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Risk Classification of Patients With Advanced Urothelial Carcinoma Treated With Enfortumab Vedotin

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Abstract. *Background/Aim: Enfortumab Vedotin (EV) is a widely used antibody-drug conjugate for patients with advanced urothelial carcinoma (UC) who have previously been treated with platinum-based chemotherapy and immune checkpoint inhibitors. However, limited information is currently available on prognostic factors and risk classification. Therefore, the present study attempted to identify clinical factors that predict outcomes in patients with advanced UC treated with EV and to develop a novel risk classification model. Patients and Methods: We conducted a multicenter retrospective study including patients with advanced UC treated with EV. Oncological outcomes were assessed using progression-free survival (PFS) and overall survival (OS), and prognostic factors for PFS and OS were investigated. We then examined the usefulness of risk classification based on the prognostic factors identified. Results: Median PFS and OS were 7.1 and 16.3 months, respectively. High C-reactive protein levels (CRP level ≥0.5 mg/dl) and hypercalcemia (corrected calcium level >10.2 mg/dl) were identified as prognostic factors for PFS (p=0.012 and p=0.003, respectively) and OS (p=0.035 and p<0.001, respectively). We then divided patients into three risk groups: no prognostic factors group, one prognostic factor group, and two prognostic factors group. Significant differences were observed in PFS and OS among the three groups (p<0.001 and p<0.001, respectively) and c-indices were 0.766 for PFS and 0.800 for OS. Conclusion: The risk classification using CRP and hypercalcemia is useful for predicting the outcomes of patients with advanced UC treated with EV.*

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Key Words: Enfortumab Vedotin, prognostic factor, risk classification.

The treatment of advanced urothelial carcinoma (UC) remains challenging. Locally advanced or metastatic UC is a highly aggressive disease, and its oncological outcome is still unsatisfactory even when managed with platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) (1, 2). To improve oncological outcomes, Enfortumab Vedotin (EV), an antibody-drug conjugate targeting Nectin-4, has been developed as a subsequent therapy after platinum-based chemotherapy and ICIs. The EV-301 clinical trial revealed that progression-free survival (PFS) and overall survival (OS) in patients with locally advanced or metastatic UC who had previously received platinum-based chemotherapy and ICIs were significantly longer with EV than with other chemotherapies (3). The findings of

previous retrospective studies on PFS and OS in real-world settings were similar to those of the EV-301 trial (4-8); however, few studies have focused on the factors that predict clinical outcomes (5-7). Therefore, we herein attempted to identify clinical factors that predict the outcomes of patients with advanced UC treated with EV and also develop a novel risk stratification model.

Patients and Methods

This retrospective study was conducted as a multi-institutional collaborative study including Hamamatsu University Hospital (Hamamatsu, Japan), Seirei Mikatahara General Hospital (Hamamatsu, Japan), Iwata City Hospital (Iwata, Japan), Hamamatsu Medical Center (Hamamatsu, Japan), Chutoen General Medical Center (Kakegawa, Japan), Fujieda Municipal General Hospital (Fujieda, Japan), and JA Shizuoka Kohseiren Enshu Hospital (Hamamatsu, Japan), and was approved by the Institutional Review Board at the principal institution (approved number: 21-090). The need to obtain informed consent from patients was waived because of the retrospective design of this study; however, an opportunity to opt out was provided through the website of each institution.

The medical records of 66 patients who were treated with EV for locally advanced or metastatic UC between December 2021 and March 2024 were retrospectively reviewed. Seven patients were excluded because of incomplete data; therefore, 59 were ultimately analyzed. Relevant clinicopathological data were obtained from medical records, including age, sex, the Eastern Cooperative Oncology Group Performance Status (ECOG PS), histology, the primary lesion, metastatic organs, history of radical surgery and previous systemic therapies, and laboratory data [hemoglobin, platelets, corrected calcium, and C-reactive protein (CRP)].

EV was intravenously administrated at a dose based on 1.25 mg/kg of body weight on days 1, 8, and 15 of a 28-day cycle. The dosage (reduction, extension, or discontinuation) of EV was accordingly adjusted in consideration of the severity of treatment-related adverse events (AEs) by the physician. During the treatment period, a follow-up radiographic evaluation using computed tomography was performed every 2-3 months. The tumor response to EV was assessed based on Response Evaluation Criteria in Solid Tumors version 1.1. PFS was defined as the time from the initiation of EV to the date of disease progression or death, while OS was defined as the time from EV initiation to death from any cause.

Statistical analyses were performed using SPSS software version 28.0.1.1 (IBM Institute Corp., Armonk, NY, USA). PFS and OS were estimated using the Kaplan-Meier method. The prognostic impact of each variable was assessed by uni- and multivariate Cox proportional regression analyses. High CRP was defined as a CRP level ≥0.5 mg/dl and hypercalcemia as a corrected calcium level >10.2 mg/dl. To evaluate risk stratification, a comparison of patient outcomes among groups was performed using the Log-rank test, and the c-index was then calculated. A p-value <0.05 was considered to be significant.

Results

This study cohort consisted of 59 patients treated with EV. The baseline characteristics of these patients are summarized in Table I. Median age was 74 years (range=37-87 years) and 69.5% were male. Forty-eight patients (81.4%) were pathologically diagnosed with pure UC. The primary lesions were as follows: the upper urinary tract accounted for 59.3% and the lower urinary tract for 40.7%. All patients received both chemotherapy and ICIs before the administration of EV. Chemotherapy regimens, including neoadjuvant or adjuvant chemotherapy, were gemcitabine/cisplatin in 17 patients (28.8%), gemcitabine/carboplatin in 46 (78.0%), and other chemotherapies in 9 (15.3%). ICIs prior to EV were pembrolizumab in 41 patients (69.5%), avelumab in 20 (33.9%), and nivolumab in six (10.2%), including duplicate cases.

Table I. *Patient characteristics*.

	Overall (N=59)
Age	
Median age (range) – yr	74 (37-87)
<75 yr – no.(%)	31 (52.5)
≥75 yr – no.(%)	28 (47.5)
Sex – no. (%)	
Male	41 (69.5)
Female	18 (30.5)
ECOG PS – no.(%)	
0-1	53 (89.8)
≥2	6 (10.2)
Histology – no.(%)	
Pure UC	48 (81.4)
UC with a histological subtype or unknown	11 (18.6)
Primary lesion – no.(%)	
Upper tract (renal pelvis, ureter)	35 (59.3)
Bladder/other	24 (40.7)
Radical surgery – no.(%)	
Yes	32 (54.2)
No	27 (45.8)
Previous systemic therapies – no.(%)	
0-2	41 (69.5)
≥3	18 (30.5)
CRP level ≥0.5 mg/dl	40 (67.8)
Corrected calcium >10.2 mg/dl	7 (11.9)
Sites of metastasis – no.(%)	
Regional lymph node	31 (52.5)
Extra - regional lymph node	22 (37.3)
Lung	35 (59.3)
Bone	9 (15.3)
Liver	16 (27.1)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; UC: urothelial carcinoma; CRP: C-reactive protein.

The median follow-up period was 11.0 months (interquartile range, 3.0 to 14.6 months). During this period, there were 35 cases of disease progression and 26 deaths. Median PFS was 7.1 months [95% confidence interval (CI)=3.2-11.0 months] and median OS was 16.3 months (95%CI=8.8-23.8 months). As the best response, a complete response, partial response, stable disease, and progressive disease were observed in five (8.5%), 19 (32.2%), 19 (32.2%), and 10 (16.9%) patients, respectively.

Table II. *Cox regression analysis of progression-free survival.*

Variables		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (years)	≥75	0.911 (0.47-1.78)	0.785		
Sex	Female	2.26 (1.14-4.47)	0.019	1.80 (0.90-3.61)	0.097
ECOG PS	≥2	1.13 (0.34-3.74)	0.839		
Primary site	Upper tract	0.96 (0.48-1.92)	0.917		
Radical surgery	Yes	0.58 (0.30-1.14)	0.115		
Hemoglobin	Male: <13.7 mg/dl Female: <11.6 mg/dl	4.12 (0.97-17.48)	0.055		
Platelet count	>34.8×10^3/μl	0.83 (0.32-2.14)	0.701		
CRP	≥0.5 mg/dl	6.24 (1.90-20.47)	0.003	4.78 (1.42-16.12)	0.012
Corrected calcium	>10.2 mg/dl	5.43 (2.12-13.95)	<0.001	4.22 (1.61-11.06)	0.003
Site of metastasis					
Regional lymph node	Present	1.24 (0.64-2.43)	0.525		
Extra-regional lymph node	Present	1.12 (0.57-2.20)	0.754		
Lung	Present	1.24 (0.63-2.46)	0.532		
Bone	Present	1.43 (0.65-3.16)	0.376		
Liver	Present	1.59 (0.78-3.21)	0.199		

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CRP: C-reactive protein.

Table III. *Cox regression analysis of overall survival.*

Variables		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (years)	≥75	1.13 (0.53-2.41)	0.754		
Sex	Female	1.38 (0.61-3.09)	0.377		
ECOG PS	≥2	1.63 (0.48-5.48)	0.433		
Primary site	Upper tract	0.978 (0.44-2.19)	0.957		
Radical surgery	Yes	0.67 (0.31-1.43)	0.298		
Hemoglobin	Male: <13.7 mg/dl Female: <11.6 mg/dl	6.49 (0.86-48.86)	0.07		
Platelet count	>34.8×10^3/μl	0.89 (0.31-2.59)	0.835		
CRP	≥0.5 mg/dl	6.01 (1.42-25.41)	0.015	4.82 (1.12-20.72)	0.035
Corrected calcium	>10.2 mg/dl	10.48 (3.57-30.74)	<0.001	7.68 (2.60-22.70)	<0.001
Site of metastasis					
Regional lymph node	Present	1.03 (0.48-2.20)	0.942		
Extra-regional lymph node	Present	1.30 (0.61-2.80)	0.497		
Lung	Present	1.14 (0.53-2.49)	0.735		
Bone	Present	1.42 (0.57-3.54)	0.447		
Liver	Present	1.54 (0.71-3.38)	0.278		

ECOG PS: Eastern Cooperative Oncology Group Performance Status; CRP: C-reactive protein.

Accordingly, the overall response rate and disease control rate were 40.7 and 72.9%, respectively. In the present study, adverse events (AEs) were as follows; a skin reaction in 28 cases (47.5%), hyperglycemia in two (3.4%), and peripheral neuropathy in 23 (39.0%). Eleven patients (18.6%) discontinued EV therapy due to AEs.

We attempted to identify significant prognostic factors for PFS and OS using Cox proportional regression analyses (Table II and Table III). A univariate analysis revealed that female sex, high CRP levels, and hypercalcemia were prognostic factors for PFS (p=0.019, p=0.003, and p<0.001, respectively), while high CRP levels and hypercalcemia were prognostic factors for OS (p=0.015 and p<0.001, respectively). In a multivariate analysis, high CRP levels and hypercalcemia were both significant prognostic factors for PFS (p=0.012 and p=0.003, respectively) and OS (p=0.035 and p<0.001, respectively).

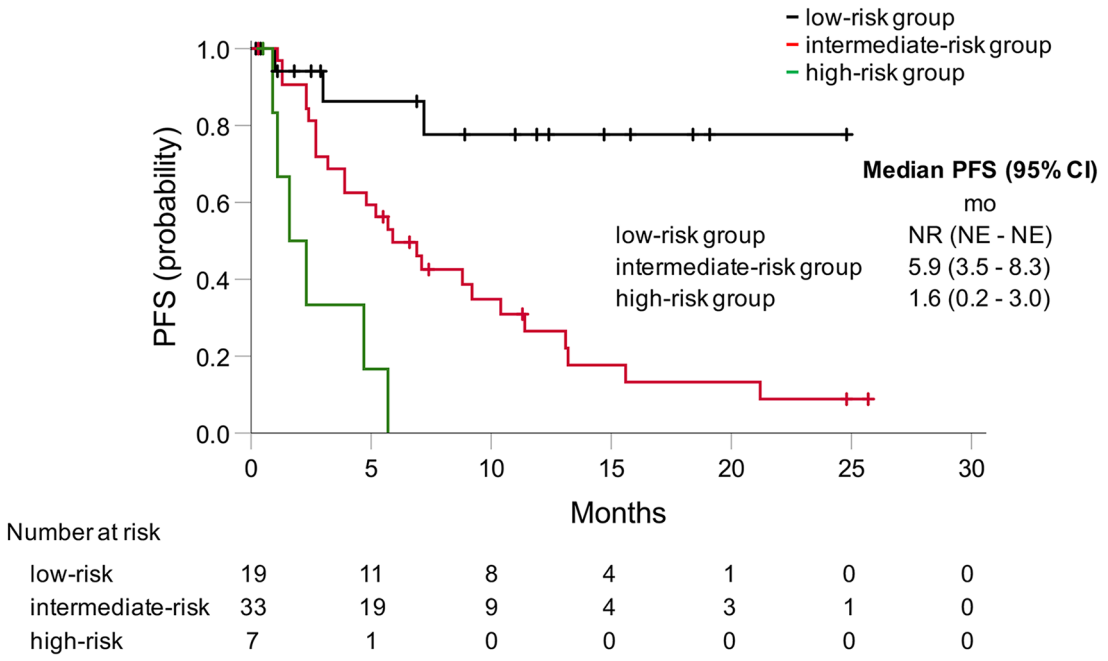

Figure 1. *Progression-free survival (PFS) stratified by low-, intermediate-, and high-risk groups.*

To characterize prognostic features more precisely in this cohort, we divided patients into multiple groups according to the number of significant risk factors identified in the multivariate analysis, and a risk classification model was developed. To predict PFS and OS, 59 patients were stratified into the following three groups: 19 with no risk factors (low-risk group), 33 with a single risk factor (intermediate-risk group), and 7 with both risk factors (high-risk group). Median PFS in the low-, intermediate-, and high-risk groups were "not reached", 5.9 months, and 1.6 months, respectively (Figure 1), while median OS were "not reached", 11.2 months, and 2.3 months, respectively (Figure 2). Significant differences were observed in PFS and OS among the three groups ($p<0.001$ and $p<0.001$, respectively). To evaluate the usefulness of this novel risk stratification model, we calculated c-indices. C-indices were 0.766 for PFS and 0.800 for OS.

Discussion

Platinum-based chemotherapy was the only recommended regimen for advanced UC until the KYENOTE-045 study in 2017 showed that OS was longer with pembrolizumab than with other chemotherapy regimens (1). Bellmunt developed a risk stratification system using hemoglobin <10 g/dl, liver metastasis, and ECOG PS ≥1 for the patients who experienced treatment failure with the platinum-based regimen (9). Other risk stratification systems from real-world data have also been reported (10). After the EV-301 study described the significant impact of EV on oncological outcomes in patients previously treated with platinum-based chemotherapy and ICIs, it was approved and used worldwide for patients with advanced UC as a subsequent therapy. However, limited information is available on prognostic factors and the risk classification system (5-7). Therefore, we investigated prognostic factors and developed a risk classification system for patients with advanced UC treated with EV.

In the present study, median PFS was 7.1 months, and median OS was 16.3 months. In the EV-301 trial, median PFS and OS were 5.55 and 12.91 months, respectively, and in real-world data, they were 4.2 to 6.8 months and 9.7 to 14.7 months, respectively (4-8, 11). These findings are consistent with the present results.

We focused on prognostic factors in patients treated with EV and showed the significant impact of high CRP and hypercalcemia on both PFS and OS. Hara *et al*. reported the significant impact of high CRP on PFS and high CRP and low PS on OS (5). Furthermore, Hirasawa *et al*. demonstrated that high CRP, low albumin, the presence of a histological subtype, and liver metastasis were prognostic factors for OS (6). The impact of high CRP was consistent throughout these studies; therefore, we considered it to be a promising prognostic factor in patients treated with EV. However, further investigations are needed to select an appropriate cut-off value because it was not confirmed in these studies. The impact of hypercalcemia on PFS and OS in patients with advanced UC also warrants further study. The mechanisms underlying the development of hypercalcemia in patients with malignant tumors involve the production of parathyroid

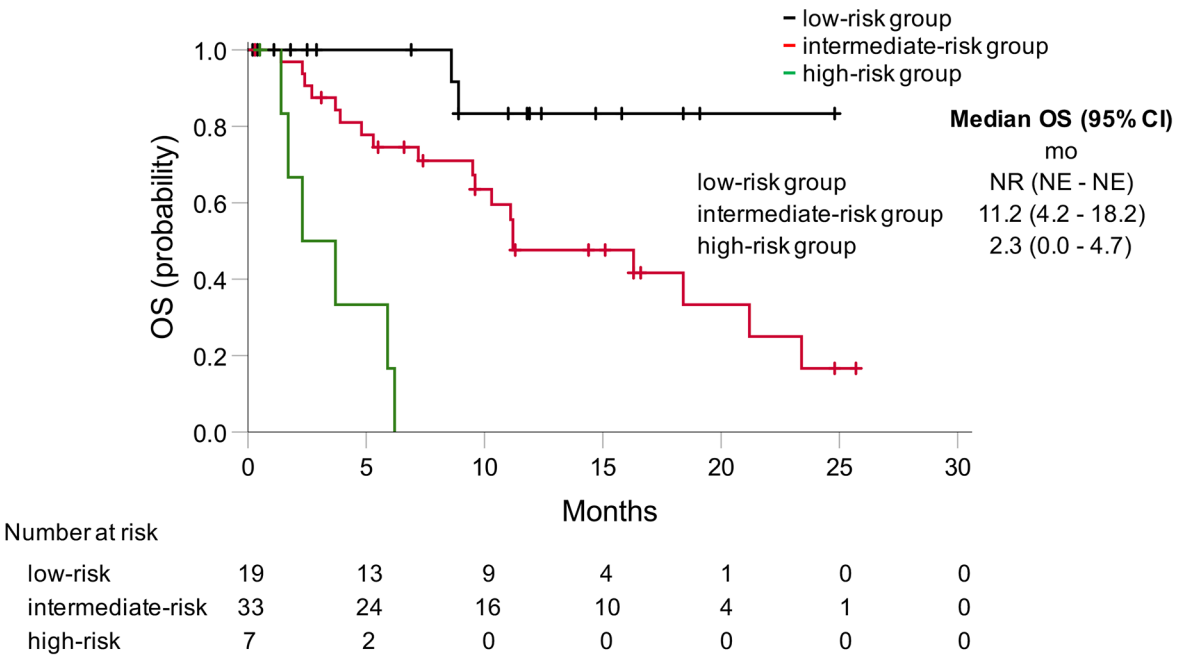

Figure 2. *Overall survival (OS) stratified by low-, intermediate-, and high-risk groups.*

hormone–related peptides, osteolytic cytokines, and excess 1,25-dihydoxyvitamin D (12). Hypercalcemia is a significant prognostic factor in patients with advanced renal cell carcinoma and is one of the variables in the International Metastatic Renal Cell Carcinoma Database Consortium risk classification (13). Tumor-induced hypercalcemia has been reported in several patients with UC (14, 15). This is the first study to show that hypercalcemia was a poor prognostic factor in patients treated with EV. Therefore, hypercalcemia has potential as a useful prognostic factor in patients with advanced UC.

According to the prognostic factors identified herein, namely, a high CRP level and hypercalcemia, we developed a new risk classification system. This system makes it possible to effectively stratify PFS and OS into three risk groups and may be regarded as acceptable discrimination according to previously reported criteria (16). Moreover, this is the first study to develop a risk classification system for patients with advanced UC treated with EV. The benefits of risk classification are not only the ability to stratify PFS and OS, but also its simpleness and objectiveness because it uses only two numeric factors acquired from a blood examination. However, the lack of a balance in the distribution of patients into the three risk groups is a disadvantage of this system.

Study limitations. Since this was a multicenter study without a strict protocol, there was a potential bias of dose adjustments and the discontinuation of EV among institutions and physicians. Furthermore, the sample size was small and, thus, a validation cohort is needed. Moreover, a new regimen combining with EV and pembrolizumab was recently approved (17). Therefore, further investigations are needed to establish whether this system may be applied to patients with advanced UC receiving the new combination therapy in the future.

Conclusion

The present study, which included 59 patients with advanced UC treated with EV, identified a high CRP level and hypercalcemia as significant prognostic factors. Furthermore, the novel risk classification model developed using these two risk factors is simple and acceptable for predicting a better outcome with EV treatment.

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Conflicts of Interest

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

Authors' Contributions

Conceptualization: Yuto Matsushita and Gaku Ishikawa. Data curation: Gaku Ishikawa, Yuichi Kitagawa, Asuka Uchiyama, Yuya Oishi, Hiroki Tanaka, Shinya Watanabe, Eito Suzuki, Shunsuke Watanabe, Kyohei Watanabe, Yuto Matsushita, Hiromitsu Watanabe, Keita Tamura, Daisuke Motoyama Rikiya Matsumoto, Toshiki Ito,

Masao Nagata, Toshiyuki Unno, Hiroshi Furuse, and Takuji Mizuno. Formal analysis and visualization: Gaku Ishikawa. Writing – original draft: Gaku Ishikawa. Writing – review & editing: Yuto Matsushita and Atsushi Otsuka. Supervision: Atsushi Otsuka.

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