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Response to Platinum-based Chemotherapy Rechallenge for Patients With Pembrolizumab-refractory Urothelial Carcinoma

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Abstract. *Background: This study aimed to investigate the response to platinum-based chemotherapy rechallenge in patients with pembrolizumab-refractory urothelial carcinoma. Patients and Methods: We retrospectively reviewed 14 patients with pembrolizumab-refractory urothelial carcinoma. Each patient received a regimen that they had not previously received (paclitaxel plus carboplatin in 10, gemcitabine plus docetaxel and carboplatin in four). Tumor response and adverse events were assessed. We evaluated overall survival from the chemotherapy rechallenge start date until death. Results: The median overall survival was 11.2 months. The disease-control rate was 85.7%. Partial responses occurred in the metastases in lymph nodes in three (37.5%) patients, lung in one (25%), peritoneal in three (75%), and liver in three (100%). Neutropenia of grade ≥3 occurred in 13 (92.9%) patients. Conclusion: The activity of platinum-based chemotherapy rechallenge after pembrolizumab was maintained. Neutropenia was observed in most patients.*

Urothelial carcinoma (UC) is associated with >165,000 global deaths annually (1, 2). In Japan, approximately 20,000 patients are newly diagnosed with UC, resulting in 8000 deaths annually (3). The gold standard therapy for metastatic UC has been chemotherapy. The first-line regimen of chemotherapy has for some time been platinum-based combination chemotherapy, a combination of gemcitabine and cisplatin (GC), and a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). However, the clinical benefit of first-line chemotherapy for UC in progression-free survival (7-8 months) is limited. The majority of patients with metastatic UC treated with platinum-based chemotherapy ultimately experience disease progression due to resistance (4). Recently, pembrolizumab, an immune checkpoint inhibitor (ICI) targeting the PD-1 axis, has shown response rates of approximately 20% (5) in platinum-refractory patients. Similarity, in a Japanese subgroup, pembrolizumab provided durable antitumor activity in patients with locally advanced/metastatic UC that progressed after platinum-containing chemotherapy (6). In Japan, pembrolizumab is a second-line therapy for patients with platinum-based chemotherapy-refractory disease. However, the response rates were only 20%, so the outcome of metastatic UC remains unsatisfactory.

There has been no evidence reported for efficacy of a third-line regimen for patients with UC after pembrolizumab. There are few reports of patients with metastatic UC after pembrolizumab (7-9), and the reported regimens were GC rechallenge, paclitaxel, and carboplatin (TC), and docetaxel. This study aimed to retrospectively assess the clinical outcomes of platinum-based chemotherapy rechallenge in patients with pembrolizumab-refractory metastatic UC.

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Key Words: Urothelial carcinoma, platinum-based chemotherapy, pembrolizumab, response, adverse events.

Patients and Methods

Patients. We retrospectively reviewed 14 patients with metastatic UC whose disease had progressed after pembrolizumab and who underwent chemotherapy at our Institution between January 2018 and December 2020. In all patients, UC was histopathologically diagnosed, and disease progression after platinum-based chemotherapy was assessed. Pembrolizumab was administered intravenously on day 1 at a dose of 200 mg and repeated every 21 days. This treatment was continued until disease progression.

The patients underwent platinum-based chemotherapy rechallenge with either TC or gemcitabine, docetaxel, and carboplatin (GDC). Each patient received the regimen that they had not previously received. In the TC regimen, paclitaxel 175 mg/m^2 and carboplatin at an area under the curve of 5 were administered according to the Calvert formula on day 1. The GDC regimen was 1,000 mg/m^2 gemcitabine on days 1 and 8, 70 mg/m^2 docetaxel on day 1, with carboplatin at an area under the curve of 5 on day 1. In both regimens, the cycle was basically repeated every 21 days. Both regimens were continued until disease progression or unacceptable adverse events (AEs) occurred.

Response to platinum-based chemotherapy rechallenge and overall survival. Tumor measurements were generally performed by computed tomography. The tumor response was evaluated as the best response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (10). The baseline was measured before platinum-based chemotherapy rechallenge. The best response was classified as either a complete response (CR) defined as disappearance of all target lesions, a partial response (PR) defined as a ≥30% decrease in the sum of the longest diameters of the target lesions relative to baseline, progressive disease (PD) defined as the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions, or stable disease (SD) defined as neither PR or PD. Bone metastases were defined as PD, with new lesions. We evaluated overall survival (OS) defined as the time from the start of chemotherapy rechallenge until death.

Adverse events (AEs). AEs were assessed according to the Common Terminology Criteria for Adverse Events, version 5.0 (11).

Statistical analysis. Statistical analysis was performed using SPSS Statistics software version 15.0 (SPSS Inc., Chicago, IL, USA). Survival curves were constructed using Kaplan–Meier analyses. A *p*-value of less than 0.05 was considered to be statistically significant.

This study was approved by the Ethics Committee of Tottori University, Faculty of Medicine (approval number 18A038).

Results

Patients. The patients' characteristics are presented in Table I. The median age was 69 years (range=45–84 years). Twelve patients were male and two were female. Seven patients had primary bladder tumors, and seven had primary upper-urinary tract tumors. The Eastern Cooperative Oncology Group Performance Status was 0 in 11 patients and 1 in three. The regimens before pembrolizumab were GC for all patients, TC in four, MVAC in three, and GDC in one. The median number of pembrolizumab cycles was 4.5 (range=2-16), and no patient had a CR as the best response to pembrolizumab, one (7%) patient had a PR, five (36%) had SD, and eight (57%) had PD. Metastasis at rechallenge was observed in lymph nodes in eight patients, bone in five, lung in four, peritoneum in four, liver in three, and adrenal glands in one. In platinum-based chemotherapy rechallenge, 10 patients underwent TC, and four patients underwent GDC as platinum-based chemotherapy rechallenge.

Table I. *Patient characteristics*.

Characteristic	Value
Age, years	
Median (range)	69 (45-84)
Gender	
Male	12
Female	2
BMI, kg/m^2	
Median (range)	23.6 (20.3-28.0)
PS, n (%)	
0	11 (78.6)
1	3 (21.4)
Primary tumor, n (%)	
Bladder	7 (50)
Upper urinary tract	7 (50)
Baseline laboratory data, median (range)	
Albumin, g/dl	3.8 (2.4-4.7)
BUN, mg/dl	17 (7.4-27.8)
Cre, mg/dl	1.02 (0.76-1.4)
CRP, mg/dl	1.03 (0.02-12.64)
WBC, n/μl	5,000 (3,700-23,700)
Hb, g/dl	10.8 (7.8-13.8)
Plt, 10^3/μl	23.1 (7.9-47.2)
Location of metastasis, n	
Lymph node	8
Bone	5
Lung	4
Liver	3
Peritoneal	4
Adrenal	1
Chemotherapy regimen pre pembrolizumab	
Methotrexate, vinblastine, doxorubicin, cisplatin	3
Gemcitabine, cisplatin or carboplatin	14
Paclitaxel, carboplatin	4
Gemcitabine, docetaxel, carboplatin	1
Number of pembrolizumab cycles	
Median (range)	4.5 (2-16)
Response to pembrolizumab, n (%)	
CR	0 (0)
PR	1 (7)
SD	5 (36)
PD	8 (57)

BUN: Blood urea nitrogen; CR: complete response; Cre: creatinine; CRP: C-reactive protein; Hb: hemoglobin; PD: progressive disease; Plt: platelets; PR: partial response; SD: stable disease; WBC: white blood cells.

OS and response. Figure 1 shows the Kaplan–Meier survival curve for OS. The median OS was 11.2 months.

Regarding the response to chemotherapy rechallenge according to RECIST, the objective response rate (ORR) was 28.6%, including no CR, PR in four, SD in eight, and PD in two. The disease-control rate (CR + PR + SD) was 85.7%. Two patients had bone metastases: One was PD with only a new bone metastasis, and the other was SD.

Figure 2 shows the best changes from baseline in size of metastases, excluding the two patients with bone metastasis only. The median best changes from baseline were −19% (range=−43 - +27%). Regarding the treatment effect of platinum-based chemotherapy, according to the RECIST for lymph-node metastasis, no (0%) patient had a CR, three (37.5%) had a PR, three (37.5) had SD, and two (25%) had PD; in lung metastasis, one (25%) patient had a PR, two (50%) had SD, and one (25%) had PD; in the peritoneal, three (75%) had a PR and one (25%) had SD; in the liver, three (100%) had a PR; and in the adrenal, one (100%) had SD.

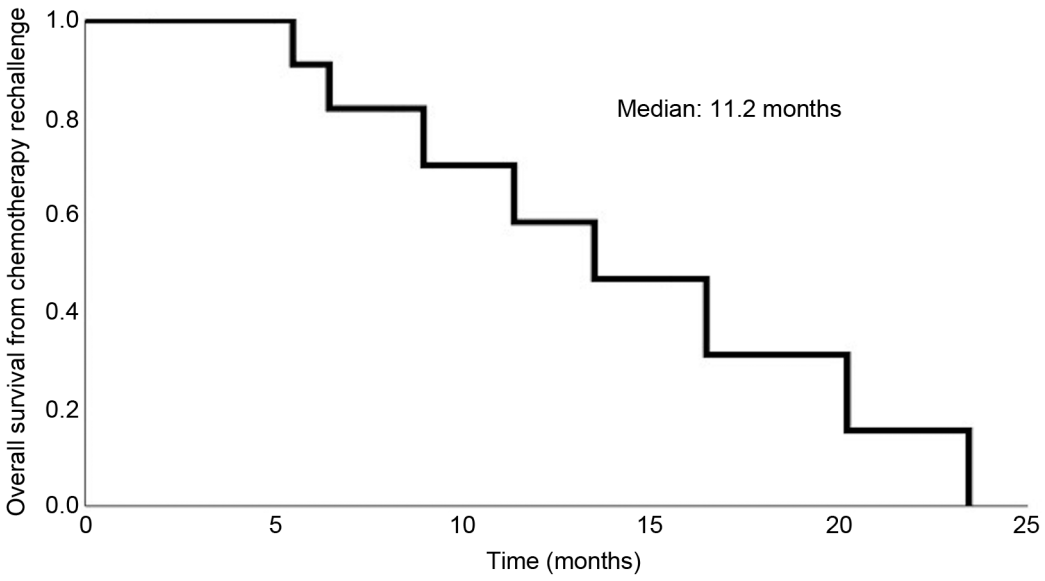

Figure 1. *Overall survival from chemotherapy rechallenge.*

Adverse events. Eight (57.1%) patients had neutropenia grade 4, five (35.7%) had grade 3, and one (7.2%) had grade 2. Thirteen (92.9%) patients had neutropenia grade 3 or higher. One (7.2%) patient had febrile neutropenia. Five (35.7%) patients had anemia grade 3, six (42.9%) had grade 2, and three (21.4%) had grade 0. Four (28.6%) patients had thrombocytopenia grade 4, three (21.4%) had grade 2, one (7.2%) had grade 1, and six (42.9%) had grade 0. No patient died.

Relationship between pembrolizumab and platinum-based chemotherapy rechallenge. Table II shows the relationships between response, number of cycles, and immune-related AEs in pembrolizumab therapy and response to platinum-based chemotherapy rechallenge. One (100%) pembrolizumab-treated patient with PR showed PD, two (40%) patients with SD had PRs, and three (60%) patients had SD; among the patients with PD, two (25%) showed PR, five (62.5%) showed SD, and one (12.5%) continued with PD. The response to platinum-based chemotherapy rechallenge was not significantly associated with the response to pembrolizumab (p=0.134). Furthermore, the response to platinum-based chemotherapy rechallenge was not significantly associated with the number of pembrolizumab cycles (p=0.070) and immune-related AEs (p=0.776).

Discussion

In this study, we evaluated platinum-based chemotherapy rechallenge for patients with pembrolizumab-refractory UC. There were no CRs but the rate of PRs plus SD was 85.7%. Therefore, the platinum-based chemotherapy rechallenge may suppress tumor progression.

The gold-standard first-line chemotherapy for advanced UC has been platinum-based chemotherapy, MVAC, and GC for many years. However, there has been no standard second-line chemotherapy in Japan until pembrolizumab was approved. Previously, the second-line chemotherapy used various multi-drug regimens, such as paclitaxel plus ifosfamide, docetaxel plus ifosfamide, gemcitabine plus paclitaxel, methotrexate plus paclitaxel, gemcitabine plus ifosfamide plus cisplatin, GDC, paclitaxel plus carboplatin, and gemcitabine plus paclitaxel. However, these studies were in small samples, and the median OS ranged from 4.8 to 14.4 months (12). These results remained unsatisfactory, so there has been no evidence of a useful second-line chemotherapy for patients with advanced UC to date. In 2017, Bellmunt *et al.* reported that pembrolizumab was associated with significantly longer OS and a lower rate of treatment-related AEs than chemotherapy as second-line chemotherapy for patients with platinum-based chemotherapy-refractory advanced UC (5). Recently, the second-line gold standard therapy has been pembrolizumab. However, the ORR (CR+PR) to pembrolizumab was 20.0%, and the disease-control rate (CR+PR+SD) was 26.7% in a Japanese subgroup analysis of the phase-3 KEYNOTE-045 trial, and the other responses were PD (66.7%) (6). Furthermore, hyper-progression of disease has recently been reported in patients receiving pembrolizumab (13, 14). Saâda–Bouzid *et al.* reported that hyper-progression was observed in 29% (10/34) of patients with recurrent/metastatic head and neck

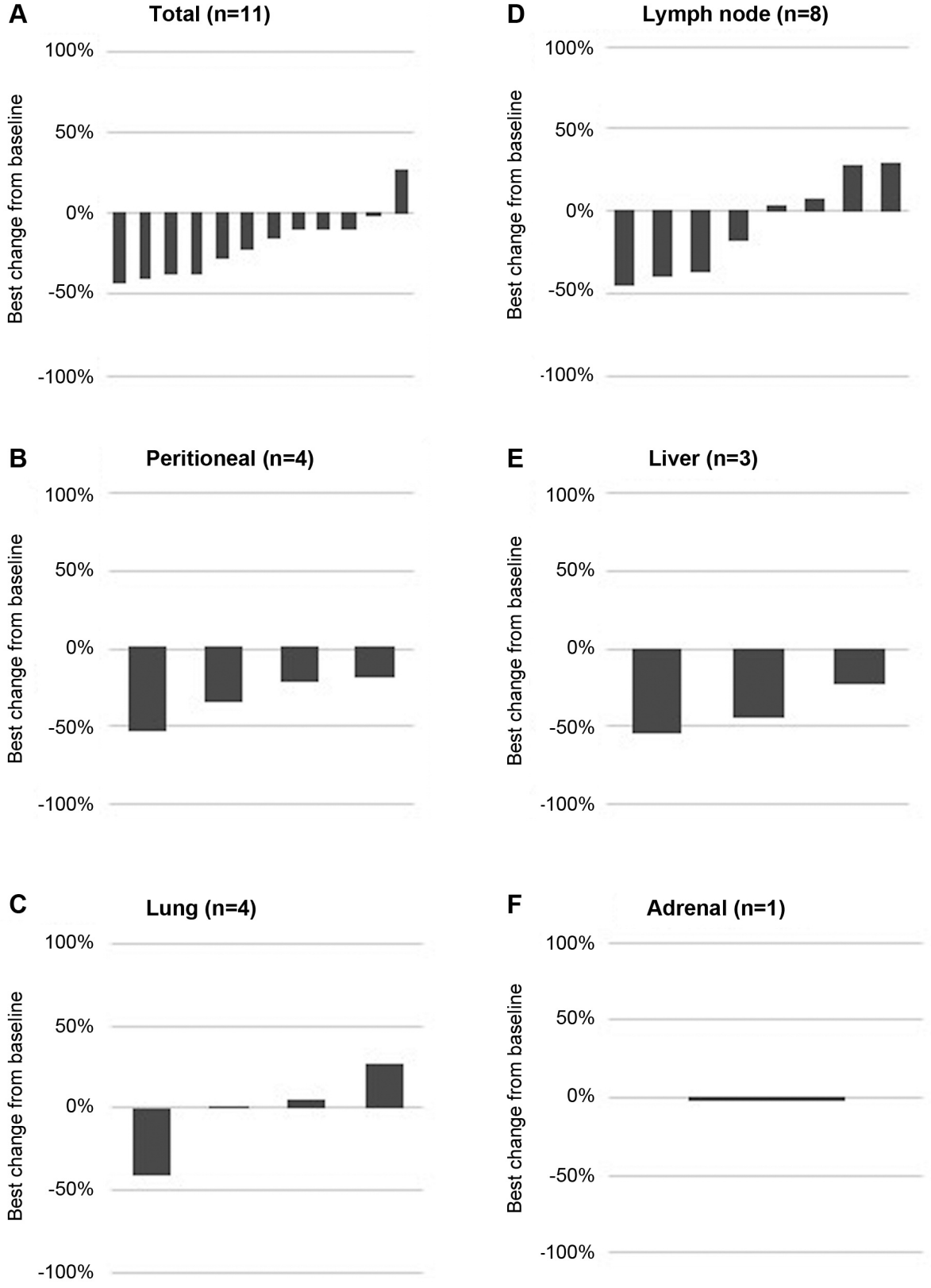

Figure 2. *Best change from baseline in size of metastases*.

Table II. *Relationship between pembrolizumab and platinum-based chemotherapy rechallenge.*

	Response to rechallenge			*p*-Value
Response to pembrolizumab				
PR (n=1)	0	0	1	0.134
SD (n=5)	2	3	0	
PD (n=8)	2	5	1	
Number of pembrolizumab cycles				
0-4 (n=7)	4	2	1	0.070
≥5 (n=7)	0	6	1	
irAEs (all grade)				
Yes (n=6)	1	4	1	0.776
No (n=8)	3	4	1	

irAEs: Immune-related adverse events; PD: progressive disease; PR: partial response; SD: stable disease.

squamous-cell carcinoma following anti-PD-1 and anti-PD-L1 treatment (13). Champiat *et al*. also reported that 2/8 of patients treated with anti-PD-1/anti-PD-L1 showed accelerated tumor growth after treatment relative to that observed during the previous therapy for advanced UC (14). Patients with metastatic UC require additional treatment, and in particular, those with PD and hyper-progression who have received pembrolizumab require a third treatment.

A few studies on salvage chemotherapy for patients with pembrolizumab-refractory UC have been reported (7-9). Therefore, we assessed the efficacy of platinum-based chemotherapy rechallenge. No standard salvage chemotherapy after pembrolizumab has been established. Gravis *et al*. reported unexpected responses to cisplatin rechallenge after ICIs. They evaluated 12 patients with UC who received cisplatin rechallenge after ICIs. The ORR was 66.7%, the disease-control rate was 75%, and median progression-free survival was 7.9 months (8). In Japanese patients, Furubayashi *et al*. assessed TC for patients with pembrolizumab-refractory UC, and the median OS was 10.9 months and ORR was 25.0%. Furthermore, they evaluated the metastatic organ-specific therapeutic effect and found that lymph node, lung, and liver metastases may respond to TC (7). Szabados *et al*. investigated the response of chemotherapy after ICIs for patients with metastatic UC. The post-ICI chemotherapy was GC rechallenge, TC, and docetaxel. The results showed that in patients who received ICIs after first-line chemotherapy, 21% showed a PR, 71% achieved SD, and one patient showed PD (9). The present study evaluated 14 patients with pembrolizumab-refractory UC, and the ORR was 28.6%, but the disease-control rate was 85.7%, and the median OS was 11.2 months. In our study, the responses to platinum-based chemotherapy rechallenge in the patients who showed best response to pembrolizumab but developed PD were 25% with PR, 62.5% with SD, and 12.5% with PD. Platinum-based chemotherapy rechallenge was effective for the patients who showed the best response to pembrolizumab but developed PD. Furthermore, the response to platinum-based chemotherapy rechallenge was not significantly associated with the response to pembrolizumab, number of pembrolizumab cycles, or immune-related AEs. We believe that platinum-based chemotherapy may suppress tumor growth for patients with pembrolizumab-refractory UC.

The biological mechanisms involved in platinum re-sensitization are still controversial. There are arguments in favor of the sequential association of ICIs and chemotherapy. Saleh *et al*. reported response to salvage chemotherapy after ICIs in metastatic squamous-cell carcinoma of the head and neck. They concluded that ICIs induce tumor microenvironment modification, resulting in re-sensitization to chemotherapy (15). The DNA damage induced by platinum-based agents leads to interferon-γ production and results in immune reactivation after ICI cessation, explaining the observed response (16). Future studies should investigate platinum re-sensitization after ICIs.

To our knowledge, this is the first report to describe AEs in patients with pembrolizumab-refractory UC. The present study showed that 13 (92.9%) patients had neutropenia grade 3 or higher, five (35.7%) had anemia grade 3 or higher, and four (28.6%) had thrombocytopenia grade 3 or higher. Neutropenia occurred at a higher rate than those with GC (71.1%) and MVAC (82.3%), and anemia was observed at a higher rate than with GC (27.0%) and MVAC (17.6%). The thrombocytopenia rate was lower than with GC (57.0%) but higher than with MVAC (20.6%) (17). This study also demonstrated that platinum-based chemotherapy rechallenge may be more toxic than first-line chemotherapy. We previously reported that a predictive factor for neutropenia associated with GC was pretherapeutic sarcopenia, and a predictor for anemia and thrombocytopenia was a lower level of serum albumin (18). Chemotherapy is known to cause sarcopenia. Chen *et al*. reported that cisplatin led to loss of myogenesis *in vivo* and *in vitro* (19). The patients in this study sample had received GC, so sarcopenia was worse than before therapy. As a result, hematological side-effects were high in our study. However, febrile neutropenia was observed in only one patient, and there were no deaths. The most appropriate approach to minimizing hematological side-effects is an important consideration.

A clinical trial of a new treatment for patients with pembrolizumab-refractory UC is ongoing. Enfortumab vedotin (EV), an antibody–drug conjugate, targets nectin-4. EV has provided clinical responses in patients with metastatic UC in EV-101, a phase-1 trial (20). EV-201 was a phase-2 trial for patients with UC who received platinum chemotherapy and anti-PD-1/L1 therapy. The results showed that the ORR was

44%, including 12% of patients who showed a CR, and the median duration of response was 7.6 months (21). Recently, the results of a phase-3 trial (EV-301) of EV in previously treated patients with UC were published (22). Overall survival was longer for EV than for chemotherapy (median 12.88 *vs*. 8.97 months, p=0.001), and progression-free survival was also longer with EV than with chemotherapy (median 5.55 *vs*. 3.71 months, p<0.001). Furthermore, AEs were similar between EV and chemotherapy (93.9% *vs*. 91.8%). EV significantly prolonged survival. However, our study demonstrated efficacy of platinum-based chemotherapy in patients with pembrolizumab-refractory UC.

This study had some limitations. This was a retrospective study at a single institution with a small patient sample. However, this study has shown the possibility of platinum-based chemotherapy rechallenge for patients with pembrolizumab-refractory UC.

In conclusion, the activity of platinum-based chemotherapy rechallenge after pembrolizumab was maintained and suppressed tumor progression in some patients. However, neutropenia was observed in most patients. Therefore, neutropenia must be carefully monitored if this chemotherapy is used.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

TY, MH, SM, and AT contributed significantly to the design of this study. TY, MH, RS, ST, NY, BK, HI, SM, and KH acquired the data. TY, MH, MH, and AT analyzed and interpretated the data. TY and MH drafted the article. All Authors read and approved the final article.

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