in vivo *38*: 873-880 (2024)
doi:10.21873/invivo.13513

Efficacy of Platinum-based Chemotherapy in Patients With Metastatic Urothelial Carcinoma With Variant Histology

AKINORI MINATO[1], KAZUKI MUROOKA[2], YUTAKA OKUMURA[1], TOMOHISA TAKABA[1], KATSUYOSHI HIGASHIJIMA[1], YUJIRO NAGATA[1], IKKO TOMISAKI[1], KENICHI HARADA[1] and NAOHIRO FUJIMOTO[1]

[1]*Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan;*
[2]*Department of Urology, Kyushu Rosai Hospital, Kitakyushu, Japan*

Abstract. *Background/Aim: Variant urothelial carcinoma (VUC, defined herein as urothelial carcinoma with any histological variant) is frequently observed at an advanced stage. However, the efficacy of systemic chemotherapy against VUC in metastatic disease has rarely been reported. This study assessed the therapeutic response and survival outcomes of platinum-based chemotherapy as first-line treatment in patients with metastatic VUC. Patients and Methods: We retrospectively analyzed consecutive patients with metastatic bladder and upper urinary tract cancer who received gemcitabine plus cisplatin (or carboplatin) at the University of Occupational and Environmental Health Hospital between November 2008 and November 2022. Progression-free survival and overall survival were evaluated using the Kaplan-Meier method and Cox proportional hazard models. Results: Out of 131 patients recorded, 86 (65.6%) had pure urothelial carcinoma (PUC) and 45 (34.4%) had VUC. The most common variant element was squamous differentiation (44.4%). Compared to those with PUC, patients with VUC showed a comparable objective response rate (33.3% vs. 41.9%, p=0.451) and disease control rate (64.5% vs. 75.6%, p=0.221). They also had poorer progression-free survival (median=4.9 months vs. 7.9 months, p=0.014) and overall survival (median=10.9 months vs. 18.2 months, p=0.037) than those with PUC. On multivariate analysis, VUC was an independent predictor of progression (hazard ratio=1.79; 95% confidence interval=1.19-2.69; p=0.005) and mortality (hazard ratio=1.64; 95% confidence interval=1.08-2.48; p=0.020). Conclusion: Although the response of metastatic VUC to platinum-based chemotherapy was not inferior to that of PUC, VUC had progressed faster than PUC. VUC was significantly associated with a poor prognosis after platinum-based chemotherapy as first-line treatment.*

Correspondence to: Akinori Minato, MD, Ph.D., Department of Urology, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. Tel: +81 936917446, Fax: +81 936038724, e-mail: a-minato@med.uoeh-u.ac.jp

Key Words: Variant histology, urothelial carcinoma, chemotherapy, prognosis.

Platinum-based combination chemotherapy as first-line treatment is the gold standard for advanced urothelial carcinoma (UC) (1, 2). In a large randomized phase III trial (3), the median duration of progression-free survival (PFS) and overall survival (OS) was 7.7 and 14.0 months, respectively, in patients with locally advanced or metastatic UC treated with gemcitabine plus cisplatin. Novel effective drugs, such as immune checkpoint inhibitors (ICIs) and antibody drug conjugates have recently emerged as late-line therapies for advanced UC (4-7). Therefore, the increasing importance of initial platinum-based chemotherapy is a key role in daily clinical practice. Although Bellmunt *et al.* (8) identified performance status, hemoglobin level, and liver metastasis as pretreatment prognostic factors for OS in patients with metastatic UC, their analyses did not include the pathologic subtype.

Recent studies have focused on the prognostic value of variant histology in UC in patients with locally advanced bladder cancer (9-11) and upper urinary tract cancer (12, 13). Variant UC (VUC, defined herein as UC with any histological variant (14) has been frequently observed, with an incidence of approximately 25%-33% in radical surgery series (13, 15, 16). For patients with metastatic VUC, the efficacy of platinum-based chemotherapy has rarely been reported, and little evidence is available with regard to survival from first-line chemotherapy (17). Currently, the insight into whether platinum-based chemotherapy yields a

Table I. *Patient characteristics*.

Characteristic	PUC (n=86)	VUC (n=45)	*p*-Value
Median age, years (IQR)	72 (66-79)	74 (64-78)	0.614
Sex, n (%)			0.217
Male	59 (68.6)	36 (80.0)	
Female	27 (31.4)	9 (20.0)	
Primary tumor site, n (%)			0.069
Bladder	40 (46.5)	31 (69.9)	
Upper urinary tract	43 (50.0)	13 (28.9)	
Bladder+upper urinary tract	3 (3.5)	1 (2.2)	
ECOG PS score, n (%)			0.592
0	44 (51.2)	26 (57.8)	
≥1	42 (48.8)	19 (42.2)	
Hemoglobin, n (%)			0.825
≥10 g/dl	66 (76.7)	36 (80.0)	
<10 g/dl	20 (23.3)	9 (20.0)	
Liver metastasis, n (%)			1.000
Presence	8 (9.3)	4 (8.9)	
Absence	78 (90.7)	41 (91.1)	
No. of metastatic sites, n (%)			0.566
1	58 (67.4)	28 (62.2)	
≥2	28 (32.6)	17 (37.8)	
Platinum-based chemotherapy, n (%)			0.174
Gemcitabine+cisplatin	65 (75.6)	39 (86.7)	
Gemcitabine+carboplatin	21 (24.4)	6 (13.3)	
Chemotherapy cycles, median (IQR)	3 (2-5)	3 (2-4)	0.370
Subsequent ICI therapy, n (%)			0.245
Administered	33 (38.4)	12 (26.7)	
Not administered	53 (61.6)	33 (73.3)	

IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor; PUC: pure urothelial carcinoma; VUC: variant urothelial carcinoma.

Table II. *Radiographic response to platinum-based chemotherapy stratified by histologic type*.

Characteristic	PUC (n=86)	VUC (n=45)	*p*-Value
Response, n (%)			0.591
CR	7 (8.2)	3 (6.7)	
PR	29 (33.7)	12 (26.7)	
SD	29 (33.7)	14 (31.1)	
PD	21 (24.4)	16 (35.5)	
Objective response rate (CR+PR)	36 (41.9)	15 (33.4)	0.451
Disease control rate (CR+PR+SD)	65 (75.6)	29 (64.5)	0.221

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; PUC: pure urothelial carcinoma; VUC: variant urothelial carcinoma.

similar response between metastatic VUC and locally advanced disease is still unclear.

Hence, this study aimed to assess the clinical significance of VUC with respect to the efficacy of platinum-based chemotherapy and prognosis in patients with stage IV bladder and upper urinary tract cancer.

Patients and Methods

Patient population. We retrospectively reviewed 131 consecutive patients with metastatic UC in the bladder and upper urinary tract who had received platinum-based chemotherapy at the University of Occupational and Environmental Health Hospital (Kitakyushu, Japan) between November 2008 and November 2022. We only enrolled patients histologically diagnosed with pure UC (PUC) or VUC according to the reports provided by dedicated pathologists at our institution without central review. This study defined VUC as the combined presence of UC and divergent differentiation or histological variants based on the World Health Organization Classification of Tumors (16). The University of Occupational and Environmental Health Institutional Review Board approved this study protocol (approval no.: UOEHCRB21-048).

Patient management. Gemcitabine plus cisplatin (or carboplatin) was administered intravenously every 4 weeks until disease progression (gemcitabine: 1,000 mg/m^2 on days 1, 8, and 15; cisplatin: 70 mg/m^2 on day 2 or carboplatin: area under the curve=5 on day 2). Patients who were unfit for cisplatin due to renal function received carboplatin. Follow-up evaluation included physical examination, laboratory tests, and chest–abdominal–pelvic computed tomography. Imaging evaluation was performed at baseline and after every two to three cycles of chemotherapy. When bone lesions were suspected on computed tomography, bone scintigraphy was performed. If symptoms appeared, appropriate additional examinations were conducted.

Evaluation. Tumor response was assessed as the best response according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (18). We defined objective response rate (ORR) as the percentage of patients with complete response (CR) or partial response (PR), and the disease control rate as the percentage of patients with CR, PR, or stable disease (SD) without progressive disease (PD).

The duration of PFS was estimated from the date of administration of platinum-based first-line chemotherapy to the date of disease progression or death, whichever occurred earlier, or to the last follow-up in patients without disease progression. OS duration was estimated from the date of administration of the chemotherapy to the date of death caused by any cause, or to the last follow-up in patients who survived.

Statistical analysis. All statistical data were analyzed using EZR ver.1.40 (Easy R, Saitama Medical center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (19). Between-group differences with respect to categorical variables were assessed using the Fisher's exact test and c^2 test, whereas those with respect to continuous variables were assessed using the Mann-Whitney *U*-test. PFS and OS were estimated using the Kaplan-Meier method,

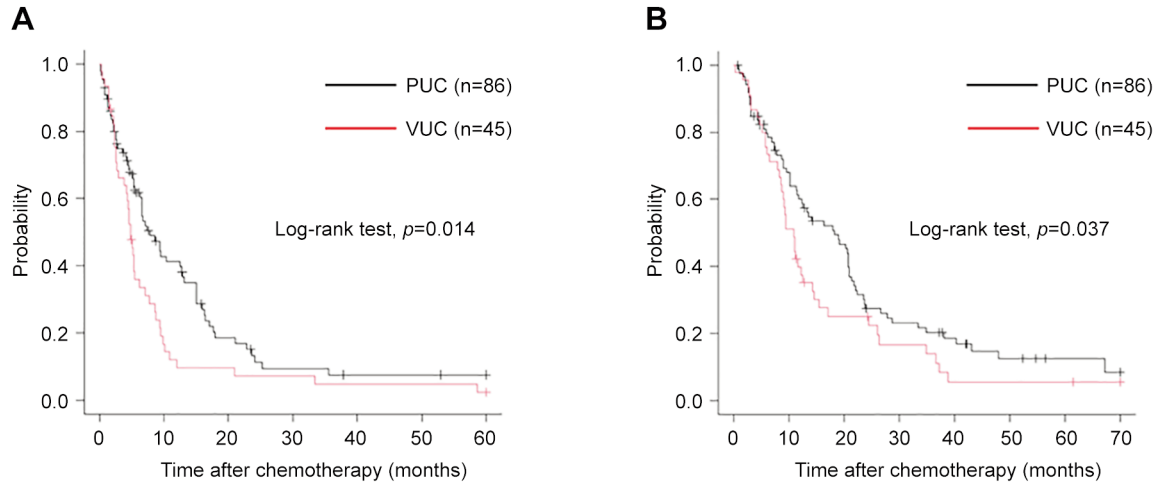

Figure 1. *Kaplan-Meier curves for (A) progression-free survival and (B) overall survival after the initiation of platinum-based chemotherapy in patients with PUC and VUC. PUC: Pure urothelial carcinoma; VUC: variant urothelial carcinoma.*

and differences between the groups were determined using the log-rank test. For univariate and multivariate analyses of clinicopathological factors predicting DFS and OS, we used the Cox proportional hazard models. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics. Out of 131 patients enrolled, 86 (65.6%) and 45 (34.4%) had PUC and VUC, respectively. The most common variant element was squamous differentiation (21, 46.7%), followed by glandular differentiation (10, 22.2%), sarcomatoid variant (5, 11.1%), micropapillary variant (3, 6.7%), nested variant (2, 4.4%), plasmacytoid variant (2, 4.4%), clear cell variant (1, 2.2%), and neuroendocrine differentiation (1, 2.2%).

Table I summarizes the baseline characteristics of patients with PUC and VUC. Age, sex, primary tumor site, Eastern Cooperative Oncology Group performance status (ECOG-PS), anemia, presence of liver metastasis, and the number of metastatic sites were not significantly different between the two patient groups. Gemcitabine plus cisplatin was administered to 65 (75.6%) patients with PUC and 39 (86.7%) patients with VUC, whereas gemcitabine plus carboplatin was administered to 21 (24.4%) and 6 (13.3%) patients, respectively (p=0.174). After platinum-based chemotherapy, the proportion of patients with VUC receiving subsequent ICI treatment (avelumab or pembrolizumab) was comparable to that of patients with PUC (26.7% *vs*. 38.4%, p=0.245).

Oncological outcomes. Table II shows the response of the PUC and VUS groups to platinum-based chemotherapy. Patients with VUC had comparable ORR (33.4% *vs*. 41.9%, p=0.451) and disease control rate (64.5% *vs*. 75.6%, p=0.221) compared with those with PUC. In the VUC group, the CR, PR, SD, and PD rates of patients with squamous differentiation were 0 (0%), 5 (23.8%), 9 (42.9%), and 7 (33.3%), respectively.

The median follow-up period was 14.1 months (interquartile range=7.0-24.9 months), during which 107 (81.7%) experienced progression and 106 (80.9%) died. Patients with VUC had poorer PFS (median=4.9 months *vs*. 7.9 months, p=0.014) (Figure 1A) and OS (median=10.9 months *vs*. 18.2 months, p=0.037) (Figure 1B) than those with PUC. The 1-year PFS rates were 39.8% and 9.6% in the PUC and VUC groups, whereas the 1-year OS rates were 58.8% and 37.5%, respectively. In the VUC group, the PFS (Figure 2A) and OS (Figure 2B) of patients with squamous differentiation was comparable to that of patients with other histological variants. In patients receiving subsequent ICI therapy, the OS from the start of the first-line chemotherapy showed no significant differences between the two groups (Figure 3). In the VUC group, the OS was significantly longer in patients who received subsequent ICI therapy than in those who did not (median=15.5 months *vs*. 9.4 months, p=0.043) (Figure 4).

Table III and Table IV show the results of univariate and multivariate Cox regression analyses predicting PFS and OS after adjusting for clinicopathological factors. ECOG-PS, liver metastasis, and VUC presence were significant independent predictors of PFS. As for OS, the significant independent predictors were ECOG-PS, anemia, liver metastasis, the number of metastatic lesions, and VUC presence.

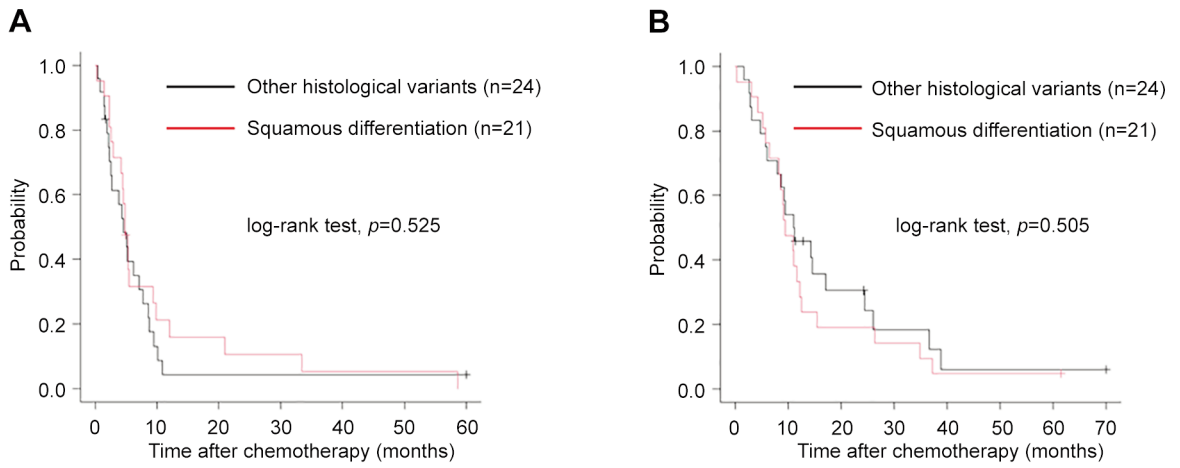

Figure 2. *Kaplan-Meier curves for (A) progression-free survival and (B) overall survival after initiation of platinum-based chemotherapy in patients with squamous differentiation and other histological variants.*

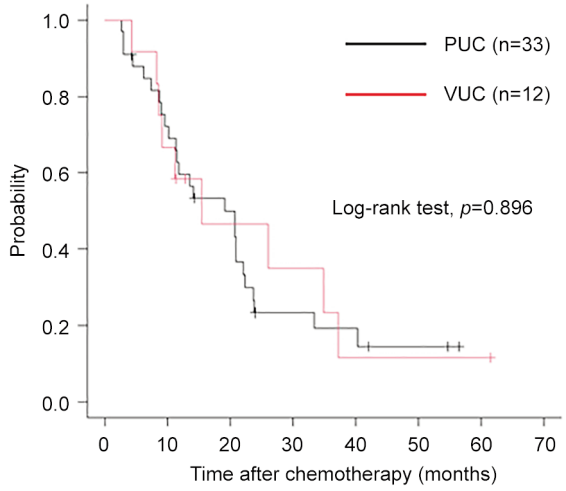

Figure 3. *Kaplan-Meier curves for overall survival after initiation of platinum-based chemotherapy in patients with PUC and VUC with the use of subsequent ICI therapy. PUC: Pure urothelial carcinoma; VUC: variant urothelial carcinoma; ICI: immune checkpoint inhibitor.*

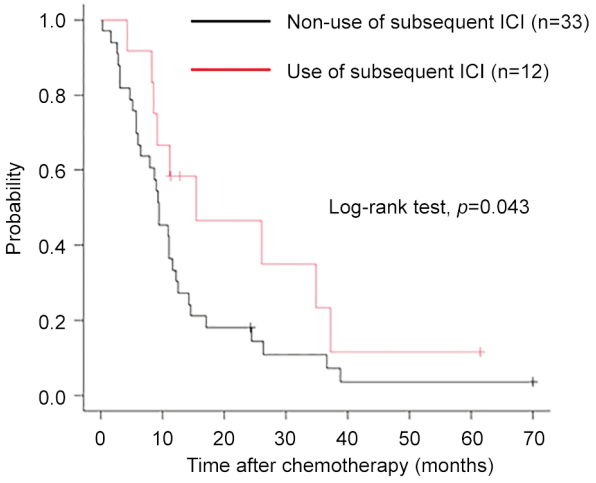

Figure 4. *Kaplan-Meier curves for overall survival after initiation of platinum-based chemotherapy in patients with VUC with or without the use of subsequent ICI therapy. VUC: Variant urothelial carcinoma; ICI: immune checkpoint inhibitor.*

Discussion

To assess the efficacy of platinum-based chemotherapy as first-line treatment on clinical outcomes according to histological subtype, this study evaluated the therapeutic response and survival of patients treated with gemcitabine plus cisplatin (or carboplatin) for PUC and VUC. In the VUC group, squamous differentiation was the most common variant element. Patients with VUC had similar ORR and disease control rate compared to those with PUC. However, PFS and OS were significantly different between the PUC and VUC groups. The presence of histological variant in metastatic UC was an independent predictor for PFS and OS from the start of first-line chemotherapy.

The efficacy of systemic chemotherapy as first-line treatment for metastatic disease in patients with VUC remains insufficiently investigated. In 2015, Hsieh *et al.* was the first to show that VUC adversely influenced patients' response to platinum-based chemotherapy (20). The ORR to platinum-based chemotherapy in patients with PUC was 61.4%, whereas that in patients with VUC was 45.3% (p=0.053). Additionally, the median durations of PFS and OS were 3.8 and 11.3 months for VUC (n=53), respectively. In their study, the majority received

Table III. *Univariate and multivariate analyses for progression-free survival.*

		Univariate		Multivariate	
Variable	Comparison	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	Continuous	0.99 (0.98-1.02)	0.895		
Sex	Female *vs.* male	1.21 (0.79-1.86)	0.375		
ECOG PS	≥1 *vs.* 0	2.27 (1.52-3.39)	<0.001	2.38 (1.58-3.59)	<0.001
Hemoglobin	<10 g/dl *vs.* ≥10 g/dl	1.50 (0.93-2.42)	0.093		
Liver metastasis	Presence *vs.* absence	2.93 (1.55-5.54)	0.001	2.39 (1.14-4.99)	0.021
No. of metastatic sites	≥2 *vs.* 1	1.73 (1.16-2.56)	0.007	1.41 (0.89-2.22)	0.134
Platinum agent	Carboplatin *vs.* cisplatin	1.17 (0.72-1.89)	0.531		
Histologic type	VUC *vs.* PUC	1.62 (1.09-2.41)	0.015	1.79 (1.19-2.69)	0.005

ECOG PS: Eastern Cooperative Oncology Group performance status; VUC: variant urothelial carcinoma; PUC: pure urothelial carcinoma; HR: hazard ratio; CI: confidence interval.

Table IV. *Univariate and multivariate analyses for overall survival.*

		Univariate		Multivariate	
Variable	Comparison	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	Continuous	1.00 (0.98-1.02)	0.824		
Sex	Female *vs.* male	1.19 (0.78-1.82)	0.428		
ECOG PS	≥1 *vs.* 0	2.66 (1.79-3.96)	<0.001	2.97 (1.95-4.52)	<0.001
Hemoglobin	<10 g/dl *vs.* ≥10 g/dl	2.45 (1.58-3.81)	<0.001	2.10 (1.32-3.35)	0.001
Liver metastasis	Presence *vs.* absence	2.88 (1.52-5.45)	0.001	2.04 (1.29-4.22)	0.035
No. of metastatic sites	≥2 *vs.* 1	1.99 (1.34-2.95)	<0.001	2.21 (1.37-3.58)	0.001
Platinum agent	Carboplatin *vs.* cisplatin	1.09 (0.59-1.66)	0.980		
Histologic type	VUC *vs.* PUC	1.73 (1.06-2.12)	0.027	1.64 (1.08-2.48)	0.020

ECOG PS: Eastern Cooperative Oncology Group performance status; VUC: variant urothelial carcinoma; PUC: pure urothelial carcinoma; HR: hazard ratio; CI: confidence interval.

gemcitabine plus cisplatin (47.2%), followed by gemcitabine plus carboplatin (28.3%) and the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (24.5%) (20). Conversely, the study by Epaillard *et al*., the median PFS and OS of patients with VUC (n=37) were 7.3 and 21.6 months, respectively (21). However, they included patients with non-UC or receiving first-line immunotherapy. Furthermore, their study also did not compare patient survival between VUC and PUC.

Gemcitabine plus cisplatin chemotherapy was developed in three prospective clinical trials (3, 22, 23). The ORR was 49%-66%, and the median duration of PFS was approximately 8 months. Our cohort of metastatic VUC had a poor ORR (33.4%) and a short duration of PFS (median=4.9 months) compared with the results in previous clinical trials. Regarding VUC's sensitivity to chemotherapy, most of the previous studies were mainly focused on patients treated with neoadjuvant chemotherapy. In some reports, patients with VUC showed a poorer response to neoadjuvant chemotherapy than those with PUC (24-26), whereas in other reports, both patient groups demonstrated a similar response (27-29). A recent systematic review by Veskimae *et al*. showed that neoadjuvant chemotherapy may be beneficial for patients with micropapillary variant, plasmacytoid variant, sarcomatoid variant, squamous differentiation, glandular differentiation, and neuroendocrine differentiation (17). Although the heterogeneity in VUC populations may affect the rate of response to chemotherapy, VUC might harbor more aggressive biological features in metastatic disease than in locally advanced disease. Furthermore, the duration of efficacy of platinum-based chemotherapy on metastatic VUC was short.

We previously reported that the proportion of histological variants in cancer lesions is associated with survival outcomes in a radical cystectomy cohort (9). The presence of histological variant in UC by 80% or more was an independent predictor of OS (hazard ratio=2.27; 95% confidence interval=1.15-4.49) (9). Although examining the difference in the response to chemotherapy according to histological variant proportion is important, the extent of histological variants in metastatic lesions is difficult to identify.

In 2022, we conducted a multicenter retrospective study showing the survival outcomes of ICI therapy in patients with chemotherapy-resistant VUC (14). Interestingly, the OS from the start of pembrolizumab therapy exhibited no significant differences between the PUC and VUC groups. The response to pembrolizumab might be beneficial for VUC. In fact, our current study showed no significant differences between the PUC and VUC groups with respect to the OS from the start of first-line chemotherapy in patients receiving subsequent ICI therapy (avelumab or pembrolizumab).

This study has certain limitations, such as its retrospective non-randomized design and small sample size. Moreover, the regimens of chemotherapy were not uniform, with most patients receiving gemcitabine plus cisplatin and others received gemcitabine plus carboplatin. However, PFS and OS showed no significant differences between these two platinum agents. Some PUC and VUC diagnoses were based on a radical surgery specimen, whereas others were solely based on a small biopsy specimen. The limited number of patients in our cohort also did not allow for comparison according to the VUC subtype in terms of response to platinum-based chemotherapy.

Despite these limitations, our data suggest that VUC has a more aggressive behavior after the initiation of first-line platinum-based chemotherapy than PUC in metastatic disease. Furthermore, the use of subsequent ICI was found to play a crucial role against VUC. Recently, we reported that enfortumab vedotin monotherapy as a third-line therapy for patients with metastatic disease was effective regardless of histological subtypes (30). Thus, early sequential therapy from platinum-based chemotherapy to ICI therapy or enfortumab vedotin monotherapy may be recommended to patients with metastatic VUC. We suggest a rapid switch to pembrolizumab therapy by early detecting patients showing PD with bi-monthly imaging evaluation. Considering the median duration of PFS was 4.9 months for VUC, the optimal timing for switching from platinum-based chemotherapy to avelumab maintenance therapy might be considered around cycle four. We believe that our study will facilitate sequential systemic treatment without delay for patients with VUC.

Conclusion

Although the response of metastatic VUC to platinum-based chemotherapy was not inferior to that of PUC, VUC had progressed faster. The presence of VUC was an independent predictor of mortality after initiation of first-line chemotherapy in metastatic disease.

Funding

This work was supported by JSPS KAKENHI Grant Number JP23K15773.

Conflicts of Interest

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

Authors' Contributions

AM: Conceptualization, methodology, investigation, data curation, statistical analysis, writing of the original draft. KM, YO, and TT: Investigation, data curation. KH and YN: Data curation. IT, KH, and NF: Reviewing, editing, supervision. All Authors discussed, verified, and approved the final version of the article.

Acknowledgements

The Authors thank Enago (www.enago.jp) for the English language editing.

References

1 Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Chan K, Chang S, Friedlander T, Greenberg RE, Guru KA, Herr HW, Hoffman-Censits J, Kishan A, Kundu S, Lele SM, Mamtani R, Margulis V, Mian OY, Michalski J, Montgomery JS, Nandagopal L, Pagliaro LC, Parikh M, Patterson A, Plimack ER, Pohar KS, Preston MA, Richards K, Sexton WJ, Siefker-Radtke AO, Tollefson M, Tward J, Wright JL, Dwyer MA, Cassara CJ, Gurski LA: NCCN Guidelines® Insights: Bladder Cancer, Version 2.2022. J Natl Compr Canc Netw 20(8): 866-878, 2022. DOI: 10.6004/jnccn.2022.0041

2 Cathomas R, Lorch A, Bruins HM, Compérat EM, Cowan NC, Efstathiou JA, Fietkau R, Gakis G, Hernández V, Espinós EL, Neuzillet Y, Ribal MJ, Rouanne M, Thalmann GN, van der Heijden AG, Veskimäe E, Alfred Witjes J, Milowsky MI: The 2021 updated European Association of Urology Guidelines on metastatic urothelial carcinoma. Eur Urol 81(1): 95-103, 2022. DOI: 10.1016/j.eururo.2021.09.026

3 von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A, Arning M: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 23(21): 4602-4608, 2005. DOI: 10.1200/JCO.2005.07.757

4 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF, KEYNOTE-045 Investigators: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 376(11): 1015-1026, 2017. DOI: 10.1056/NEJMoa1613683

5 Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, Radulović S, Demey W, Ullén A, Loriot Y, Sridhar SS, Tsuchiya N, Kopyltsov E, Sternberg CN, Bellmunt J, Aragon-Ching JB, Petrylak DP, Laliberte R, Wang J, Huang B, Davis C, Fowst C, Costa N, Blake-Haskins JA, di Pietro A, Grivas P: Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 383(13): 1218-1230, 2020. DOI: 10.1056/NEJMoa2002788

6 Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, Matsubara N, Vulsteke C, Castellano D, Wu C, Campbell M, Matsangou M, Petrylak DP: Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 384(12): 1125-1135, 2021. DOI: 10.1056/NEJMoa2035807

7 Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, Jain RK, Agarwal N, Bupathi M, Barthelemy P, Beuzeboc P, Palmbos P, Kyriakopoulos CE, Pouessel D, Sternberg CN, Hong Q, Goswami T, Itri LM, Grivas P: TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol 39(22): 2474-2485, 2021. DOI: 10.1200/JCO.20.03489

8 Bellmunt J, Choueiri TK, Fougeray R, Schutz FA, Salhi Y, Winquist E, Culine S, von der Maase H, Vaughn DJ, Rosenberg JE: Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 28(11): 1850-1855, 2010. DOI: 10.1200/JCO.2009.25.4599

9 Minato A, Noguchi H, Moriya R, Higashijima K, Yamasaki G, Kimuro R, Hasegawa Y, Tomisaki I, Fujimoto N: Evaluation of the extent of variant histology in urothelial carcinoma as a predictive marker of clinical outcomes after radical cystectomy. Cancer Diagn Progn 1(4): 345-351, 2021. DOI: 10.21873/cdp.10046

10 Mori K, Abufaraj M, Mostafaei H, Quhal F, Karakiewicz PI, Briganti A, Kimura S, Egawa S, Shariat SF: A systematic review and meta-analysis of variant histology in urothelial carcinoma of the bladder treated with radical cystectomy. J Urol 204(6): 1129-1140, 2020. DOI: 10.1097/JU.0000000000001305

11 Minato A, Noguchi H, Tomisaki I, Fukuda A, Kubo T, Nakayama T, Fujimoto N: Clinical significance of squamous differentiation in urothelial carcinoma of the bladder. Cancer Control 25(1): 1073274818800269, 2018. DOI: 10.1177/1073274818800269

12 Minato A, Noguchi H, Kimuro R, Mirii H, Yujiro N, Hasegawa Y, Tomisaki I, Harada K, Fujimoto N: Prognostic value of squamous differentiation in upper tract urothelial carcinoma treated with radical nephroureterectomy. Anticancer Res 42(1): 263-269, 2022. DOI: 10.21873/anticanres.15481

13 Mori K, Janisch F, Parizi MK, Mostafaei H, Lysenko I, Kimura S, Enikeev DV, Egawa S, Shariat SF: Prognostic value of variant histology in upper tract urothelial carcinoma treated with nephroureterectomy: a systematic review and meta-analysis. J Urol 203(6): 1075-1084, 2020. DOI: 10.1097/JU.0000000000000523

14 Minato A, Furubayashi N, Harada M, Negishi T, Sakamoto N, Song Y, Hori Y, Tomoda T, Tamura S, Kuroiwa K, Seki N, Tomisaki I, Harada K, Nakamura M, Fujimoto N: Efficacy of pembrolizumab in patients with variant urothelial carcinoma: a multicenter retrospective study. Clin Genitourin Cancer 20(5): 499.e1-499.e8, 2022. DOI: 10.1016/j.clgc.2022.05.001

15 Xylinas E, Rink M, Robinson BD, Lotan Y, Babjuk M, Brisuda A, Green DA, Kluth LA, Pycha A, Fradet Y, Faison T, Lee RK, Karakiewicz PI, Zerbib M, Scherr DS, Shariat SF: Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. Eur J Cancer 49(8): 1889-1897, 2013. DOI: 10.1016/j.ejca.2013.02.001

16 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE: The 2016 WHO Classification of Tumours of the urinary system and male genital organs—Part B: Prostate and bladder tumours. Eur Urol 70(1): 106-119, 2016. DOI: 10.1016/j.eururo.2016.02.028

17 Veskimäe E, Espinos EL, Bruins HM, Yuan Y, Sylvester R, Kamat AM, Shariat SF, Witjes JA, Compérat EM: What is the prognostic and clinical importance of urothelial and nonurothelial histological variants of bladder cancer in predicting oncological outcomes in patients with muscle-invasive and metastatic bladder cancer? A European Association of Urology muscle invasive and metastatic bladder cancer guidelines panel systematic review. Eur Urol Oncol 2(6): 625-642, 2019. DOI: 10.1016/j.euo.2019.09.003

18 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009. DOI: 10.1016/j.ejca.2008.10.026

19 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48(3): 452-458, 2013. DOI: 10.1038/bmt.2012.244

20 Hsieh MC, Sung MT, Chiang PH, Huang CH, Tang Y, Su YL: The prognostic impact of histopathological variants in patients with advanced urothelial carcinoma. PLoS One 10(6): e0129268, 2015. DOI: 10.1371/journal.pone.0129268

21 Epaillard N, Parent P, Loriot Y, Lavaud P, Vera-Cea EB, Martinez-Chanza N, Rodriguez-Vida A, Dumont C, Lozano R, Llácer C, Ratta R, Oudard S, Thibault C, Auclin E: Treatments outcomes in histological variants and non-urothelial bladder cancer: results of a multicenter retrospective study. Front Oncol 11: 671969, 2021. DOI: 10.3389/fonc.2021.671969

22 Dogliotti L, Cartenì G, Siena S, Bertetto O, Martoni A, Bono A, Amadori D, Onat H, Marini L: Gemcitabine plus cisplatin *versus* gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol 52(1): 134-141, 2007. DOI: 10.1016/j.eururo.2006.12.029

23 Als AB, Sengelov L, Von Der Maase H: Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer; 3- or 4-week schedule? Acta Oncol 47(1): 110-119, 2008. DOI: 10.1080/02841860701499382

24 Black PC, Brown GA, Dinney CP: The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol 27(1): 3-7, 2009. DOI: 10.1016/j.urolonc.2007.07.010

25 Hajiran A, Azizi M, Aydin AM, Zemp L, Peyton CC, Dhillon J, Nealon S, Reich RR, Cao B, Li R, Manley BJ, Sexton WJ, Gilbert SM: Pathological and survival outcomes associated with variant histology bladder cancers managed by cystectomy with or without neoadjuvant chemotherapy. J Urol 205(1): 100-108, 2021. DOI: 10.1097/JU.0000000000001325

26 Minato A, Fujimoto N, Kubo T: Squamous differentiation predicts poor response to cisplatin-based chemotherapy and unfavorable prognosis in urothelial carcinoma of the urinary bladder. Clin Genitourin Cancer 15(6): e1063-e1067, 2017. DOI: 10.1016/j.clgc.2017.07.008

27 Leite KRM, Borges LL, Filho LR, Chade D, Coelho RF, Cordeiro M, Srougi M, Nahas WC: Histological variants of urothelial carcinoma predict no response to neoadjuvant chemotherapy. Clin Genitourin Cancer 20(1): e1-e6, 2022. DOI: 10.1016/j.clgc.2021.07.011

28 Zargar-Shoshtari K, Sverrisson EF, Sharma P, Gupta S, Poch MA, Pow-Sang JM, Spiess PE, Sexton WJ: Clinical outcomes after neoadjuvant chemotherapy and radical cystectomy in the presence of urothelial carcinoma of the bladder with squamous or glandular differentiation. Clin Genitourin Cancer 14(1): 82-88, 2016. DOI: 10.1016/j.clgc.2015.08.006

29 Vetterlein MW, Wankowicz SAM, Seisen T, Lander R, Löppenberg B, Chun FK, Menon M, Sun M, Barletta JA, Choueiri TK, Bellmunt J, Trinh QD, Preston MA: Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer 123(22): 4346-4355, 2017. DOI: 10.1002/cncr.30907

30 Minato A, Kimuro R, Ohno D, Tanigawa K, Kuretake K, Matsukawa T, Takaba T, Jojima K, Harada M, Higashijima K, Nagata Y, Tomisaki I, Harada K, Fujimoto N, Miyamoto H: Efficacy and tolerability of enfortumab vedotin for metastatic urothelial carcinoma: early experience in the real world. Anticancer Res 43(9): 4055-4060, 2023. DOI: 10.21873/anticanres.16594

Received October 15, 2023
Revised November 29, 2023
Accepted December 7, 2023