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Efficacy and Tolerability of Enfortumab Vedotin for Metastatic Urothelial Carcinoma: Early Experience in the Real World

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Abstract. *Background/Aim: This study retrospectively investigated the impact of enfortumab vedotin (EV) monotherapy on the oncological outcome, safety profile, and health-related quality of life (HRQoL) in patients with metastatic urothelial carcinoma. Patients and Methods: We assessed 26 consecutive patients who had received EV monotherapy after failure of platinum-based chemotherapy and immune checkpoint blockade therapy at our single institution from December 2021 to January 2023. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), incidence of adverse events (AEs), and EORTC QLQ-C30 as an HRQoL instrument were evaluated. Results: The ORR and DCR were 57.7% and 80.8%, respectively. EV was effective regardless of the patient and tumor characteristics, including the efficacy of previous systemic therapy, performance status, number of Bellmunt risk factors, and presence of variant histology. With a median follow-up time of 7.5 months, the median durations of PFS and OS were 5.4 months and 10.3 months, respectively. Grade ≥3 AEs included neutropenia (15.4%), fatigue (7.7%), appetite loss (7.7%), rash (3.8%), febrile neutropenia (3.8%), hyperglycemia (3.8%), and interstitial pneumonia (3.8%). AEs resulting in withdrawal of EV, interruption of EV, and dose reduction occurred in two (7.7%), nine (34.6%), and 13 patients (50.0%), respectively. The EORTC QLQ-C30 scores from baseline to post-EV introduction remained stable. Conclusion: EV monotherapy demonstrated promising anti-tumor activity and tolerability in patients with metastatic urothelial carcinoma.*

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Platinum-based combination chemotherapy has been the standard treatment of advanced urothelial carcinoma (UC) for over three decades (1, 2). However, the advent of immune checkpoint inhibitors (ICIs) has remarkably changed the treatment of advanced UC in the last few years. In Japan, pembrolizumab (anti-programmed death 1 antibody) was approved for patients after failure of platinum-based chemotherapy in December 2017 based on the results of the KEYNOTE-045 trial (3). Subsequently, in Japan, avelumab [anti-programmed death ligand 1 (PD-L1) antibody] was approved for patients without progression after platinum-based chemotherapy in February 2021 based on the results of the JAVELIN Bladder 100 trial (4). However, while platinum-based chemotherapy and ICIs have shown survival benefits, the majority of patients with advanced UC tend to progress and only few patients can achieve a long-term disease control (1-4). In fact, although we have previously reported on the efficacy of platinum-based chemotherapy and pembrolizumab (5, 6), the results on survival outcomes were insufficient. In addition, the clinical use of certain ICIs, such as atezolizumab and durvalumab, for UC is still not approved in Japan.

In 2021, the EV-301 phase 3 trial showed that enfortumab vedotin (EV), an antibody-drug conjugate (ADC) directed against nectin-4, could significantly prolong survival in patients with advanced UC who had previously received platinum-based chemotherapy and ICIs (7). Based on the results, EV monotherapy was approved in November 2021 in Japan. With the development of immune checkpoint blockade therapy, late-line treatments for metastatic UC have thus relatively increased. Despite the fact that EV monotherapy was approved as third-line therapy for patients with advanced UC, clinical data on the therapeutic experience of EV in daily practice are lacking. Additionally,

EV was the first approved drug as ADC for malignancies of the genitourinary system (7).

The current study aimed to assess the early experience of EV monotherapy on oncological outcomes and safety profiles in patients with metastatic UC. In addition, we evaluated the health-related quality of life (HRQoL) by using self-reported outcomes in these patients.

Patients and Methods

Patient population. This study retrospectively evaluated 26 consecutive patients with metastatic bladder or upper urinary tract cancer who had received EV after failure of platinum-based chemotherapy and immunotherapy (avelumab or pembrolizumab) at the University of Occupational and Environmental Health (UOEH; Kitakyushu, Japan) between December 2021 and January 2023. All patients were histologically diagnosed with UC with or without histological variants and showed radiologically confirmed disease progression after chemotherapy followed by immune checkpoint blockade therapy for metastatic disease. This study protocol was approved by the UOEH Institutional Review Board (approval no. UOEHCRB20-134).

Patient management. EV was administered intravenously on days 1, 8, and 15 at a dose of 1.25 mg/kg, and the cycle was repeated every four weeks. EV treatment continued until disease progression, unacceptable adverse events (AEs), or consent withdrawal. Routine follow-up consisted of physical examinations, laboratory tests, and chest–abdominal–pelvic computed tomography (CT). CT was performed at baseline and after every 1-3 cycles of EV. Appropriate additional tests were conducted when symptoms were noted on clinical examination.

Evaluation. The objective response to EV treatment was assessed according to the Response Evaluation of Criteria in Solid Tumours, version 1.1. (8). The objective response rate (ORR) was defined as the proportion of patients with complete response (CR) and partial response (PR), but not stable disease (SD) and progressive disease (PD). Furthermore, the disease control rate (DCR) comprised of ORR and SD.

Safety analyses were evaluated using the Common Terminology Criteria for Adverse Events version 5.0 (9) to summarize the frequency of treatment-related AEs. Additionally, we evaluated the HRQoL as a patient-reported outcome measure. In cases where patients provided their informed consent, HRQoL was assessed at baseline and post-EV introduction (after cycle 1) using the European Organization for Research and Questionnaire-Core 30 items (QLQ-C30) (10), which consists of three thematic sections, namely global health status, functional domain, and symptom domain (each score from 0 to 100).

Statistical analysis. All statistical analyses were performed using EZR version 1.40 (Easy R, Vienna, Austria), a graphical user interface for R (The R Foundation for Statistical Computing) (11). Between-group differences with respect to categorical variables were assessed using the Fisher exact test. Changes in the EORTC QLQ-C30 score from the baseline to post-EV introduction were examined using the Wilcoxon signed-rank test. The duration of progression-free survival (PFS) was calculated from the beginning of EV administration to the date of disease progression or last follow-up in patients without progression. The OS duration was calculated from the beginning of EV administration to the date of death due to any cause or last follow-up in patients who survived. PFS and OS were estimated using the Kaplan–Meier method. A value of $p<0.05$ was considered to indicate statistically significant differences.

Results

Patient characteristics. The baseline characteristics of the 26 patients, who had received EV monotherapy, are summarized in Table I. The majority of the patients were male (84.6%), and the median age was 73 years [interquartile range (IQR)=65-76]. Regarding the primary tumor site, 11 (42.3%) and 15 (57.7%) were in the bladder and upper urinary tract, respectively, while 26.9% of patients had liver metastasis. Twenty-six point nine percent of the patients had an Eastern Cooperative Oncology Group performance status (PS) of ≥2, 53.8% had Bellmunt risk factors (12) of ≥2, and 34.6% had variant histology. The number of therapy lines administered before EV therapy was two in 69.2% of the patients, and ≥3 in 30.8%. Prior immunotherapy involved avelumab (26.9%) and pembrolizumab (73.1%).

Clinical outcomes and survival. The tumor response to EV is shown in Table II. The response rates in the studied patients were: CR in two patients (7.7%), PR in 13 (50.0%), SD in six patients (23.1%), and PD in five patients (19.2%). Furthermore, the ORR and DCR values were 57.7% and 80.8%, respectively. The associations between the response to EV and clinical factors, including primary tumor site, efficacy of prior platinum-based chemotherapy and ICI therapy, PS, number of prior therapy lines, number of Bellmunt risk factors, and histologic type, are shown in Table III. The ORRs in non-responders to prior platinum-based chemotherapy, non-responders to prior ICI therapy, patients with a PS of ≥2, patients with Bellmunt risk factors of ≥2, and patients with UC with variant histology groups, was 50.0%, 53.3%, 71.4%, 64.3%, and 66.7%, respectively. At the time of analysis, the median follow-up duration was 7.5 months (IQR=4.9-10.8 months), during which 20 (76.9%) patients experienced progression and 15 (57.7%) patients died from metastatic UC. The median durations of PFS (Figure 1A) and OS (Figure 1B) after EV initiation were 5.4 months [95% confidence interval (CI)=4-7.5] and 10.3 months (95%CI=6.8-12), respectively.

Treatment-related AE profile. As shown in Table IV, the major AEs occurred in ≥25% of patients included appetite loss (46.2%), rash (42.3%), fatigue (34.6%), alopecia (30.8%), pruritis (30.8%), dysgeusia (26.9%), and neutropenia (26.9%). Furthermore, grade 3≤ AEs included neutropenia (15.4%), fatigue (7.7%), appetite loss (7.7%), rash (3.8%), febrile neutropenia (3.8%), hyperglycemia (3.8%), and interstitial pneumonia (3.8%). AEs resulting in withdrawal of EV, interruption of EV, and dose reduction occurred in two patients (7.7%), nine patients (34.6%), and 13 patients (50.0%), respectively. Regardless of their severity, we did not note any deaths caused by AEs during the EV monotherapy period.

Table I. *Patient characteristics*.

Characteristic	Patients receiving EV (N=26)
Median age, years (IQR)	73 (65-76)
Sex, n (%)	
Male	22 (84.6)
Female	4 (15.4)
Performance status, n (%)	
0	10 (38.5)
1	9 (34.6)
2	5 (19.2)
3	2 (7.7)
Primary tumor site, n (%)	
Bladder	11 (42.3)
Upper urinary tract	15 (57.7)
Metastatic lesion, n (%)	
Lymph node	21 (80.8)
Liver	7 (26.9)
Lung	10 (38.5)
Bone	6 (23.1)
Histology, n (%)	
Pure UC	17 (65.4)
UC with variant histology	9 (34.6)
Bellumunt risk factors, n (%)	
0, 1	12 (46.2)
≥2	14 (53.8)
Prior therapy lines, n (%)	
2	18 (69.2)
≥3	8 (30.8)
Prior immune checkpoint blockade, n (%)	
Avelumab	7 (26.9)
Pembrolizumab	19 (73.1)
EV cycles, median (IQR)	5 (3-7)
Follow-up duration, median (IQR) months	7.5 (4.9-10.8)

IQR: Interquartile range; UC: urothelial carcinoma; EV: enfortumab vedotin.

HRQoL assessments. Twenty-one patients (80.8%) completed the EORTC QLQ-C30 at baseline and post-EV introduction (after cycle 1). Table V shows the changes in score from baseline to post-EV introduction. Pertaining to the global health status and functional domain scores, higher scores represent better conditions, whereas lower symptom domain scores represent symptom improvement (10). In the present study, both global health status and functional domain scores remained constant after EV introduction with similar mean scores. With respect to the symptom domain, each individual score did not change significantly from baseline to post-EV introduction. A trend of improvement was only noted in the pain scores (mean score at baseline=23.8 *vs*. mean score at post-EV introduction=15.9, p=0.082). In contrast, symptom scores, including those for appetite loss and diarrhea, indicated a slight worsening of symptoms although not statistically significant.

Table II. *Results of radiographic response to enfortumab vedotin (EV) monotherapy.*

Response to EV (N=26)	n (%)
CR	2 (7.7)
PR	13 (50.0)
SD	6 (23.1)
PD	5 (19.2)
ORR (CR+PR)	20 (57.7)
DCR (CR+PR+SD)	26 (80.8)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

Table III. *Relationship between the efficacy of enfortumab vedotin (EV) and clinicopathological factors*.

Subgroup	SD+PD n (%)	CR+PR n (%)	p-Value
Primary tumor site			1.000
Bladder	5 (45.5)	6 (54.5)	
Upper urinary tract	6 (40.0)	9 (60.0)	
Platinum-based chemotherapy			0.692
Responder	5 (35.7)	9 (64.3)	
Non-responder	6 (50.0)	6 (50.0)	
Immune checkpoint blockade			0.701
Responder	4 (36.4)	7 (63.6)	
Non-responder	7 (46.7)	5 (53.3)	
Performance status			0.658
0, 1	9 (47.4)	10 (52.6)	
≥2	34 (79.1)	5 (71.4)	
Prior therapy lines			1.000
2	8 (44.4)	10 (55.6)	
≥3	3 (37.5)	5 (62.5)	
Bellumunt risk factors			0.692
0, 1	6 (50.0)	6 (50.0)	
≥2	5 (53.7)	9 (64.3)	
Histologic type			0.683
Pure UC	8 (47.1)	9 (52.9)	
UC with variant histology	3 (33.8)	6 (66.7)	

UC: Urothelial carcinoma; SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response.

Discussion

To assess the influence of EV monotherapy on the clinical outcomes of patients with metastatic UC, we evaluated the tumor response, survival, and tolerability status, including treatment-related AEs profile and HRQoL. EV monotherapy after failure of platinum-based chemotherapy and ICI therapy exhibited a high therapeutic effect on both ORR and DCR. Our cohort of patients with metastatic UC had similar PFS and OS compared with those included in the EV-301 trial (7). The AEs of EV were acceptable for safety, and the

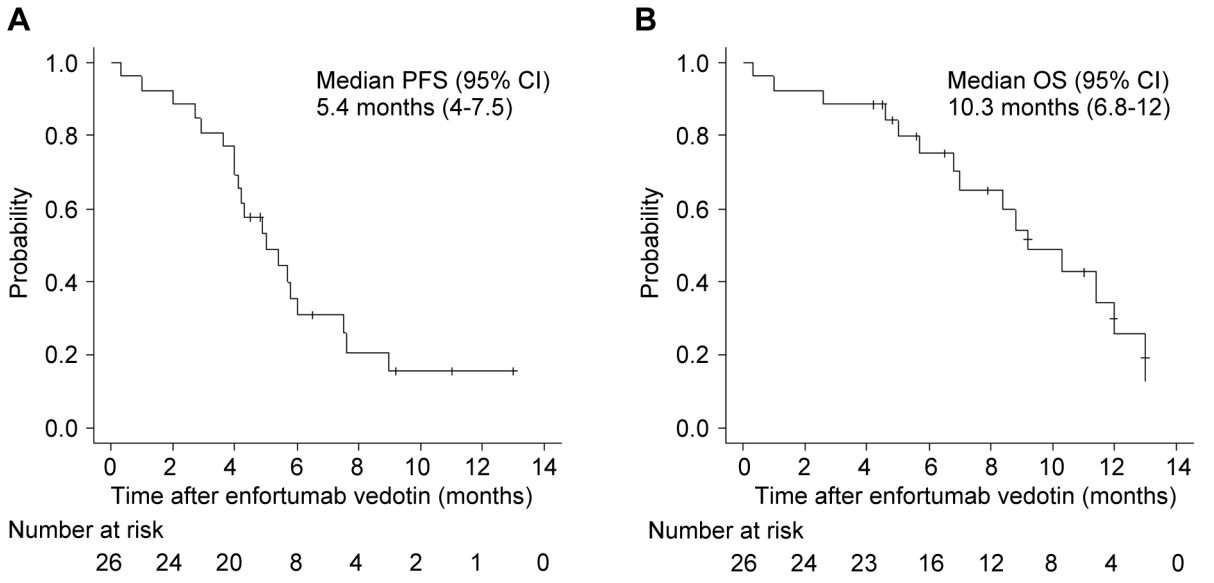

Figure 1. *Kaplan–Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS) after initiation of enfortumab vedotin in patients with metastatic urothelial carcinoma.*

HRQoL of patients in the current cohort was maintained even after the introduction of EV monotherapy.

In the EV-301 trial (7) and Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study (a large multicenter retrospective cohort) (13), the ORR/DCR for patients treated with EV monotherapy were 40.6%/71.9% and 52%/78%, respectively. Moreover, the median durations of PFS and OS were 5.6 and 12.9 months, and 6.8 and 14.4 months, respectively. It should be noted, however, that compared with the EV-301 trial, the UNITE study population included both platinum-pretreated and platinum-naïve patients (13). Nonetheless, our findings showed high-response rates and similar survival compared with these previous studies. Interestingly, our findings demonstrated that EV monotherapy was effective regardless of the patients' background, including primary tumor site, efficacy of prior platinum-based chemotherapy and ICI therapy, PS, number of prior therapy lines, Bellmunt risk factors, and histologic subtype. In the KEYNOTE-045 trial (14), the ORR and median durations of PFS for pembrolizumab, which is widely used as second-line therapy, was 21.9% and 2.1 months, respectively. Considering that EV is a later-line treatment compared with pembrolizumab, our results are worth noting. Because, the ORR and median durations of PFS for EV monotherapy in this study were higher and longer than that for pembrolizumab. Given the lack of recommended third-line regimens for metastatic UC, the efficacy of EV could play an important role in the treatment of advanced UC disease. Real-world studies from the United States have reported the opportunities for systemic therapy in UC, but only approximately 3%-7% of patients with newly diagnosed metastatic disease receive third-line therapy (15).

Although the characteristic AEs of EV included the development of rashes, peripheral sensory neuropathy, and hyperglycemia, our study showed that these grade ≥3 AEs only occurred in a few patients. Compared with the EV-301 population (7), the patients in the present study had a higher incidence of any grade AEs, including appetite loss (46.2% *vs.* 30.7%), rash (42.3% *vs.* 16.2%), and neutropenia (26.9% *vs.* 10.1%). Thus, symptoms such as the manifestation of rashes and neutropenia appeared to be higher in the Japanese patients than in the global population in the EV-301 trial (7, 16). Consequently, it could be inferred that there may be significant differences in the toxicities of EV between Asian and Caucasian populations. AEs of EV resulting in withdrawal of treatment, interruption of treatment, and dose reduction occurred in 7.7%, 34.6%, and 50.0% in our population, and in 13.5%, 51.0%, and 32.4% in the EV-301 population (7), respectively.

Patients with poor general conditions including the elderly and those with poor PS, have not been fully included in current clinical trial (7), it is still debatable whether these patients should receive EV therapy. The patients in our cohort were older (median age: 73 *vs.* 68 years) and had a poor PS (proportion of patients with PS of ≥2: 26.9% *vs.* 0%) compared with those in the EV-301 trial. Although EV treatment caused numerous AEs, we consider that the toxicities appeared to be both tolerable and manageable in patients with metastatic UC.

The present study found no significant differences in the EORTC QLQ-C30 scores between the baseline and post-EV introduction. Although HRQoL analysis was not performed

Table IV. *Treatment-related adverse events of enfortumab vedotin.*

Event	Any grade, n (%)	Grade ≥3, n (%)
Pyrexia	5 (19.2)	0
Alopecia	8 (30.8)	0
Peripheral sensory neuropathy	6 (23.1)	0
Fatigue	9 (34.6)	2 (7.7)
Dysgeusia	7 (26.9)	0
Appetite loss	12 (46.2)	2 (7.7)
Diarrhea	5 (19.2)	0
Pruritis	8 (30.8)	0
Rash	11 (42.3)	1 (3.8)
Neutropenia	7 (26.9)	4 (15.4)
Febrile neutropenia	1 (3.8)	1 (3.8)
Anemina	4 (15.4)	0
Thrombocytopenia	6 (23.1)	0
Hyperglycemia	4 (15.4)	1 (3.8)
Interstitial pneumonia	1 (3.8)	1 (3.8)

Table V. *EORTC QLQ-C30 scores from baseline to post-enfortumab vedotin introduction.*

Variable	Mean score (SD)		*p*-Value
	Baseline	After cycle 1	
Global health status	64.7 (29.8)	65.9 (28.9)	0.692
Functional domain			
Physical functioning	74.0 (26.2)	77.4 (26.1)	0.432
Role functioning	69.1 (34.7)	78.6 (23.6)	0.210
Cognitive functioning	80.9 (19.9)	83.3 (23.0)	0.178
Emotional functioning	80.6 (21.8)	85.3 (22.9)	0.183
Social functioning	76.2 (26.6)	76.2 (28.2)	0.722
Symptom domain			
Nausea and vomiting	8.7 (18.7)	10.3 (22.7)	1.000
Fatigue	33.9 (31.9)	33.8 (26.4)	0.683
Dyspnea	22.2 (28.6)	19.0 (29.0)	0.569
Pain	23.8 (30.5)	15.9 (24.9)	0.082
Insomnia	23.8 (31.9)	22.2 (28.5)	0.865
Appetite loss	25.4 (37.9)	31.7 (37.2)	0.692
Constipation	26.9 (32.7)	20.6 (26.8)	0.441
Diarrhea	11.1 (19.2)	17.5 (27.1)	0.408
Financial difficulties	15.9 (24.9)	17.5 (29.1)	1.000

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 items (scored from 0 to 100); SD: standard deviation.

in the EV-301 trial, our results were consistent with the findings of the EV-201 phase 2 trial (17). The global health status, physical functioning, and symptom scores remained stable in patients receiving third-line or more treatment. Interestingly, patients with bone metastases in the EV-201 population had lower mean pain scores at cycle 3 compared with the baseline (ranging from 43.0 to 24.7) (17). Further investigations comparing the scores of EORTC QLQ-C30 after the introduction and maintenance period of EV monotherapy for metastatic UC should be performed.

The present study has several limitations, including a single-institutional design and a small sample size without comparators. The follow-up in our cohort was relatively shorter. The timing of EV monotherapy was not uniform, with most patients receiving two regimens and the remaining patients receiving three or more regimens. Furthermore, molecular testing data, such as expression of nectin-4 and PD-L1, and tumor mutation burden, were not obtained. Immunohistochemical analyses for nectin-4 and PD-L1 are not routinely performed in daily practice in Japan. However, nectin-4 expression was not required for entry into the EV-301 trial (7).

The efficacy of EV against advanced UC is rarely reported in the real-world clinical settings. Therefore, the results of the present study provide clinicians with a better understanding of EV monotherapy introduction in patients with metastatic UC. The oncological effects of EV may help improve survival in patients with poor prognostic features, including poor PS, unresponsive status of platinum-based chemotherapy and immune checkpoint blockade therapy, numerous Bellmunt risk factors, and variant histology. Multi-institutional studies with larger cohorts are required to further validate our results from daily clinical practice. In addition, examining the differences in response to EV regarding with skin toxicity, blood cell count markers, and body mass index, may be interest (18, 19).

In conclusion, EV monotherapy demonstrated promising anti-tumor activity and tolerability in patients with metastatic UC after failure of platinum-based chemotherapy and ICI therapy.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AM: Conceptualization, investigation, data curation, formal analysis, and writing of the first draft of the manuscript. RK and DO: Investigation and data curation. KT, KK, TM, TT, KJ, MH, KH, and YN: Data curation. IT, KH, and NF: Supervision. HM: Supervision, review, and revision of the manuscript. All Authors discussed, verified, and approved the final version of the article.

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