patients undergoing dialysis. Mori *et al.* also reported that two hemodialysis patients, an 85-year-old man and a 73-year-old man, were treated with EV after platinum-based chemotherapy and pembrolizumab; the older patient achieved a partial response with grade 3 neutropenia, whereas the younger patient progressed without severe adverse events, indicating that in patients on dialysis, antitumor efficacy may vary, but toxicities

remain manageable (8). Tsubonuma *et al.* reported that a 41-year-old man with mUC on hemodialysis who received standard-dose EV after platinum-based chemotherapy and avelumab, achieved a durable complete response lasting two years, and experienced no grade ≥3 toxicities, underscoring the agent's safety and activity during dialysis (9). Thus, although case reports suggest that both pembrolizumab and EV monotherapy can be used safely and sometimes effectively in patients with mUC undergoing hemodialysis, we found no study on EVP therapy in these patients; consequently, its efficacy and safety remain unknown. Furthermore, recent studies have provided additional insights into prognostic factors and treatment modification strategies during EV therapy. Hashimoto *et al.* reported that cancer-induced pain prior to EV administration was a significant predictor of poor overall survival, highlighting the importance of early initiation of EV before symptomatic disease progression (10). Additionally, Furubayashi *et al.* analyzed the impact of relative dose intensity in patients treated with EV and found that dose reductions or interruptions due to adverse events did not significantly compromise treatment efficacy (11). These findings support the feasibility of modifying EV dosage to manage adverse events even in vulnerable populations, such as patients on hemodialysis.

The FDA approval summary noted that the proportion of patients experiencing grade ≥3 treatment-related adverse events was essentially the same, approximately 50%, across all creatinine-clearance strata (≥90, 60-<90, 30-<60, and 15-<30 ml/min), indicating that the degree of renal impairment had no clinically meaningful impact on the safety profile of EVP (12). In our case, although only three cycles of EVP therapy were administered, the patient experienced grade 2 pruritus and grade 1 fatigue, but no grade ≥3 toxicities were observed. Therefore, although its efficacy remains to be determined in hemodialysis patients with mUC, EVP may be considered in the same manner as in non-hemodialysis patients in terms of safety. The strength of this report lies in its novelty of being the first to report standard-dose EVP therapy for a dialysis-dependent patient with mUC. The main limitation is that it describes only one case, and no pharmacokinetic monitoring or long-term treatment data were available.

## Conclusion

In this study, we report the case of a patient with mUC undergoing hemodialysis treated with EVP and observed an uneventful course without any grade ≥3 adverse events. This finding suggests that EVP could be a viable treatment option for hemodialysis patients with mUC, comparable to its use in non-hemodialysis patients.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

## Authors' Contributions

Takafumi Mizuno was involved in patient care, reviewed the literature, collected the patient data, and prepared the manuscript. Yuki Kobari prepared and revised the manuscript. Toshio Takagi revised the manuscript. Haruka Ito, Maki Yoshino, Kazutaka Nakamura, Takashi Ikeda, Takayuki Nakayama, Ryo Minoda, Arisa Wada, Hironori Fukuda, Kazuhiko Yoshida, and Junpei Iizuka treated the patient. All Authors have read and approved the final version of the manuscript.

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## Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for

language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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