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Original Article

Re-challenging chemotherapy after pembrolizumab in platinum-refractory urothelial carcinoma

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Objectives

To assess the real-world clinical benefit of re-challenging chemotherapy after pembrolizumab in patients with metastatic urothelial carcinoma (mUC), as there have been several reports suggesting that programmed cell death protein-1/programmed death-ligand 1inhibitors can restore platinum sensitivity.

Patients and Methods

Of 236 patients treated with pembrolizumab, we excluded 45 patients who did not experience progressive disease (PD) for pembrolizumab during the follow-up and 86 patients who discontinued pembrolizumab by the diagnosis of PD followed by the best supportive care. A total of 105 patients were identified for a logistic regression propensity score model to compare the survival outcomes between patients treated with continuing pembrolizumab (80) and re-challenging chemotherapy (25) after the diagnosis of PD for pembrolizumab.

Results

A median overall survival (OS) from PD for pembrolizumab was 11 months in 105 patients. Of 25 patients treated with re-challenging chemotherapy, platinum-including chemotherapy (gemcitabine and cisplatin; gemcitabine/cisplatin/paclitaxel [GCP]; methotrexate and vinblastine and adriamycin and cisplatin; and methotrexate and carboplatin and vinblastine MCAVI) was offered in 20 patients (80%). The objective response rate (ORR) for the first-line chemotherapy in the 105 patients was 30%, with a comparable ORR in 25 patients treated with re-challenging chemotherapy of 28%. GCP as a re-challenging regimen was offered in 12 of 25 (48%) patients. The ORR for the GCP regimen was 50%. Propensity score matching was performed using putative clinical factors, from which 34 patients were identified as pair-matched groups. The OS for patients treated with re-challenging chemotherapy was significantly longer than continuing pembrolizumab (a median of 13.9 and 5.8 months, respectively: $P = 0.048$).

Conclusion

Re-challenging chemotherapy including platinum agents after PD with pembrolizumab offers clinical benefits in patients with mUC.

Keywords

urothelial carcinoma, pembrolizumab, platinum-refractory, re-challenging chemotherapy, overall survival, objective response

Introduction

Platinum-based chemotherapy, such as gemcitabine and cisplatin (GC) regimen, is a mainstay as first-line treatment for patients with metastatic urothelial carcinoma (mUC) [1]. However, the survival benefit has been limited due to the lack of reliable subsequent therapy following disease progression with first-line chemotherapy. In 2017, the results from KEYNOTE-045 (ClinicalTrials.gov: NCT02256436) showed a significant survival benefit of administering pembrolizumab, the programmed cell death protein-1 (PD-1) antibody, compared to second-line chemotherapy in patients with advanced platinum-refractory UC, leading to the approval of the drug by the Food and Drug Administration (FDA) [2]. After >2 years of follow-up, the updated results from the KEYNOTE-045 trial reported that the 1- and 2-year overall survival (OS) rates were significantly higher with pembrolizumab (44% and 27%) than with second-line chemotherapy (30% and 14%), and the objective response rate (ORR) was 21% and 11% in patients treated with pembrolizumab and second-line chemotherapy, respectively [3]. In the trial, 49% of patients were diagnosed with progressive disease (PD) as their best overall response (BOR). Although, most recently, enfortumab vedotin, an antibody–drug conjugate directed against nectin-4, has been approved by FDA in the late clinical setting (post-platinum-based chemotherapy and PD-1/programmed death-ligand 1 [PD-L1] inhibitor) [4], the real-world outcomes from the clinical practice are still unknown. There have been several reports that indicate the unexpected tumour response by re-challenging chemotherapy after pembrolizumab treatment for patients with mUC [5–8]. Although those studies encompassed relatively limited sample sizes, these studies raise the hypothesis that PD-1/PD-L1 inhibitors could re-sensitise platinum sensitivity in platinum-refractory mUC. In the present study, we investigated the clinical benefit of re-challenging chemotherapy in patients with mUC whose disease had progressed with pembrolizumab treatment utilising our multi-institutional cohort dataset.

Patients and Methods

Study Cohort and Ethical Statement

We conducted the present study using a multi-institutional dataset from Osaka Medical and Pharmaceutical University (Osaka, Japan), the Jikei University School of Medicine (Tokyo, Japan), Tokyo Medical University (Tokyo, Japan), and Fujita-Health University School of Medicine (Aichi, Japan) between January 2018 and October 2021. The project was approved by the Institutional Review Board of the principal institution (Osaka Medical and Pharmaceutical University; approval number: RIN–750–2571, date of approval: 24 January 2020) and performed according to the principles of the World Medical Association Declaration of Helsinki [9]. Written informed consent was obtained from the patients at enrolment in the study.

Radiographic Follow-up for the First-Line and Re-Challenging Chemotherapies

A CT scan of the chest, abdomen, and pelvis was scheduled at 6 weeks of pembrolizumab, followed by every 6 weeks during their follow-up. Response to chemotherapy including re-challenging chemotherapy was evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 [10]. MRI, bone scintigraphy, and positron emission tomography/CT were performed when necessary to make a definitive diagnosis.

Pembrolizumab Treatment and Radiographic Follow-Up

Pembrolizumab was administrated either at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks, as previously approved [2,11]. PD for pembrolizumab was identified as immune-confirmed PD (iCPD) using immune RECIST (iRECIST) [12]. In detail, iRECIST defines immuno-unconfirmed PD (iUPD) based on RECIST 1.1 definition. Next, iUPD requires additional confirmation, which is done based on observing either a further increase in the size or number of new lesions (iCPD). When progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of immune complete response (iCR), immune partial response (iPR), or immune stable disease (iSD), then the bar is reset so that iUPD needs to occur again. Discontinuation of pembrolizumab due to disease progression or immune-related adverse events (irAEs) was decided at the physician's discretion and the patient's will.

Inclusion and Exclusion Criteria

Inclusion criteria were patients who had been treated with platinum-including chemotherapy as the first-line treatment, followed by second-line pembrolizumab (236 patients). The following patients were excluded from the study: 45 patients who did not experience iCPD with pembrolizumab treatment during the follow-up and 86 patients who discontinued pembrolizumab after the diagnosis of iCPD, followed by the best supportive care (BSC). Consequently, 105 patients treated with either continuing pembrolizumab (80 patients) or re-challenging chemotherapy (25 patients) after the diagnosis of iCPD were found to be eligible for the present study.

Endpoints and Clinical Variables

In the present study, we set the primary endpoint as OS from PD with pembrolizumab to the last follow-up or death of all

causes. The secondary endpoint was ORR for the re-challenging chemotherapy evaluated by RECIST, version 1.1 [10]. During their follow-up, irAEs were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Clinical characteristics were queried at the diagnosis of PD for pembrolizumab including age (<70/≥70 years), sex (male/female), smoking status (not current/current), the primary site of the tumour (bladder/upper tract), objective response for the prior chemotherapy (no/yes), visceral metastasis (no/yes), lymph node metastasis (no/yes), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0/≥1), and progression-free survival (PFS) from the initiation of pembrolizumab (<3/≥3 months).

Propensity Score Matching and Statistical Analysis

To reduce bias by potential confounding factors that affect the treatment outcomes for the re-challenging chemotherapy, propensity score matching was utilised. The following variables that could impact the outcomes were involved in the regression model: age (<70/≥70 years), sex (male/female), smoking status (current/not current), the primary site of the tumour (bladder/upper tract), BOR of the prior (first-line platinum including) chemotherapy (no/yes), visceral metastasis at iCPD (no/yes), lymph node metastasis at iCPD (no/yes), ECOG-PS at iCPD (0/≥1), haemoglobin level at iCPD (<100/≥100 g/L), and PFS from the initiation of pembrolizumab (<3/≥3 months). A 1:1 matching without replacement between the two groups was conducted by the nearest neighbour method with a 0.5-width calliper of the SD for the logit of the propensity scores.

The distribution of categorical variables between two treatment groups was evaluated by Fisher's exact test (two categorical variables) and chi-square test (more than two categorical variables). To compare variables with normal distribution, a Student's *t*-test or one-way ANOVA was adopted to assess the difference between the variables. For variables with non-normal distribution, the Mann–Whitney *U*-test was performed to assess the difference. Kaplan–Meier curves were generated to estimate the survival function, and the log-rank test was used to test the null hypothesis that the survival curves were the same. The statistical tests were two-sided, with $P < 0.05$ considered to delineate statistical significance. All the analyses were carried out using JMP® 15 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

Results

Of the 236 patients treated with pembrolizumab, we excluded 45 patients who did not experience iCPD for pembrolizumab treatment during the follow-up and 86 patients who discontinued pembrolizumab due to a diagnosis of iCPD with pembrolizumab followed by BSC. A total of 105 patients were treated with either continuing pembrolizumab (80 patients) or re-challenging chemotherapy (25) after the diagnosis of iCPD. Patient characteristics at the diagnosis of iCPD with pembrolizumab (105 patients) are summarised in Table 1. For the 105 patients, the median age was 71 years and the median follow-up was 9 months. In all, 99 patients (94%) were pathologically diagnosed with pure UC. The number of cycles for the first-line (platinum-including) chemotherapy administered was one in 22 patients (21%), two in 49 (47%), and three or more in 34 (32%), with a median of two cycles. Objective responses to first-line chemotherapy were as follows: three (3%) patients with CR, 29 (28%) with PR, 34 (32%) with SD, and 39 (37%) with PD. The metastatic sites at the diagnosis of iCPD for pembrolizumab were as follows: 42 (40%) patients in the lung, 27 (26%) in the liver, and 70 (67%) in the lymph nodes. The ECOG-PS was 0 and ≥1 for 46 (44%) and 59 (56%) patients, respectively. In all, 37 (35%) patients experienced irAEs, of which 12 (11%) were reported as CTCAE Grade ≥3. The median PFS from the initiation of pembrolizumab was 2.5 months. The median OS from iCPD for pembrolizumab was 11 months (6-, 12- and 18-month OS rates were 65%, 46%, and 28%, respectively), with a median follow-up of 6 months for patients who were alive. A total of 57 patients died during their follow-up: 45 in the continuing pembrolizumab group and 12 in the re-challenging chemotherapy group. Regimen of the first-line chemotherapy, number of cycles of first-line chemotherapy, PFS for first-line chemotherapy, and BOR for first-line chemotherapy, were comparable between continuing pembrolizumab (80 patients) and re-challenging chemotherapy (25) groups.

Table 2 summarises the re-challenging chemotherapy in 25 patients with mUC. The regimens of re-challenging chemotherapy in the 25 patients were as follows: five (20%) patients had GC, 12 (48%) had gemcitabine and cisplatin and paclitaxel (GCP), two (8%) had methotrexate and vinblastine and adriamycin and cisplatin (MVAC), one (4%) had methotrexate and carboplatin and vinblastine (MCAVI), three (12%) had gemcitabine and paclitaxel (GemP), one (4%) had paclitaxel (PTX), and one (4%) had docetaxel (DOC). Platinum-including chemotherapy (GC, GCP, MVAC, and MCAVI) was offered in 20 patients (80%). There were 12 (48%), four (16%), and nine (36%) patients treated with one, two, and three or more cycles of re-challenging chemotherapy, respectively. The median PFS from the initiation of re-challenging chemotherapy was 5 months (3- and 6-month PFS rate: 73% and 27%, respectively), with the median follow-up of 8 months for patients without disease progression. Table 3 shows the BOR at first-line and re-challenging chemotherapy in the 25 patients with mUC. The ORR and disease control rate (DCR) for first-line chemotherapy (GC: 23 patients, gemcitabine/carboplatin

Table 1 Patient characteristics in the 105 patients with mUC at the diagnosis of iCPD with pembrolizumab treatment.

Clinical variable	Total cohort (*n* = 105)	Continuing pembrolizumab (*n* = 80)	Re-challenging chemotherapy (*n* = 25)	*P*
Age, years				
Median (IQR)	71 (65–77)	72 (67–77)	69 (61–75)	0.135
<70, *n* (%)	50 (48)	35 (44)	15 (60)	0.175
≥70, *n* (%)	55 (52)	45 (56)	10 (40)	
Sex, *n* (%)				
Male	80 (76)	56 (70)	24 (96)	0.001*
Female	25 (24)	24 (30)	1 (4)	
Smoking status, *n* (%)				
Not current	96 (91)	74 (93)	22 (88)	0.441
Current	9 (9)	6 (8)	3 (12)	
Primary site of tumour, *n* (%)				
Bladder	65 (62)	48 (60)	17 (68)	0.488
Upper tract	40 (38)	32 (40)	8 (32)	
Visceral metastasis at iCPD with pembrolizumab, *n* (%)				
No	49 (47)	38 (48)	11 (44)	0.821
Yes	56 (53)	42 (53)	14 (56)	
Location of visceral metastasis, *n* (%)				
Lung	42 (40)	31 (39)	11 (44)	0.647
Liver	27 (26)	20 (25)	7 (28)	0.796
Lymph node metastasis at iCPD with pembrolizumab, *n* (%)				
No	35 (33)	29 (36)	6 (24)	0.333
Yes	70 (67)	51 (64)	19 (76)	
ECOG-PS at iCPD with pembrolizumab, *n* (%)				
0	46 (44)	31 (39)	15 (60)	0.069
≥1	59 (56)	49 (61)	10 (40)	
Hb at iCPD with pembrolizumab (g/L), *n* (%)				
<100	31 (30)	30 (38)	1 (4)	<0.001*
≥100	74 (70)	50 (63)	24 (96)	
PFS from the initiation of pembrolizumab, months				
Median (IQR)	2.5 (1.9–2.8)	2.2 (1.6–2.6)	2.8 (1.9–2.8)	0.284
<3, *n* (%)	73 (70)	58 (73)	15 (60)	0.325
≥3, *n* (%)	32 (30)	22 (28)	10 (40)	
Regimen of the first-line chemotherapy, *n* (%)				
GC	94 (90)	71 (89)	23 (92)	1.000
GCarbo	11 (10)	9 (11)	2 (8)	
Number of cycles in the first-line chemotherapy				
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.955
1, *n* (%)	22 (21)	17 (21)	5 (20)	0.227
2, *n* (%)	49 (47)	35 (44)	14 (56)	
≥3, *n* (%)	34 (32)	28 (35)	6 (24)	
PFS for the first-line chemotherapy, months				
Median (IQR)	6 (4.5–9)	6 (4.5–9)	6 (3–9)	0.281
BOR at the first-line chemotherapy, *n* (%)				
CR	3 (3)	3 (4)	0 (0)	0.623
PR	29 (28)	22 (27)	7 (28)	
SD	34 (32)	24 (30)	9 (36)	
PD	39 (37)	31 (39)	9 (36)	
ORR (CR or PR)	32 (30)	25 (31)	7 (28)	0.809
DCR (CR or PR or SD)	66 (63)	49 (61)	16 (64)	0.633

*Hb, haemoglobin; IQR, interquartile range. *p < 0.05.*

[GCarbo]: two patients) were 28% and 64%, respectively. The ORR and DCR for re-challenging chemotherapy was 28% and 48%, respectively. The regimen most frequently administrated for re-challenging chemotherapy was GCP in 12/25 (48%) patients, with an ORR and DCR of 50% and 75%, respectively.

As shown in Fig. 1a, OS in patients with re-challenging chemotherapy (25 patients) appeared to be longer than patients treated with continuing pembrolizumab (80) after the diagnosis of iCPD (a median OS of 13.9 and 7.1 months, respectively; $P = 0.004$). The median follow-up for patients alive was 12 and 5 months in the re-challenging chemotherapy and continuing pembrolizumab groups. Given the immortal time bias in the re-challenging chemotherapy group that at least requires completion of the first cycle of the re-challenging chemotherapy, we adopted the landmark analysis. We assessed OS from the time point of 3 months after the diagnosis of iCPD with pembrolizumab (Fig. 1b).

Table 2 Regimens of re-challenging chemotherapy in the present study (n = 25).

Variable	Value
Type of the re-challenging chemotherapy (n = 25)	
Platinum-based chemotherapy (n = 20), n (%)	
GC	5 (20)
GCP	12 (48)
MVAC	2 (8)
MCAVI	1 (4)
Non-platinum-based chemotherapy (n = 5), n (%)	
GemP	3 (12)
PTX	1 (4)
DOC	1 (4)
Number of cycles of the re-challenging chemotherapy	
Median (range)	2 (1–5)
1, n (%)	12 (48)
2, n (%)	4 (16)
≥3, n (%)	9 (36)
PFS in the re-challenging chemotherapy, months	
Median (range)	5 (2–NR)
3-month PFS rate, %	73
6-month PFS rate, %	27

NR, not reached.

There were 11 and no patients who died during the 3 months in the continuing pembrolizumab and re-challenging chemotherapy groups, respectively. OS in the re-challenging chemotherapy group (56 patients) was still significantly longer than continuing pembrolizumab group (25) (P = 0.043). To reduce biases due to potential confounders that could affect treatment outcomes between the continuing pembrolizumab and re-challenging chemotherapy groups, propensity score matching was adopted with putative factors as shown in Fig. 2, by which 17 patients in each group were extracted as pair-matched groups. In the pair-matched cohort (34 patients), all the clinical variables at the diagnosis of iCPD for pembrolizumab were comparable between the two treatment groups (Table 4). The types of re-challenging chemotherapy in the pair-matched cohort (n = 17) were GC in one (6%) patient, GCP in nine (52%), GemP in two (12%), MVAC in two (12%), MCAVI in one (6%), PTX in one (6%), and DOC in one (6%). Platinum-based chemotherapy (GC, GCP, MVAC, and MCAVI) was administrated in 13/17 (76%) patients. Kaplan–Meier curves revealed significantly favourable OS from iCPD for patients treated with re-challenging chemotherapy compared to patients treated with continuing pembrolizumab (a median of 13.9 and 5.8 months in the re-challenging chemotherapy and continuing pembrolizumab groups, respectively; P = 0.048) (Fig. 3a). In the landmark analysis from the time point of 3 months after the diagnosis of iCPD with pembrolizumab (one and no patients died during the 3 months in the continuing pembrolizumab and re-challenging chemotherapy groups, respectively), a median OS in the landmark analysis was 5.8 and 13.9 months in the continuing pembrolizumab (14 patients) and the re-challenging chemotherapy group (17), respectively (P = 0.104, Fig. 3b).

Discussion

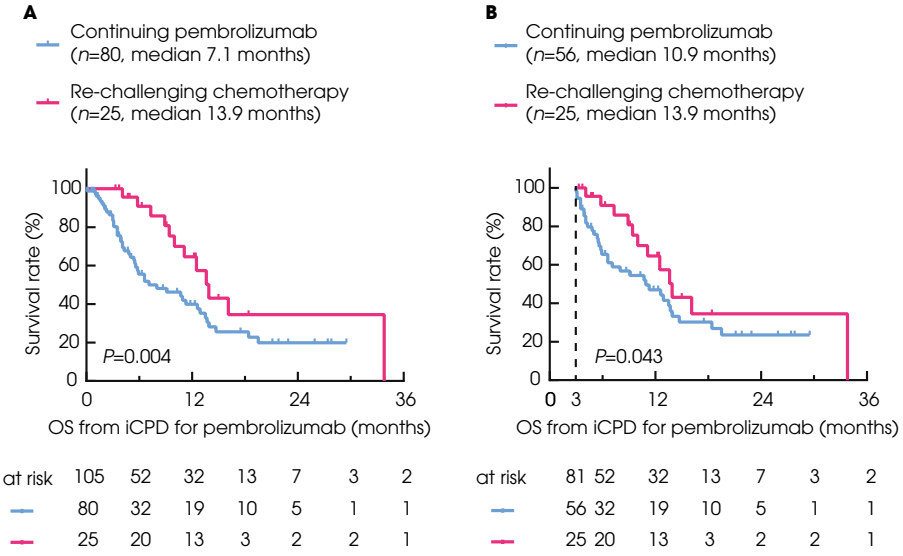
For patients with mUC, pembrolizumab has now become a standard of care, although the treatment effect of the drug substantially differs among individuals. The results from the KEYNOTE-045 trial after >2 years of follow-up exhibited a modest PFS rate (2.1 months, 95% CI 2.0–2.2 months), ORR (21%, 95% CI 16%–27%), and DCR (39%, 95% CI 33%–45%) [3]. Patients who achieved an objective response had a durable response (>24 months of the median response duration), consequently resulting in a longer median OS (10.1 months, 95% CI 8.0–12.3 months) than second-line chemotherapy (median OS of 7.3 months). Of note, the 2-year OS rates in their final analysis were 79%, 23%, and 10% with the best response for 'CR or PR,' 'SD,' and 'PD,'

Table 3 Summary of the BOR at first-line and re-challenging chemotherapy in the 25 patients with mUC.

Clinical variable	*N*	BOR at the first-line chemotherapy (GC: 23, GCarbo: 2*)					BOR at the re-challenging chemotherapy				
		CR + PR, *n*	SD, *n*	PD, *n*	ORR, %	DCR, %	CR + PR, *n*	SD, *n*	PD + unknown, *n*	ORR, %	DCR, %
Total number	25	7	9	9	28	64	7	5	13	28	48
Platinum-including chemotherapy (n = 20)	20						6	4	10	30	50
GC	5						0	1	4	0	20
GCP	12						6	3	3	50	75
MVAC	2						0	0	2	0	0
MCAVI	1						0	0	1	0	0
Non-platinum-including chemotherapy (n = 5)	5						1	1	3	20	40
GemP	3						0	0	3	0	0
PTX	1						0	1	0	0	100
DOC	1						1	0	0	100	100

**Two patients treated with GCarbo in the first-line chemotherapy underwent MCAVI and GemP as the re-challenging chemotherapy.*

Fig. 1 (**a**) Kaplan–Meier curves for OS from the diagnosis of iCPD with pembrolizumab to the last follow-up in 105 patients with mUC. (**b**) Kaplan–Meier curves for OS from the time point of 3 months after the diagnosis of iCPD with pembrolizumab in 105 patients with mUC.

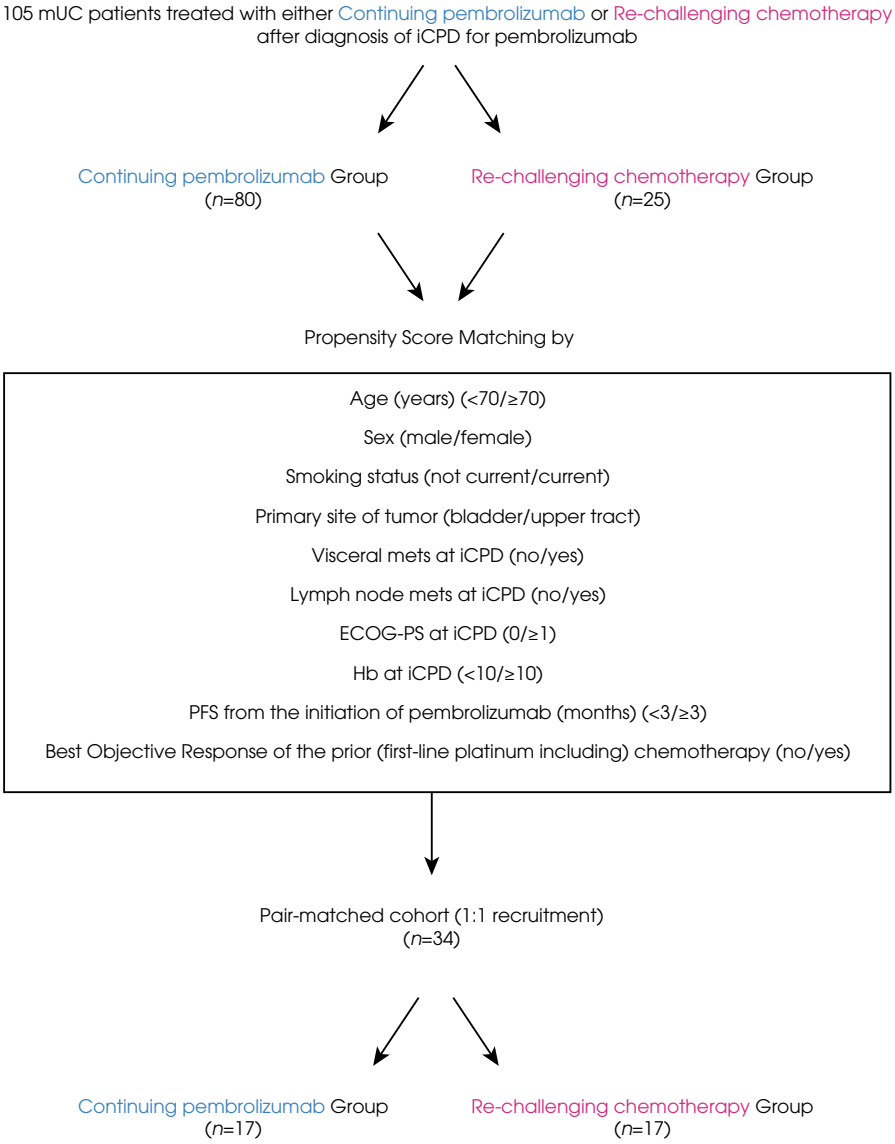


respectively. Patients with PD at their BOR accounted for 49% with no survival benefit compared to the second-line chemotherapy. Thus, to assess the subsequent treatment options for patients with mUC whose tumour progressed after pembrolizumab treatment, we queried our multi-institutional dataset. Adjusting the effect of confounding factors among the treatment options including continuing pembrolizumab and re-challenging chemotherapy by propensity score matching offered the pair-matched cohort of 34 patients, with no significant differences among all clinical characteristics between the two treatment options. This allowed us to assess the survival outcomes from the diagnosis of iCPD of pembrolizumab. Our results demonstrated significantly longer OS from the diagnosis of iCPD in patients treated with re-challenging chemotherapy than patients treated with pembrolizumab beyond iCPD.

Recently, enfortumab vedotin, an antibody–drug conjugate directed against nectin-4, has been approved by FDA in the late clinical setting [4]. In their trial, patients with locally advanced or mUC whose tumour had progressed with platinum-containing chemotherapy and PD-1/PD-L1 inhibitors were enrolled in a 1:1 ratio to receive enfortumab vedotin or investigator-chosen chemotherapy. At their interim analysis, OS was significantly longer in the enfortumab vedotin group (12.9 months) than in the chemotherapy group (9.0 months). The ORR was 41% in the enfortumab vedotin group and 18% in the chemotherapy group. The DCR in the chemotherapy group was 53%. Strikingly, investigator-chosen chemotherapy was designated in single-agent regimens: DOC at a dose of 75 mg/m^2 of the body surface area; PTX at 175 mg/m^2; or vinflunine at a dose of 320 mg/m^2. Those chemotherapy treatments were administered on day 1 of a 21-day cycle. In the present study, we presented the real-world outcomes of re-challenging chemotherapy after disease progression of pembrolizumab. Platinum-containing regimens were administrated in 20 of 25 (80%) patients in our dataset. OS from the diagnosis of iCPD with pembrolizumab in 25 patients treated with re-challenging chemotherapy was 13.9 months. Interestingly, GCP treatments were administrated in 12 of 25 (48%) patients, and the ORR for the GCP regimen was 50% (six of 12). This is in line with the data from Gravis et al. [6]. Despite the limited sample size (12 patients), they reported that re-challenging chemotherapy with platinum-based chemotherapy unexpectedly exerted 67% of ORR [6]. Yumioka et al. [13] reported the treatment outcomes of re-challenging chemotherapy after pembrolizumab in platinum-refractory UC. In their report, 14 cases were offered re-challenging chemotherapy that they had not previously received (PTX plus carboplatin in 10, gemcitabine plus DOC and carboplatin in four cases). They concluded that the median OS of 11.2 months and the DCR of 86% in 14 cases seem to encourage considering re-challenging chemotherapy after pembrolizumab. Szabados et al. [7] investigated the activity of chemotherapy after progression on immune-checkpoint inhibitors (ICIs). They showed the response rate of chemotherapy in two cohorts: 64% in Cohort A (receiving first-line ICIs followed by chemotherapy after progression) and 21% in Cohort B (receiving chemotherapy after failure of first-line platinum-based chemotherapy followed by ICIs). They concluded that sequencing chemotherapy after ICIs is likely important in maximising outcomes in patients with mUC.

Similar findings that re-challenging chemotherapy after progression with PD-1/PD-L1 inhibitors may improve

Fig. 2 Schematic of the propensity score matching analysis to reduce bias between continuing pembrolizumab (80 patients) and re-challenging chemotherapy group (25). A 1:1 matching across the two treatment arms was conducted using the nearest neighbour method with a 0.5-width calliper of the standard deviation of the logit of the propensity scores.



survival outcomes have been reported in other tumours including non-small cell lung cancer (NSCLC) [14], squamous cell carcinoma of head and neck [15,16,17], and Hodgkin lymphoma [18,19]. In Particular, Park et al. [14] reported comparing treatment response between salvage chemotherapy administered after immunotherapy (73 patients) and the last chemotherapy administered before immunotherapy (63) in NSCLC. In their study, of the 73 patients treated with salvage chemotherapy administered after immunotherapy, 53% of patients achieved the ORR, whereas the ORR of the last chemotherapy administered before immunotherapy was 35%. Notably, the ORRs for platinum-doublet regimens were 67% for salvage chemotherapy administered after immunotherapy and 40% for the last chemotherapy administered before immunotherapy, being in line with the results of the present study, showing the benefit of re-challenging chemotherapy of platinum-containing regimens after pembrolizumab in patients with mUC. Based on these findings, it seems that PD-1/PD-L1 inhibitors may restore platinum sensitivity in mUC being refractory to platinum-based chemotherapy at their first line. A number of studies have addressed the cross-talk between DNA damage agents and the immune modulation [20,21,22,23]. Mortara et al. [23] proposed the reciprocal regulation between immunity and angiogenesis. In short, $CD4^+$ T-cell activation induced by PD-1/PD-L1 inhibitors increases vessel

Table 4 Clinical variables at the diagnosis of iCPD with pembrolizumab in the pair-matched cohort (n = 34).

Clinical variable	Continuing pembrolizumab (n = 17), n (%)	Re-challenging chemotherapy (n = 17), n (%)	P
Age, years			
<70	10 (59)	11 (65)	1.000
≥70	7 (41)	6 (35)	
Sex			
Male	17 (100)	17 (100)	1.000
Female	0 (0)	0 (0)	
Smoking status			
Not current	15 (88)	14 (82)	1.000
Current	2 (12)	3 (18)	
Primary site of tumour			
Bladder	10 (59)	12 (71)	0.720
Upper tract	7 (41)	5 (29)	
Visceral metastasis at iCPD with pembrolizumab			
No	7 (41)	7 (41)	1.000
Yes	10 (59)	10 (59)	
Lymph node metastasis at iCPD with pembrolizumab			
No	5 (29)	4 (24)	1.000
Yes	12 (71)	13 (76)	
ECOG-PS at iCPD with pembrolizumab			
0	6 (35)	7 (41)	1.000
≥1	11 (65)	10 (59)	
Hb at iCPD with pembrolizumab, g/L			
<100	1 (6)	1 (6)	1.000
≥100	16 (94)	16 (94)	
PFS from the initiation of pembrolizumab, months			
<3	11 (65)	9 (53)	0.728
≥3	6 (35)	8 (47)	
Objective response at the first-line chemotherapy			
No	5 (29)	5 (29)	1.000
Yes	12 (71)	12 (71)	

Hb, haemoglobin.

normalisation with a positive feedback loop between Type 1 T-helper cells augmentation and vessel normalisation, which results in enhancing platinum diffusion in the tumour, increasing the intra-tumoral platinum concentration.

The present study has several limitations. The study was conducted retrospectively, and the sample size was too small to derive firm conclusions. In addition, our findings are still subject to selection bias (such as nutrition/general status and treatment discretion by physicians), although a propensity score-matched model was utilised for approximate random assignment. We could not assess the survival outcomes of the re-challenging chemotherapy in each primary tumour site (bladder: 65 patients or upper tract: 40 patients) due to the limited sample size. Although there was no significant difference, more patients in continuing pembrolizumab group were classified as poor ECOG-PS in pair-matched cohorts. Given the retrospective nature of the present study, the date of progression was influenced to some degree by the follow-up schedule of individual patients and institutes. Thus, we chose the integer number for dichotomisation of PFS months. Lastly, discontinuation of pembrolizumab treatment was not standardised among the institutes. Further studies are warranted to substantiate the results of the present study.

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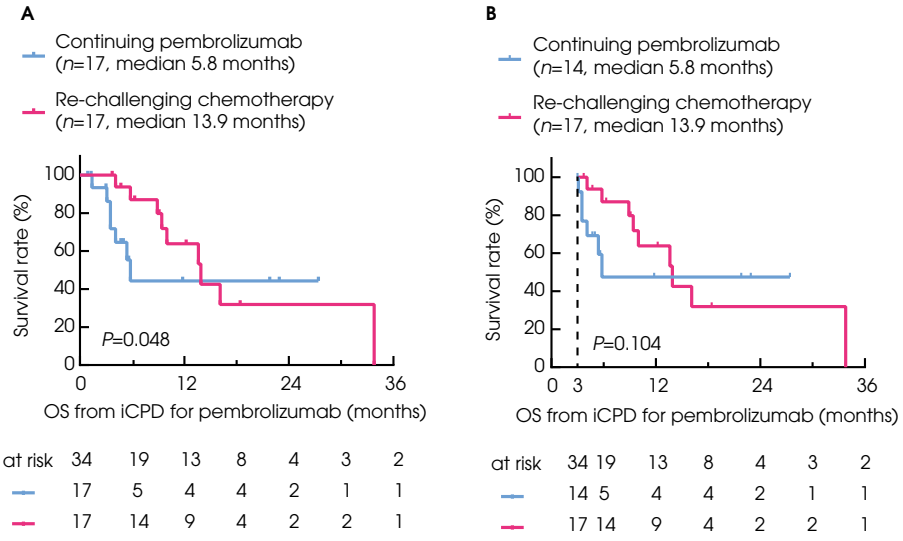
Fig. 3 (**a**) Kaplan–Meier curves for OS from the diagnosis of iCPD with pembrolizumab to the last follow-up in the pair-matched cohort (n = 34). (**b**) Kaplan–Meier curves for OS from the time point of 3 months after the diagnosis of iCPD with pembrolizumab in pair-matched cohort.



Disclosure of Interests

None declared.

References

1 **von der Maase H**, **Hansen SW**, **Roberts JT** et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; 18: 3068–77

2 **Bellmunt J**, **de Wit R**, **Vaughn DJ** et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017; 376: 1015–26

3 **Fradet Y**, **Bellmunt J**, **Vaughn DJ** et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. *Ann Oncol* 2019; 30: 970–6

4 **Powles T**, **Rosenberg JE**, **Sonpavde GP** et al. Enfortumab Vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021; 384: 1125–35

5 **Furubayashi N**, **Hori Y**, **Morokuma F** et al. Paclitaxel and carboplatin chemotherapy after platinum-based chemotherapy and pembrolizumab for metastatic urothelial carcinoma. *Mol Clin Oncol* 2021; 14: 91

6 **Gravis G**, **Billon E**, **Baldini C** et al. Unexpected response to cisplatin rechallenge after immune checkpoint inhibitors in patients with metastatic urothelial carcinoma refractory to platinum regimen. *Eur J Cancer* 2018; 104: 236–8

7 **Szabados B**, **van Dijk N**, **Tang YZ** et al. Response rate to chemotherapy after immune checkpoint inhibition in metastatic urothelial cancer. *Eur Urol* 2018; 73: 149–52

8 **Bersanelli M**, **Buti S**, **Cortellini A** et al. Clinical outcomes of patients with metastatic urothelial carcinoma after progression to immune checkpoint inhibitors: a retrospective analysis by the meet-URO group (meet-URO 1 study). *Clin Med Insights Oncol* 2021; 15: 11795549211021667

9 **Gandevia B**, **Tovell A**. Declaration of Helsinki. *Med J Aust* 1964; 2: 320–1

10 **Eisenhauer EA**, **Therasse P**, **Bogaerts J** et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–47

11 **Lala M**, **Li TR**, **de Alwis DP** et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. *Eur J Cancer* 2020; 131: 68–75

12 **Seymour L**, **Bogaerts J**, **Perrone A** et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017; 18: e143–e52

13 **Yumioka T**, **Honda M**, **Shimizu R** et al. Response to platinum-based chemotherapy Rechallenge for patients with pembrolizumab-refractory urothelial carcinoma. *Anticancer Res* 2021; 41: 5767–73

14 **Park SE**, **Lee SH**, **Ahn JS**, **Ahn MJ**, **Park K**, **Sun JM**. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol* 2018; 13: 106–11

15 **Koyama T**, **Nomura M**, **Keitaro D**, **Tateya I**, **Muto M**. Re-introducing the same chemotherapy after exposure to anti-PD-1 therapy. *Int Cancer Conf J* 2019; 8: 86–8

16 **Daste A**, **de Mones E**, **Digue L** et al. Immunotherapy in head and neck cancer: need for a new strategy? Rapid progression with nivolumab then unexpected response with next treatment. *Oral Oncol* 2017; 64: e1–3

17 **Saleh K**, **Daste A**, **Martin N** et al. Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Eur J Cancer* 2019; 121: 123–9

18 **Carreau NA**, **Pail O**, **Armand P** et al. Checkpoint blockade treatment may sensitize Hodgkin lymphoma to subsequent therapy. *Oncologist* 2020; 25: 878–85

19 **Rossi C**, **Gilhodes J**, **Maerevoet M** et al. Efficacy of chemotherapy or chemo-anti-PD-1 combination after failed anti-PD-1 therapy for relapsed and refractory Hodgkin lymphoma: a series from Lysa centers. *Am J Hematol* 2018; 93: 1042–9

20 **Nishimura K**, **Nishio K**, **Hirosuna K** et al. Efficacy of pembrolizumab and comprehensive CD274/PD-L1 profiles in patients previously treated with chemoradiation therapy as radical treatment in bladder cancer. *J Immunother Cancer* 2022; 10: e003868

21 **Komura K**, **Inamoto T**, **Tsujino T** et al. Increased BUB1B/BUBR1 expression contributes to aberrant DNA repair activity leading to resistance to DNA-damaging agents. *Oncogene* 2021; 40: 6210–22

22 **Tsujino T**, **Sugito N**, **Taniguchi K** et al. MicroRNA-143/Musashi-2/KRAS cascade contributes positively to carcinogenesis in human bladder cancer. *Cancer Sci* 2019; 110: 2189–99

23 **Mortara L**, **Benest AV**, **Bates DO**, **Noonan DM**. Can the co-dependence of the immune system and angiogenesis facilitate pharmacological targeting of tumours? *Curr Opin Pharmacol* 2017; 35: 66–74

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Abbreviations: (i)CR, (immune) complete response; (i)PR, (immune) partial response; (i)RECIST, (immune) Response Evaluation Criteria In Solid Tumors; (i)SD, (immune) stable disease; (m)UC, (metastatic) urothelial carcinoma; BOR, best overall response; BSC, best supportive care; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOC, docetaxel; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; GC, gemcitabine/cisplatin; GCarbo, gemcitabine/carboplatin; GCP, gemcitabine/cisplatin/paclitaxel; GemP, gemcitabine/paclitaxel; ICI, immune-checkpoint inhibitor; iCPD, immune-confirmed progressive disease; irAE, immune-related adverse event; iUPD, immuno-unconfirmed progressive disease; MCAVI, methotrexate/carboplatin/vinblastine; MVAC, methotrexate/vinblastine/adriamycin/cisplatin; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PTX, paclitaxel.