Original Article

Efficacy of avelumab maintenance therapy for advanced urothelial carcinoma with histologic subtype and divergent differentiation: a multicenter retrospective study conducted by the Uro-Oncology Group in Kyushu

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Background: The subtype of urothelial carcinoma (SUC) has been known to possess morphological diversity for histologic subtype or divergent differentiation. However, the efficacy of avelumab against SUC remains unclear. Therefore, the effect of the treatment as well as the survival results of avelumab monotherapy were evaluated as a first-line therapeutic maintenance in patients with advanced SUC.

Methods: A retrospective analysis was conducted on consecutive patients from the Uro-Oncology Group in Kyushu study population with advanced lower and upper urinary tract cancer who underwent avelumab maintenance therapy without progression after first-line platinum-based chemotherapy. Patients with pure urothelial carcinoma (PUC) and SUC were comparatively analyzed based on objective response rate (ORR), disease control rate, progression-free survival (PFS), and overall survival (OS).

Results: Out of 49 recorded patients, 38 and 11 had PUC and SUC, respectively. The most common subtype element was glandular differentiation (n=5), followed by squamous differentiation (n=3), micropapillary (n=1), and plasmacytoid subtypes (n=1). The SUC and PUC groups had comparable ORR (0% *vs.* 2.6%, P>0.99) and disease control rates (54.5% *vs.* 44.7%, P=0.73). These patient groups also showed no significant difference in PFS (median 3.9 *vs.* 3.1 months, P=0.33) or OS (median 16.7 *vs.* 22.1 months, P=0.47).

Conclusions: The response of SUC and PUC to avelumab was comparable in patients with advanced lower and upper urinary tract cancer, indicating that avelumab maintenance therapy is also effective for SUC.

Keywords: Histologic subtype; divergent differentiation; urothelial carcinoma (UC); avelumab; immune checkpoint inhibitors (ICIs)

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Introduction

Over the past three decades, platinum-based chemotherapy as a first-line regimen has been the common treatment for advanced urothelial carcinoma (UC). Despite high responsiveness (disease control in approximately 75–82%), progression-free survival (PFS) or overall survival (OS) durations are insufficient in patients with locally advanced or metastatic UC treated with gemcitabine plus cisplatin, or methotrexate, vinblastine, and doxorubicin plus cisplatin (1,2). Immune checkpoint blockade therapy was then introduced, dramatically transforming the management of advanced UC (3). In Japan, immune checkpoint inhibitors (ICIs) such as pembrolizumab [anti-programmed death 1 (PD-1) antibody], avelumab [anti-programmed cell death-ligand 1 (PD-L1) antibody], and nivolumab (anti-PD-1 antibody) have been approved for advanced UC, owing to the phase 3 clinical trial results (4-6). The JAVERIN bladder 100 trial showed that the 1-year OS rate was 79.1% in the avelumab group (median, 21.4 months) (5). In particular, if effective, avelumab as a maintenance therapy after platinum-based chemotherapy may offer relatively long OS duration; avelumab had been administered to 19.5% of 350 patients for more than 24 months (7). Of course, when treating with ICIs, we must pay attention to the performance status of patients and the management of immune-related adverse events (8). Additionally, there is one topic that ICI therapy is associated with a higher risk of hypertransaminasemia as liver toxicity (9).

During the last quarter century, several "subtype" forms of UC have been reported, most of which are recognized by the World Health Organization (WHO) classification (10). Owing to improvements in pathologic recognition (11), the treatment opportunities for subtype of UC (SUC) are relatively increasing. SUC was previously reported for around 31% of muscle-invasive bladder cancers, 12% of upper urinary tract cancers, and 34% of metastatic diseases (12,13). Regarding sensitivity to pharmacotherapy, recent studies have focused on the neoadjuvant setting of platinum-based chemotherapy in patients with SUC with locally advanced bladder cancer (14-16). However, results regarding survival outcomes in patients with SUC are conflicting, and evidence remains insufficient.

Generally, SUC exhibits an aggressive biological behavior and progresses faster than pure UC (PUC) (14,16). In patients with metastatic SUC, the response to systemic chemotherapy or immune checkpoint blockade therapy has rarely been reported. Discovering new treatment options for these patients is important to improve their prognosis.

Hence, the objective of this research was to evaluate the effect of avelumab maintenance therapy on the oncological results of metastatic SUC cases in real-world clinical practice from the Uro-Oncology Group in Kyushu (UROKYU) study population. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-53/rc).

Highlight box

Key findings

- The response of the subtype of urothelial carcinoma (SUC) to avelumab was similar to that of pure urothelial carcinoma (PUC) in patients with advanced lower and upper urinary tract cancer.

What is known, and what is new?

- Avelumab, as a maintenance therapy after platinum-based chemotherapy, is the standard of care. However, patients with advanced SUC are excluded from the analysis in clinical trials; thus, the efficacy of avelumab against SUC remains unclear.
- This real-world study from the Uro-Oncology Group in Kyushu (UROKYU) population showed no significant differences in progression-free survival or overall survival after initiating avelumab maintenance therapy between the PUC and SUC groups.

What are the implications, and what should change now?

- Anti-programmed cell death-ligand 1 inhibitors as an early sequential therapy may be recommended to patients with histologic subtype or divergent differentiation in advanced disease.

Methods

Patient population

We retrospectively reviewed 49 patients with advanced UC (locally advanced/unresectable or metastatic) in the lower and upper urinary tracts who already had their first-line platinum-based chemotherapy at the University of Occupational and Environmental Health Hospital, National Hospital Organization Kyushu Cancer Center,

Table 1 Histological type of patients treated with avelumab

Histologic type	No. of patients (%)
PUC	38 (77.6)
SUC	11 (22.4)
Glandular differentiation	5 (10.2)
Squamous differentiation	3 (6.1)
Micropapillary subtype	1 (2.0)
Plasmacytoid subtype	1 (2.0)
Trophoblastic differentiation	1 (2.0)

PUC, pure urothelial carcinoma; SUC, subtype of urothelial carcinoma.

Oita Prefectural Hospital, Miyazaki Prefectural Miyazaki Hospital, and Japanese Red Cross Fukuoka Hospital between November 2015 and August 2023, using the UROKYU study population. All patients without disease progression received subsequent switch maintenance with avelumab. Based on the 2022 WHO Classification of Tumors, SUC is described as the mixed presence of UC and histologic subtype or divergent differentiation (17). The morphologic group was based on the assessments delivered by devoted pathologists at each institute without central review. Previously, radical operations comprised cystectomy and nephroureterectomy. Some patients were exclusively detected with PUC or SUC based on a slight biopsy sample. The regimen, duration, and number of cycles in first-line platinum-based chemotherapy were determined by each institution (18). After first-line chemotherapy, all patients showed radiologically confirmed disease control. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our study protocol was approved by the University of Occupational and Environmental Health Institutional Review Board (approval No. CRG23-017), all participating institutions were informed and agreed the study. Individual consent for this retrospective analysis was waived due to retrospective nature.

Patient management

Avelumab was provided intravenously at 10 mg/kg dose on day 1, and the cycle was performed every 14 days until disease progression or the manifestation of intolerable side effects. Follow-up assessment included physical checkup, laboratory tests, and chest-abdominal-pelvic computed tomography. Imaging assessment was executed at baseline and after every 4 to 6 cycles of avelumab treatment, as well as when the clinical symptoms worsened (18).

Evaluation

The best response to treatment was based on the tumor response according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (19). In particular, in the analysis of maintenance avelumab therapy, the best overall response of patients who had a complete response (CR) to platinum-based chemotherapy (no evidence of disease at the start of avelumab) and who had no evidence of disease after the start of avelumab was noted as 'could not be evaluated (NE)' (18). The objective response rate (ORR) was defined as the proportion of patients with CR or partial response (PR), and disease control rate as the proportion of patients with CR, PR, and stable disease (SD) without progressive disease (PD).

Moreover, we calculated PFS from the time of avelumab delivery to that of disease progression or death, whichever happened first or the last follow-up in patients without disease development. In addition, we calculated the OS from the time of avelumab delivery to that of death from any reason or to the last follow-up in patients who survived. For those whose medical data lacked follow-up information, data was attained over phone contact.

Statistical analysis

We used EZR ver.1.40 (Easy R, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), for all statistical analyses (20). We evaluated between-group variances with Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Moreover, PFS and OS were assessed with the Kaplan-Meier method and compared using the log-rank test. Significance was considered at $P<0.05$.

Results

Patient characteristics

Of the 49 registered patients, 38 (77.6%) had PUC and 11 (22.4%) SUC. The primary subtype element was the glandular differentiation, followed by squamous differentiation (*Table 1*).

The basic characteristics of the participants with

Table 2 Patient characteristics at the initiation of avelumab maintenance therapy

Characteristic	PUC (n=38)	SUC (n=11)	P value
Age (years)	72 [68–75]	70 [64–76]	0.54
Sex			0.46
Male	25 (65.8)	9 (81.8)	
Female	13 (34.2)	2 (18.2)	
ECOG-PS score			0.57
0	27 (71.1)	7 (63.6)	
1	9 (23.7)	3 (27.3)	
≥2	2 (5.2)	1 (9.1)	
Primary tumor site			0.01
Lower urinary tract	17 (44.7)	10 (90.9)	
Upper urinary tract	21 (55.3)	1 (9.1)	
Prior radical surgery	22 (57.9)	7 (63.6)	>0.99
Prior chemotherapy regimen			>0.99
GC	22 (57.9)	6 (54.5)	
GCarbo	15 (39.5)	5 (45.5)	
dd-MVAC	1 (2.6)	0 (0.0)	
Best response to chemotherapy			0.85
CR	2 (5.3)	0 (0.0)	
PR	19 (50.0)	5 (45.5)	
SD	17 (44.7)	6 (54.5)	
No. of chemotherapy cycles	4 [2–15]	4 [2–6]	0.48
Anemia (Hb <10 g/dL)	17 (44.7)	3 (27.3)	0.49
Metastatic disease site			>0.99
Visceral metastasis	16 (42.1)	4 (36.4)	
Non-visceral metastasis	22 (57.9)	7 (63.6)	
Subsequent enfortumab vedotin use	20 (52.6)	7 (63.6)	0.73

Data are presented as median [IQR] or n (%). ECOG-PS, Eastern Cooperative Oncology Group performance status; GC, gemcitabine and cisplatin; GCarbo, gemcitabine and carboplatin; dd-MVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; CR, complete response; PR, partial response; SD, stable disease; Hb, hemoglobin; PUC, pure urothelial carcinoma; SUC, subtype of urothelial carcinoma; IQR, interquartile range.

PUC and SUC are shown in *Table 2*. Age, sex, Eastern Cooperative Oncology Group performance status (ECOG-PS), surgical history, first-line chemotherapy pattern, anemia occurrence, visceral metastasis occurrence, and use of subsequent enfortumab vedotin therapy showed no significant difference between the PUC and SUC groups. SUC mostly originated from the lower urinary tract, with only one case originating from the upper urinary tract. The proportion of ORR to platinum-based chemotherapy was 55.3% in patients with PUC and 45.5% in those with SUC.

Oncological outcomes

Figure 1 presents the best percentage change from baseline

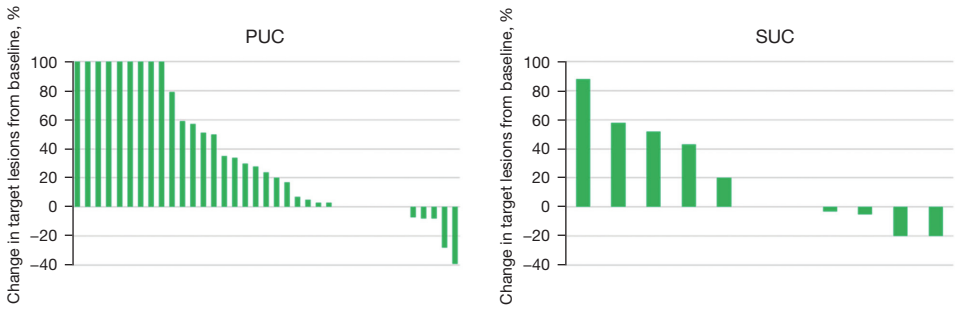

Figure 1 Waterfall plot of best percentage change from baseline in patients with PUC and SUC receiving avelumab maintenance therapy. PUC, pure urothelial carcinoma; SUC, subtype of urothelial carcinoma.

Table 3 Observed efficacy of avelumab maintenance therapy stratified by histological type

Histologic type	PUC (n=38)	SUC (n=11)	P value
Response			0.84
CR	0 (0.0)	0 (0.0)	
PR	1 (2.6)	0 (0.0)	
SD	16 (42.1)	6 (54.5)	
PD	20 (52.6)	5 (45.5)	
NE	1 (2.6)	0 (0.0)	
Objective response rate (CR + PR)	1 (2.6)	0 (0.0)	>0.99
Disease control rate (CR + PR + SD)	17 (44.7)	6 (54.5)	0.73

Data are presented as n (%). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, could not be evaluated; PUC, pure urothelial carcinoma; SUC, subtype of urothelial carcinoma.

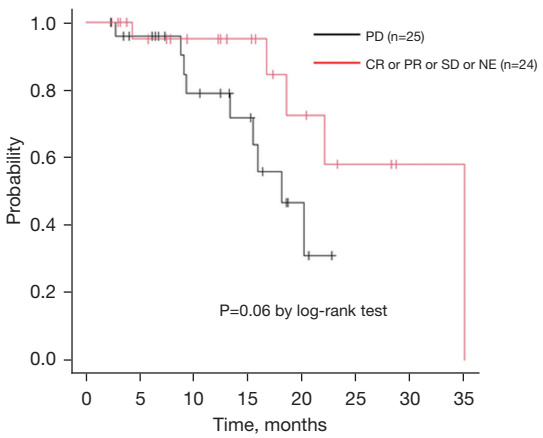

Figure 2 Kaplan-Meier curves for the overall survival after the initiation of avelumab maintenance therapy in patients with advanced urothelial carcinoma according to the best response. PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease; NE, could not be evaluated.

in patients treated with avelumab stratified by histology. The best response of the PUC and SUC groups to avelumab maintenance therapy is shown in *Table 3*. Both groups had similar ORR and disease control rates. The comprehensive response among patients with SUC according to histological type was as follows: glandular differentiation (4 patients with SD and 1 with PD), squamous differentiation (1 with SD and 2 with PD), micropapillary subtype (1 with PD), plasmacytoid subtype (1 with SD), and trophoblastic differentiation (1 with PD).

The median follow-up period after receiving first-line platinum-based chemotherapy was 17.2 months [interquartile range (IQR), 11.1–24 months], and that after receiving avelumab was 12.5 months (IQR, 6.7–18.1 months), during which 40 (81.6%) patients experienced progression, and 14 (28.6%) died. Avelumab responders were associated with close to significant differences for median OS duration [35.1 months, 95% confidence interval (CI): 16.7–not estimable and 18.1 months, 95% CI: 13.3–not estimable, P=0.06] compared with avelumab non-responders (PD) (*Figure 2*).

The two groups showed no significant difference in PFS or OS (*Figure 3*). The median PFS was 3.1 months (95% CI: 2.4–5.5) in patients with PUC and 3.9 months (95% CI: 2.1–15.8) in those with SUC (P=0.33, *Figure 3A*). As for the 1-year OS rate, the PUC and SUC groups obtained 85.0% and 77.8%, respectively [median OS: 22.1 months (95% CI: 18.1–not estimable) and 16.7 months (95% CI: 8.8–not estimable), P=0.47] (*Figure 3B*).

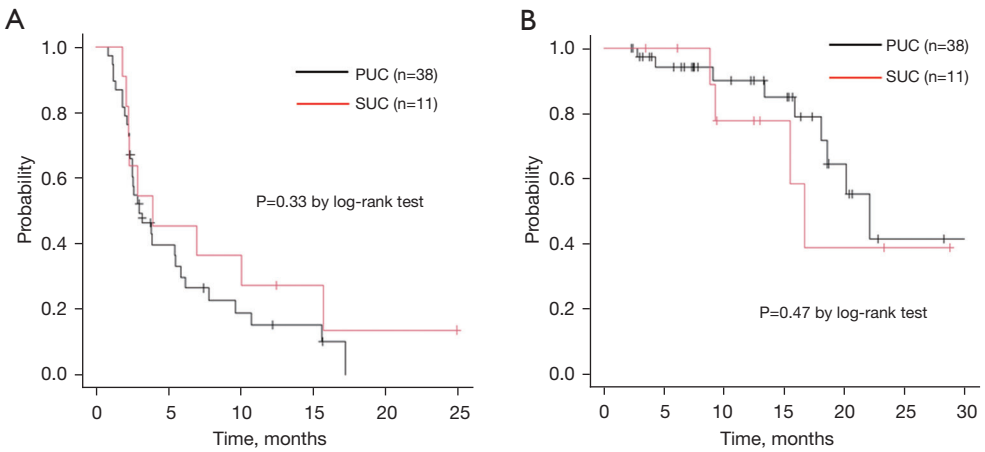

Figure 3 Kaplan-Meier curves for the (A) progression-free survival and (B) overall survival after the initiation of avelumab maintenance therapy in patients with PUC and SUC. PUC, pure urothelial carcinoma; SUC, subtype of urothelial carcinoma.

Discussion

Currently, the role of avelumab, an anti-PD-L1 antibody, against SUC has been less explored. To assess its efficacy on clinical responses following the histological type, we assessed the therapeutic feedback and survival of participants undergoing avelumab maintenance therapy for PUC and SUC after first-line platinum-based chemotherapy. The standard subtype element in the SUC group was the glandular differentiation. Compared with PUC, participants with SUC had the same ORR and disease control rates. PFS or OS after avelumab maintenance therapy also showed no significant differences between the two groups.

In a large randomized phase III trial, the median OS duration was 14–15 months in patients with locally advanced or metastatic UC treated with platinum-based chemotherapy (1). In 2020, administering avelumab as the first-line maintenance therapy for patients without disease progression after 4 to 6 cycles of platinum-based chemotherapy had improved survival outcomes (5). In our UROKYU study, avelumab responders in switch maintenance demonstrated favorable survival duration and clinical benefit.

Given that patients with metastatic SUC are excluded from analysis in clinical trials, no effective strategy has yet been established. In fact, the JAVERIN bladder 100 trial did not include the analysis of histologic subtype or divergent differentiation (21). The efficacy of avelumab switch maintenance on SUC has rarely been reported in a real-world setting. In a multicenter retrospective study conducted in the United States and Europe, patients with SUC (n=23) showed no increased risk for poor OS or PFS compared with those with PUC (n=85) (22). Moreover, the AVENANCE study revealed that patients with SUC (n=44) had a median OS of 20.2 months and a 1-year OS rate of 65.3% (23). Our findings are consistent with these previous results.

SUC adversely influences the efficacy of first-line platinum-based chemotherapy, with a median OS duration of approximately 11 months (24,25). In our previous report, the occurrence of SUC in metastatic disease was a prognosticator of mortality in a gemcitabine plus cisplatin (or carboplatin) therapy cohort (25). Interestingly, in this research, the PUC and SUC groups were not significantly different with respect to PFS or OS after introducing avelumab as the first-line maintenance therapy. Unfortunately, the number prior cycles of platinum-based chemotherapy that is considered appropriate for avelumab switch maintenance against SUC remains unknown. Given the short duration of PFS (median: 3.8–4.9 months) from the introduction of platinum-based chemotherapy in previous studies (24,25), early sequential therapy (switching to no more than four cycles) from first-line chemotherapy to avelumab maintenance therapy may be suitable for patients with advanced SUC. The DISCUS trial (EudraCT Number 2021-001975-17), an ongoing randomized trial that compares 3 and 6 cycles of platinum-based chemotherapy followed by avelumab, will help further refine the appropriate timing of switch maintenance (26).

Moreover, recent multicenter retrospective studies demonstrated similar response and survival outcomes of the

anti-PD-1 antibody pembrolizumab between patients with chemotherapy-resistant SUC and those with PUC (27,28). Thus, ICI treatment may be beneficial and a good candidate for patients with advanced-stage SUC. In the real-world setting, the ARON-2 study showed the role of ICI as first-line therapy for cisplatin-unfit patients (29). Most recently, two randomized phase III clinical trials (CheckMate-901 and EV-302) revealed that the patients with untreated advanced UC prolonged OS in the first-line setting (30,31). In the future, gemcitabine plus cisplatin with nivolumab or enfortumab vedotin [antibody-drug conjugate (ADC)] with pembrolizumab might yield a positive effect for SUC.

The identification of predictive biomarkers for ICIs represents one of the unmet needs for metastatic UC. Although PD-L1 was analyzed in the JAVELIN Bladder 100 population (7), molecular biomarkers are not routinely used in daily practice in Japan. Currently, PD-L1 status is not clinically required to be assessed when considering avelumab maintenance therapy (26). The ARIES trial found no difference in avelumab response between patients with high and low PD-L1 expression levels (32). However, a recent meta-analysis suggests that ICIs were associated with favorable OS benefits in patients with PD-L1 positive (33). Previous immunohistochemical analysis reported PD-L1 expression in a high percentage of SUCs, and squamous differentiation showed higher expression than the other SUCs (34). Moreover, some SUCs correlate with specific molecular subtypes (35). Squamous and glandular differentiations are categorized as basal/squamous and luminal/unstable, respectively. Generally, pharmacotherapy for SUC is done according to PUC in the same manner. In the future, if we can use molecular subtypes by gene expression and correlations to the response of chemotherapy or immunotherapy in daily practice, personalized healthcare would develop against SUC.

Some limitations of this research include its retrospective, nonrandomized design and small sample size. In particular, the number of patients with SUC was extremely limited, thereby requiring further investigation with larger cohorts. Considering the small sample size, we could not compare patients' response or survival to avelumab maintenance therapy according to the SUC subgroup, primary tumor site, and efficacy of first-line chemotherapy. The majority of included patients with SUC had glandular or squamous differentiation. These subtypes may have better responses to ICI compared to other histology. Moreover, the subsequent ADC therapy may have affected the prognosis after the failure of avelumab maintenance therapy.

Nevertheless, our data suggest that the efficacy of avelumab maintenance therapy for patients with SUC is relatively favorable regardless of the disease's aggressiveness. Additionally, enfortumab vedotin monotherapy was recently reported as a third-line treatment for patients with metastatic SUC disease has certain effects (36). Thus, the key is to administer effective drugs sequentially, such as platinum-based chemotherapy, ICI therapy, and ADC therapy, without delay to patients with advanced SUC. We believe that our study will support the optimal therapeutic strategy for patients with SUC.

Conclusions

The response of SUC and PUC to avelumab was similar in patients with advanced lower and upper urinary tract cancer. Therefore, administering avelumab maintenance after first-line platinum-based chemotherapy may be effective for advanced SUC disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-53/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-53/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-53/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol was approved by the University of Occupational and Environmental Health Institutional Review Board (approval No. CRG23-017), all participating institutions were informed and agreed the study. Individual consent for this retrospective analysis was waived due to retrospective nature.

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