

Cutaneous and Renal Toxicities of Enfortumab Vedotin for Advanced Urothelial Carcinoma: The UROKYU Study

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Abstract. *Background/Aim:* The clinical outcomes associated with cutaneous toxicity and changes in the renal function of patients receiving enfortumab vedotin (EV) for advanced urothelial carcinoma (UC) is unclear. *Patients and Methods:* We retrospectively analyzed the relationship between clinical outcomes and EV-related cutaneous toxicity, and the influence on the renal function in 58 patients with advanced UC who received EV after the failure of platinum-based chemotherapy and immune checkpoint inhibitors from December 2021 to July 2023. *Results:* There were no differences in the overall response and disease control rates between patients with any grade of EV-related cutaneous toxicity and without ($p=0.605$ and $p>0.99$, respectively) nor of grade ≥ 3 ($p>0.99$ and $p=0.173$, respectively). Progression-free survival was not significantly associated with EV-related cutaneous toxicity of any grade (5.4 vs. 5.6 months, $p=0.557$) nor of grade ≥ 3 (2.7 vs. 5.6 months, $p=0.053$). Overall survival was not significantly associated with EV-related cutaneous toxicity of

any grade (11.8 vs. 8.9 months, $p=0.389$), nor of grade ≥ 3 (4.6 vs. 11.4 months, $p=0.168$). The incidence of EV-related cutaneous toxicity of any grade was significantly higher in patients with any grade of ICI-related cutaneous toxicity (88.9% vs. 36.7%, $p=0.008$). There was no significant difference in the serum creatinine levels after EV treatment ($p=0.211$). Divided into two groups according to their renal function, using a serum creatinine cut-off of 2 mg/dl, there were no significant changes after EV treatment in either group ($p=0.187$ and $p=0.938$). *Conclusion:* EV-related cutaneous toxicity did not affect clinical outcomes, although it occurred in patients who experienced immune checkpoint inhibitor-related cutaneous toxicity. EV did not affect renal function.

Advanced urothelial carcinoma (UC) remains aggressive and generally incurable despite the use of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) as first-line, second-line, or maintenance therapy (1-5).

Enfortumab vedotin (EV) is an antibody–drug conjugate comprising a monoclonal antibody to nectin-4 linked to chemotherapeutic monomethyl auristatin E (6-8). EV binds to cells that express nectin-4 with high affinity, triggering internalization and the release of monomethyl auristatin E into target cells. Monomethyl auristatin E disrupts microtubule networks, leading to cell-cycle arrest and apoptotic death in cells expressing nectin-4 (8, 9).

EV-301 was a phase 3 global open-label trial that evaluated EV in comparison to standard chemotherapy chosen by the investigator (docetaxel, paclitaxel or vinflunine) in patients with locally advanced or metastatic UC who had previously received platinum-based chemotherapy and ICIs of programmed cell

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Key Words: Urothelial carcinoma, enfortumab vedotin, cutaneous toxicity, renal function toxicity.



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death protein 1 (PD1) or its ligand PD-L1. The trial showed that overall survival (OS) was significantly longer in the EV-treated group than in the chemotherapy-treated group [hazard ratio=0.70; 95% confidence interval (CI)=0.56-0.89; $p=0.001$] (10). Based on the results of the EV-301 trial, since September 2021, EV has been approved in Japan as a third-line treatment for advanced UC that has become exacerbated after platinum-based chemotherapy and ICIs, and the efficacy and tolerability of EV for patients with metastatic UC in the real world has already been reported (11).

According to the relationship between clinical outcomes and treatment-related adverse events, patients with cancer who develop immune-related adverse events (irAEs) often show a better therapeutic response than those who do not, suggesting a close link between autoimmunity and the antitumor effect elicited by ICIs (12, 13). In fact, a growing body of evidence suggests that patients with irAEs have marked improvements in progression-free survival (PFS), OS, and overall response rate (ORR) in comparison to those who do not develop irAEs, with more consistent data in patients treated with PD1 and PD-L1 inhibitors (14). We also reported similar results in patients with advanced UC with irAEs in association with pembrolizumab treatment (15).

Nectin-4 is highly expressed in several solid tumor types, including urothelial, breast, gastric, and lung carcinoma (6, 16-18). However, its expression is mild to moderate in human skin keratinocytes and appendages (6). Cutaneous toxicity is an anticipated on-target toxicity; however, it remains unclear whether patients who develop EV-related cutaneous toxicity have a better therapeutic response.

Additionally, similar to ICI as second-line or maintenance therapy, EV does not require volume adjustment based on renal function, although the regimen of platinum-based first-line chemotherapy including cisplatin or carboplatin was based on renal function because patients with advanced UC often have comorbidities, including renal dysfunction, which limit their ability to receive cisplatin, which is nephrotoxic (14, 19-21). However, the effects of long-term EV use on renal function have not yet been reported in real-world clinical practice, and the effects of EV on renal function may also have implications for post-EV treatment options.

In this study, we retrospectively evaluated the relationship between clinical outcomes and EV-related cutaneous toxicity, and the influence on the renal function in patients with advanced UC who experienced progression on platinum-based chemotherapy and ICIs.

Patients and Methods

Patients. A total of 59 consecutive patients who received EV for advanced UC (metastatic or locally advanced) that had progressed radiologically with platinum-based chemotherapy and ICIs were collected from six institutions from December 2021 to July 2023 –

the Uro-Oncology Group in Kyushu (UROKYU) study population; one case was excluded from the present study due to the lack of an imaging evaluation.

EV was administered at a dose of 1.25 mg/kg of body weight by means of intravenous infusion over 30 min on days 1, 8 and 15 for continuous 28-day cycles, until the occurrence of disease progression (PD) or adverse events that were deemed unacceptable. Tumor measurements were generally performed using computed tomography before treatment and after every 1-3 cycles of EV or when it was deemed to be clinically necessary. The tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (22). EV-related cutaneous toxicity grades were assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (23). Serum creatinine was measured before and after dosing, at the time of PD in cases in which EV-treated patients developed PD, and at the time of the last dose of EV in cases where EV-treated patients did not develop PD and were able to continue to receive treatment.

Patients' clinical information and follow-up data were obtained from their medical records.

This study was approved by the Institutional Review Board of the Kyushu Cancer Center of the National Hospital Organization (2022-33) and the Ethics Committee of each institution. This study conformed to the Declaration of Helsinki and its amendments. Written informed consent was obtained from all the participating patients.

Statistical analysis. All statistical analyses were performed using the JMP® Pro software package, version 17.0.0 (SAS Institute, Inc., Cary, NC, USA). The ORR was defined as the proportion of patients with partial or complete response to EV. The disease control rate (DCR) is a composite of the ORR and stable disease rate. Fisher's exact probability test was used to compare categorical variables. The Wilcoxon signed-rank test was used to assess differences between serum creatinine levels prior to treatment and after treatment.

PFS and OS were calculated using the Kaplan–Meier method. PFS was calculated from the date of the initiation of EV until the date of investigator-assessed clinical and/or radiographic disease, as assessed by the investigator, and OS was calculated from the date of the initiation of EV until the date of death. For both PFS and OS, patients without an event were censored on the date of the last follow-up examination. A log-rank test was used to determine the differences in PFS and OS in the presence or absence of EV-related cutaneous toxicity, including grade ≥ 3 . Statistical significance was set at $p < 0.05$.

Ethics approval and consent to participate. The present study was approved by the Institutional Review Board of National Hospital Organization Kyushu Cancer Center (2022-33), and written informed consent was obtained from all patients.

Results

Patient characteristics. The clinical characteristics of the 58 patients are shown in Table I. The median follow-up period after receiving EV was 7.2 months (interquartile range=3.6-11.5 months). In this cohort, the median age was 73 years (interquartile range=68-77 years), and 44 patients were male (75.9%). Twenty-three patients had an Eastern Cooperative

Table I. *Patient characteristics.*

Characteristic (n=58)	Value
Age, years	
Median (IQR)	73 (68-77)
Sex, n (%)	
Male	44 (75.9)
ECOG PS, n (%)	
0	23 (39.7)
1	25 (43.1)
≥2	10 (17.2)
Primary tumor site, n (%)	
Lower urinary tract	30 (51.7)
Upper urinary tract	28 (48.3)
Histologic testing, n (%)	
Pure UC	41 (70.7)
Prior immune checkpoint inhibitor, n (%)	
Anti-PD1	38 (65.5)
Anti-PD-L1	20 (34.5)
Number of regimens prior to EV	
2	41 (70.7)
≥3	17 (29.3)
Visceral metastases, n (%)	
Yes	47 (81.0)

ECOG PS: Eastern Cooperative Oncology Group performance status; EV: enfortumab vedotin; IQR: interquartile range; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; UC: urothelial carcinoma.

Oncology Group Performance Status of 0 (39.7%), 41 had pure UC according to a histological analysis (70.7%). The proportion of patients with the upper urinary tract as the primary tumor site was similar to that of the lower urinary tract group (48.3%, 51.7%, respectively). With regard to prior ICIs, 38 had received anti-PD-1 (65.5%) and others had received anti-PD-L1. Forty-seven patients (81.0%) had visceral metastases when EV was started. Twenty-eight patients (48.3%) died during the follow-up period.

ORR and DCR in patients with and without EV-related cutaneous toxicity. The ORR and DCR in patients treated with EV were 53.5% and 74.1%, respectively [best response: complete response (CR) in 3, partial response (PR) in 28, stable disease (SD) in 12 and PD in 15] (Table II). Overall, EV-related cutaneous toxicity occurred in 26 (44.8%) patients, with six (10.3%) experiencing severe cutaneous toxicity (grade ≥3). There were no differences in the ORR and DCR between patients with EV-related cutaneous toxicity of any grade and without ($p=0.605$ and $p>0.99$). Similarly, there were no differences in ORR and DCR between patients with and without grade ≥3 EV-related cutaneous toxicity ($p>0.99$ and $p=0.173$).

PFS and OS of patients with and without EV-related cutaneous toxicity. A log-rank test revealed no significant differences in

PFS between patients with and without EV-related cutaneous toxicity (5.4 vs. 5.6 months, $p=0.557$), nor with and without grade ≥3 EV-related cutaneous toxicity (2.7 vs. 5.6 months, $p=0.053$) (Figure 1). Similarly, OS was not significantly associated with EV-related cutaneous toxicity of any grade (11.8 vs. 8.9 months, $p=0.389$), nor with grade ≥3 EV-related cutaneous toxicity (4.6 vs. 11.4 months, $p=0.168$) (Figure 2).

The association between ICI-related and EV-related cutaneous toxicity. Overall, ICI-related cutaneous toxicities had occurred in nine (15.5%) patients before the administration of EV. The incidence of EV-related cutaneous toxicity of any grade was significantly higher in patients with any grade of ICI-related cutaneous toxicity (88.9% vs. 36.7%, $p=0.008$). However, there was no significant difference in the incidence of grade ≥3 EV-related cutaneous toxicity between patients with and without a history of ICI-related cutaneous toxicity (11.1% vs. 10.2%, $p>0.99$) (Figure 3).

Serum creatinine changes of patients treated with EV. There were no significant differences in the serum creatinine levels pre- and post-EV treatment in any case ($p=0.211$). Divided into two groups according to renal function by serum creatinine (<2 and ≥2 mg/dl), there were no significant change in serum creatinine with EV treatment ($p=0.187$ and $p=0.938$) (Table III). Divided into two groups by EV-related cutaneous toxicity, there were no significant change in serum creatinine level after EV treatment in the groups with EV-related and unrelated cutaneous toxicity (any grade: $p=0.210$ and $p=0.660$; grade ≥3: $p=0.625$ and $p=0.266$). Divided into two groups by objective response, there was a significant improvement in the renal function in the CR+PR group after EV treatment ($p=0.047$), while there was no significant change in the SD+PD group ($p=0.629$).

Discussion

This multicenter retrospective study sought to evaluate the relationship between EV-related cutaneous toxicity and the clinical outcomes, the relationship between ICI-related and EV-related cutaneous toxicity, and the influence of EV on renal function in patients with advanced UC treated with EV. The present study confirmed that EV-related cutaneous toxicity, regardless of grade, was not associated with a significantly higher ORR or DCR, nor longer PFS or OS in comparison to patients without EV-related cutaneous toxicity. However, it was also confirmed that patients who developed cutaneous toxicities related to therapy with ICIs developed cutaneous toxicities significantly more frequently during EV treatment. In addition, it was also confirmed that EV did not cause significant worsening of renal function and that the renal function significantly improved in patients with CR or PR during treatment with EV.

Table II. The overall response rate and disease control rate in patients with and without enfortumab vedotin (EV)-related cutaneous toxicity.

	EV-related cutaneous toxicity, n (%)			EV-related cutaneous toxicity, n (%)		
	Any grade	Without	<i>p</i> -Value	Grade ≥3	Grade ≤2	<i>p</i> -Value
Number of patients	26	32		6	52	
Overall response rate (CR+PR)	15 (57.7)	16 (50.0)	0.605	3 (50.0)	28 (53.9)	>0.99
Disease control rate (CR+PR+SD)	19 (73.1)	24 (75.0)	>0.99	3 (50.0)	40 (76.9)	0.173

CR: Complete response; PR: partial response; SD: stable disease.

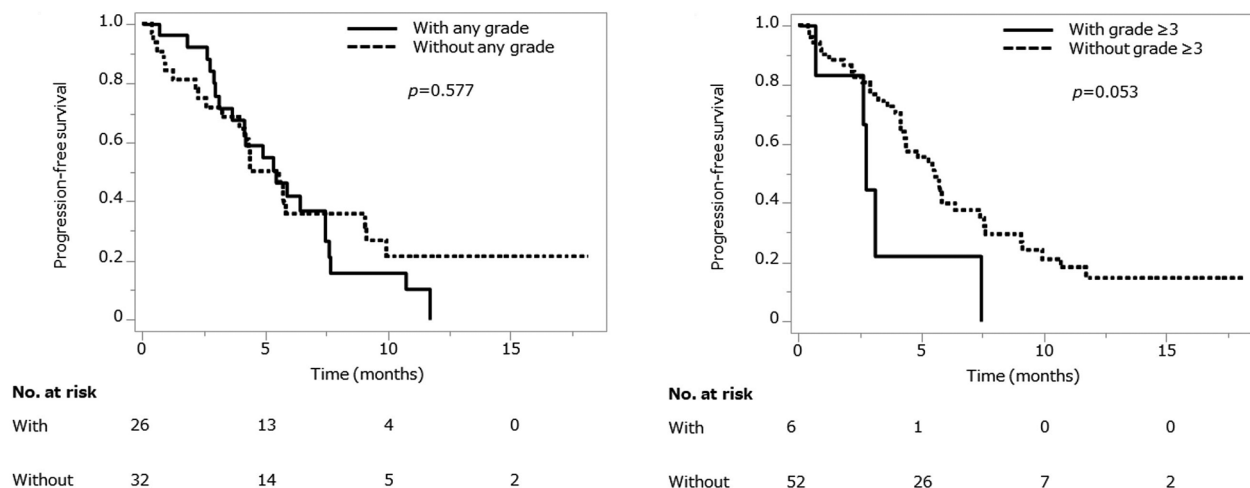


Figure 1. Progression-free survival of patients with and without enfortumab vedotin-related cutaneous toxicity.

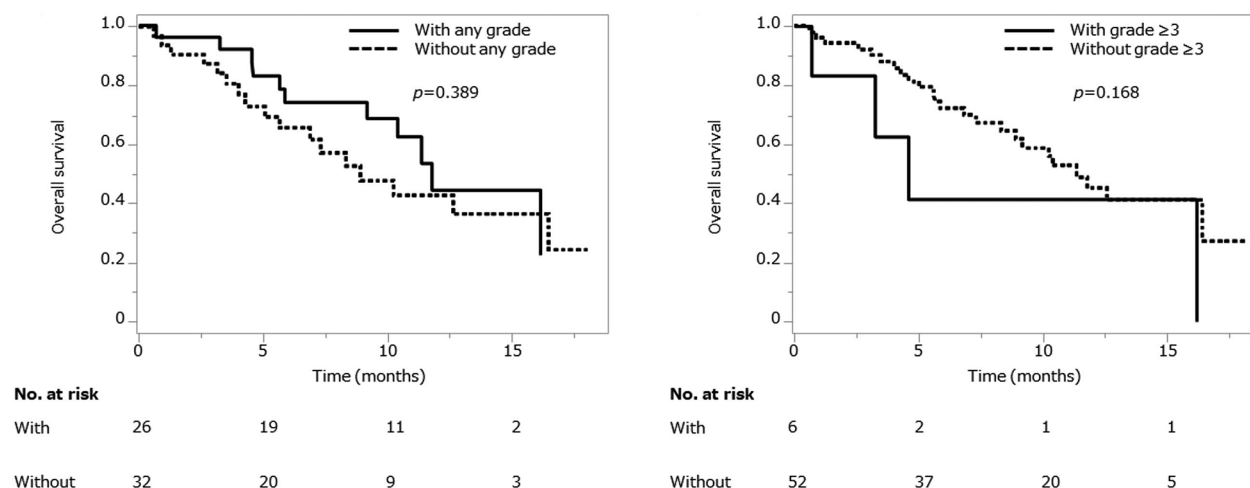


Figure 2. Overall survival of patients with and without enfortumab vedotin-related cutaneous toxicity.

The relationship between cutaneous toxicity and the clinical outcomes of patients with advanced UC receiving EV remains unclear. It was reported that in 58 adult patients treated with EV, 15 (25.9%) developed cutaneous EV-related

adverse events (all grade 1-2). However, cutaneous adverse events were not predictive of the tumor response (24). That report is supported by the results of the present study, which found that EV-related cutaneous toxicity, regardless of grade,

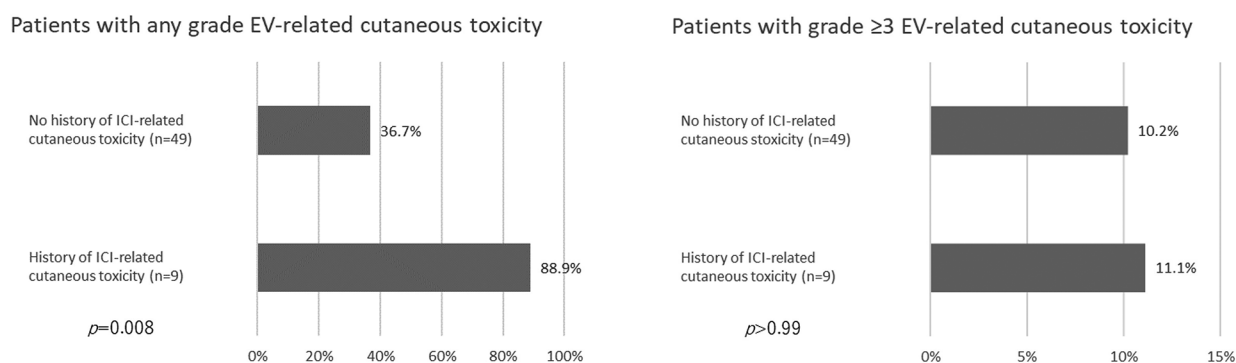


Figure 3. Association between immune checkpoint inhibitor (ICI)-related cutaneous toxicity and enfortumab vedotin-related cutaneous toxicity.

Table III. Serum creatine changes in patients treated with enfortumab vedotin (EV).

Characteristic		Median serum creatine (IQR), mg/dL		p-Value
		Pre-EV	Post-EV	
All	n=58	1.23 (0.94-1.47)	1.15 (0.91-1.63)	0.211
Serum creatine	<2 mg/dl (n=51)	1.17 (0.93-1.39)	1.11 (0.89-1.30)	0.187
	≥2 mg/dl (n=7)	4.02 (2.50-5.59)	3.52 (2.10-5.08)	0.938
Any-grade EV-related cutaneous toxicity	With (n=26)	1.31 (0.92-1.49)	1.17 (0.91-1.54)	0.210
	Without (n=32)	1.19 (0.98-1.47)	1.13 (0.89-1.64)	0.660
Grade ≥3 EV-related cutaneous toxicity	With (n=6)	1.05 (0.75-2.55)	1.27 (0.80-1.47)	0.625
	Without (n=52)	1.27 (0.95-1.47)	1.15 (0.92-1.58)	0.266
Overall response rate	CR+PR (n=31)	1.40 (1.04-1.54)	1.15 (0.96-1.62)	0.047
	SD+PD (n=27)	1.09 (0.80-1.33)	1.14 (0.79-1.65)	0.629

CR: Complete response; IQR: interquartile range; PR: partial response; SD: stable disease; PD: progressive disease.

was not associated with better clinical outcomes (ORR, DCR, PFS, and OS). Although no significant differences were observed, PFS and OS tended to worsen with EV-related grade ≥3 cutaneous toxicity, suggesting that the control of adverse events remains important.

On the other hand, it was reported that 27 out of 56 patients (48.2%) developed EV-related cutaneous toxicity. Cutaneous toxicity was significantly associated with better ORR (57.7% with vs. 24.0% without, $p=0.0145$), but there was no significant difference in PFS (6.0 vs. 4.5 months, $p=0.24$) In addition, those with cutaneous toxicity had significantly higher baseline weight (84.0 vs. 71.7 kg, $p=0.0129$) and body mass index (26.5 vs. 22.3 kg/m², $p=0.0014$) (25).

Interestingly, the present study also revealed that patients who experienced cutaneous toxicity during ICI treatment developed cutaneous toxicity significantly more frequently during EV treatment. At present, EV is the standard of care for the treatment of patients with advanced UC who have previously received platinum-containing chemotherapy and who experienced disease progression during or after PD1 or

PD-L1 inhibitor treatment (5). Previous studies have reported that rash, pruritus, colitis, and pneumonia are the most common irAEs, and may be associated with the interaction of autoantibodies with activated immune cells during ICI treatment (26-28). A systematic review and meta-analysis of treatment-related adverse events associated with PD1 or PD-L1 inhibitors also reported that these treatments had a great impact on skin disorders, and that the risk of pruritus in treated patients was 2.34 (95% CI=1.85-2.96) times greater than that in a control group and 1.53 (95% CI=1.25-1.87) times greater risk for rash (29). In our previous study of patients with advanced UC treated with pembrolizumab, we also reported that skin-related irAEs were the most common type of irAE (skin-related irAEs occurred in 14.3% of patients, while irAEs occurred overall in 32.4%) (15).

Similarly, skin reactions were the most common EV treatment-related adverse event of any grade (47.0%) in the EV-301 trial (10). With regard to factors that cause EV-related cutaneous toxicity, it was reported that factors associated with the development of cutaneous adverse events included previous exposure to cisplatin (hazard ratio=4.61,

95% CI=1.04-20.48; $p=0.044$) or radiation therapy (hazard ratio=4.76, 95% CI=1.69-13.48; $p=0.003$) (24). Therefore, based on these results and those of the present study, it can be stated that patients who develop skin toxicity due to platinum-based chemotherapy or ICIs used prior to EV treatment should be carefully observed and promptly treated for skin toxicity during EV treatment.

Although review articles about treatment-related adverse events of antibody–drug conjugates have been published, there has been little discussion of renal toxicity (30-32). In the EV-301 clinical trial, dose modifications and interruptions were permitted for the management of adverse events based on the prespecified criteria. Among non-hematological types of toxicity, dose modification is recommended for neuropathy, corneal adverse events, and hyperglycemia/elevated blood glucose depending on the grade of adverse event (10). The present study revealed that EV did not worsen renal function irrespective of the pretreatment sum creatine level and ORR, and that renal function did not influence the incidence of cutaneous toxicity. Interestingly, the present study also revealed that EV significantly improved renal function in patients with a CR or PR. This phenomenon may be caused, in part, by patient characteristics. In patients with a CR or PR as the objective response ($n=31$), 61.3% ($n=19$) of the primary tumors were located in the upper urinary tract. In contrast, in patients with SD or PD ($n=27$), only 33.3% ($n=9$) of primary tumors were located in the upper urinary tract. In other words, the shrinkage of the tumor in the upper urinary tract due to EV treatment may have caused the improvement of obstruction, which thus led to an improved renal function.

Recently, combination therapy with EV and pembrolizumab was confirmed to be associated with a high ORR of 64.5% and a rapid and durable response, with 65.4% of responders maintaining a response at 12 months during first-line treatment among cisplatin-ineligible patients with locally advanced or metastatic UC in Cohort K of the EV-103 phase Ib/II study (33). Therefore, urologic oncologists are expected to use EV in combination with pembrolizumab for a longer duration in comparison to when EV is administered in a third-line setting in clinical practice. The results of the present study may support the possibility of the safe use, in terms of renal function, of EV in patients with a poor renal function, not only as third-line or later treatment but also from the first-line treatment.

Study limitations. Firstly, it was a retrospective, non-randomized study, and included a relatively small number of patients with both lower and upper urinary tract UC. The present study was a multicenter study; therefore, there may have been some differences among the centers in the regimen and number of prior platinum-based chemotherapies and ICIs, as well as in the timing of the evaluation of clinical outcomes and the severity of adverse events associated with EV treatment. These background characteristics may have influenced the results.

Conclusion

EV-related cutaneous toxicity did not affect clinical outcomes of patients with advanced UC who received EV after platinum-based chemotherapy and ICIs. However, EV-related cutaneous toxicity tended to occur in patients who had experienced ICI-related cutaneous toxicity. EV did not affect renal function.

Conflicts of Interest

The Authors declare that they have no conflicts of interest for this study.

Authors' Contributions

Study concept and design: N. Furubayashi, A.M. T.N., K.H. and M.N.; acquisition of data: A.M., T.T., H.M., Y.H., K. Kiyoshima, T.N., Y.H., T.K. Y.S. and K.H.; statistical analysis: N. Furubayashi, and H.M.; analysis and interpretation of data: all Authors; drafting of the original article: N. Furubayashi, A.M. and M.N.; critical revision of the article for important intellectual content: all Authors; supervision: K. Kuroiwa, N.S., N. Fujimoto and M.N. All Authors have read and approved the final version of the article.

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