Favorable Response of Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma with Only Small Lesions to not be Considered Measurable by RECIST

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Purpose: Pembrolizumab is currently considered the standard second-line treatment for advanced urothelial carcinoma (UC). This study aimed to investigate the efficacy and safety of pembrolizumab in patients with advanced UC in real-world data, which is not well-reported.

Materials and Methods: The study included 97 patients with advanced UC whose lesions were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST). The median age was 73 years. Nineteen patients (20%) with performance status (PS) 2–4 were included. The percentages of liver, lung, bone, and lymph node metastasis were 18%, 27%, 19%, and 76%, respectively. The efficacy, safety, and risk factors for prognosis were evaluated for patients with and without measurable lesions.

Results: The best response was complete response in nine patients (9%) and partial response in 16 patients (17%). The median progression-free survival and overall survival were 3.7 months (95% confidence interval [CI]: 2.8–4.7) and 11.8 months (95% CI: 6.7–17.0), respectively. Twenty-one (22%) patients had no measurable lesions per RECIST. In univariate and multivariate analysis, PS 2–4 and lesions by RECIST were identified as factors associated with short overall survival (OS). The median OS of 18.3 months in patients without lesions by RECIST was significantly longer than the median OS of 6.7 months in patients with lesions by RECIST (p = .012).

Conclusion: We demonstrated that good PS 0–1 and no measurable lesions, especially small lesions, by RECIST were favorable prognostic factors in patients with advanced UC treated by pembrolizumab.

Keywords: urothelial carcinoma; pembrolizumab; performance status; small lesions; RECIST

INTRODUCTION

Methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy,[1] and gemcitabine and cisplatin chemotherapy for advanced urothelial carcinoma (UC) are established treatments.[2] Platinum-based chemotherapies as first-line treatment for advanced UC are effective, but few cases have achieved complete remission. Historically, there has been no effective second-line treatment after failure of first-line chemotherapy for advanced UC. In a randomized, phase 3 study (KEYNOTE-045) for patients with advanced UC after failure of platinum-based chemotherapy, treatment with pembrolizumab, a highly selective, humanoid monoclonal antibody against programmed death 1 (PD-1), resulted in longer overall survival (OS) than existing second-line chemotherapy (10.3 months vs 7.4 months) and achieved a 27% reduction in death risk.[3] In addition, the incidence of treatment-related adverse events (AEs) was lower with pembrolizumab, including fewer high-grade (grade 3–5) AEs that resulted in treatment discontinuation.[3] However, in the cited clinical trial, the inclusion of participants was limited by cancer and patient status, such as measurable lesions evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) and the Eastern Cooperative Oncology Group performance status (ECOG-PS).[3] Therefore, real-world clinical practice data on pembrolizumab for advanced UC is needed. In this study, we retrospectively investigated the efficacy and safety of pembrolizumab in patients with advanced UC in real-world data from Kanazawa University and related hospitals.

PATIENTS AND METHODS

This study was approved by the ethics review board of our institution and related hospitals (No. 2018-082, 2847), and we informed all patients that they could opt out at any time. We retrospectively evaluated advanced

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Received January 2021 & Accepted August 2021

Table 1. Demographics of the study population

Variable	Median (range) or n (%)
Total number of patients	97
Age, years	73 (48 to 85)
Male/Female	69 (71) / 28 (29)
Current or former smoker/non-smoker	60 (62) / 37 (38)
Primary tumor site, upper urinary tract	42 (43) / 55 (57)
Pure UC in histologic testing	86 (89) / 11 (11)
Radical surgery of the primary lesion	48 (50) / 49 (50)
ECOG PS, 0-1/2-4	78 (80) / 19 (20)
Number of prior regimens, 1/2/3	67 (69) / 27 (28) /3 (3)
Number of prier platinum agent courses	4 (1 to 30)
Metastatic sites, liver/lung/bone/lymph node*	17(18) / 26(27) / 18(19) / 74(76)
Lesions by RECIST evaluation, Yes/No	76 (78) / 21(22)
Number of metastatic organs, 1/2/3/4/5*	22(23) / 43(44) / 21(22) / 7(7) / 4(4)
Time from previous chemotherapy, <3 / >3 months	78 (80) / 19 (20)

UC, Urinary carcinoma; ECOG PS, Eastern Cooperative Oncology Group Perfromance status; RECIST, Response Evaluation Criteria in Solid Tumor.
* The lesions were evluated and reported by doctors in charge.

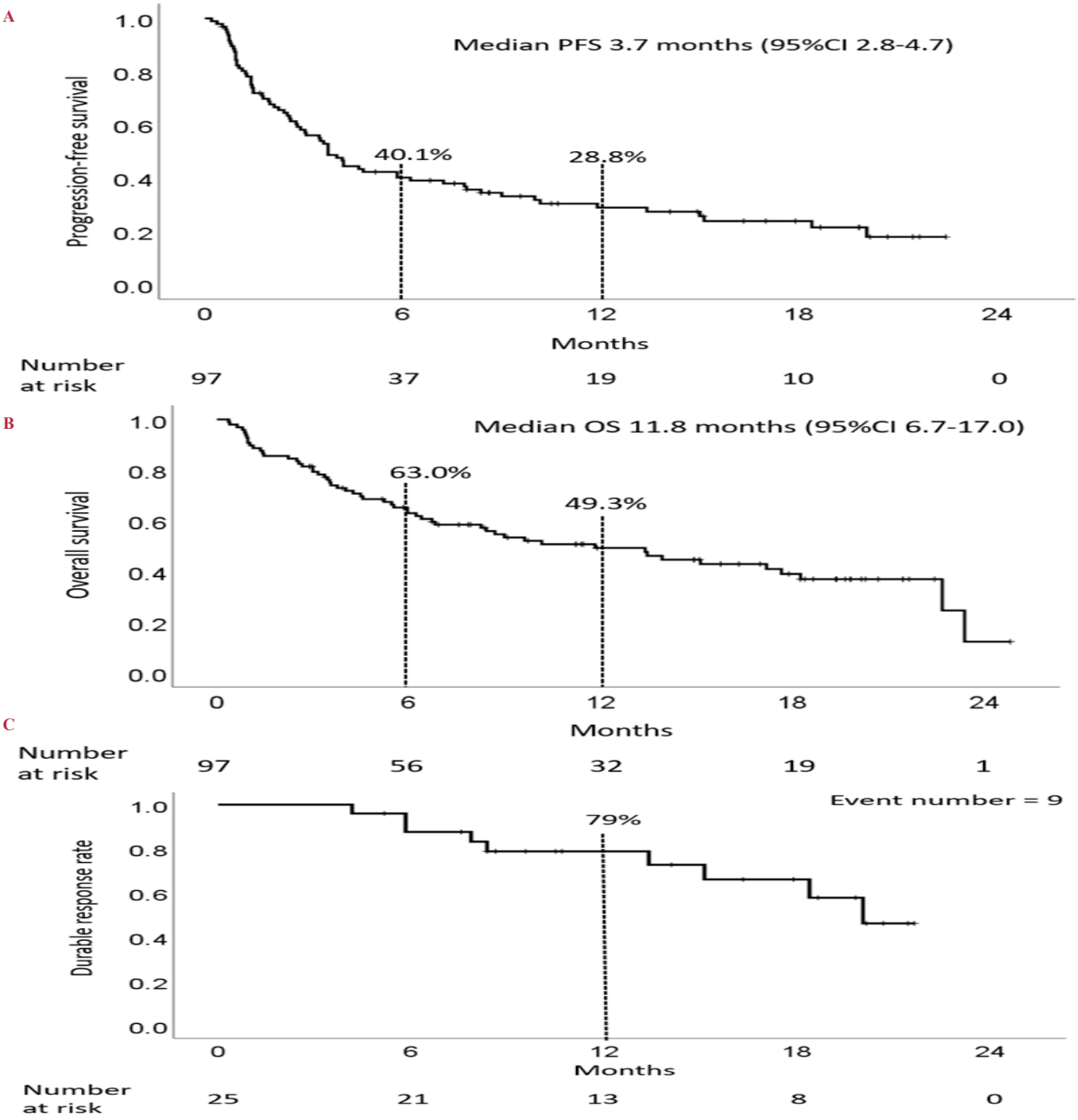

Figure1: Kaplan–Meier curves of progression-free survival (PFS) **(A)**, overall survival (OS) **(B)** and duration of response (DOR) in patients with determined objective response **(C)**.

Table 2. Univariate and multivariate analyses of prognostic factors for overall survival with pembrolizumab therapy

	Univariate		Multivariate		Reference category*
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	
Age, years	0.971 (0.938-1.005)	0.091	0.967 (0.933-1.002)	0.067	Continuous
Gender	0.737 (0.413-1.318)	0.304			Male/Female
ECOG PS	7.474 (3.955-14.124)	< 0.001	8.189 (4.178-16.051)	< 0.001	PS2-4/PS0-1
Smoking status	1.122 (0.639-1.970)	0.687			Current+Former/Never
Primary tumor site	1.710 (0.999-2.926)	0.05	1.679 (0.968-2.914)	0.065	Upper tract UC/BT
Histologic testing	1.930 (0.907-4.105)	0.088	1.409 (0.649-3.058)	0.385	With others/Pure UC
Radical surgery of the primary lesion	0.775 (0.453-1.325)	0.351			Yes/No
Lesions evaluated by RECIST	2.445 (1.187-5.037)	0.015	2.333 (1.096-4.968)	0.028	Yes/No
Time from previous chemotherapy	1.321 (0.643-2.713)	0.448			<3 months/>3months

HR, Hazard ratio, ECOG PS, Eastern Cooperative Oncology Group Performance status; RECIST, Response Evaluation Criteria in Solid Tumor.
*In a categorical values, the right side is the reference.

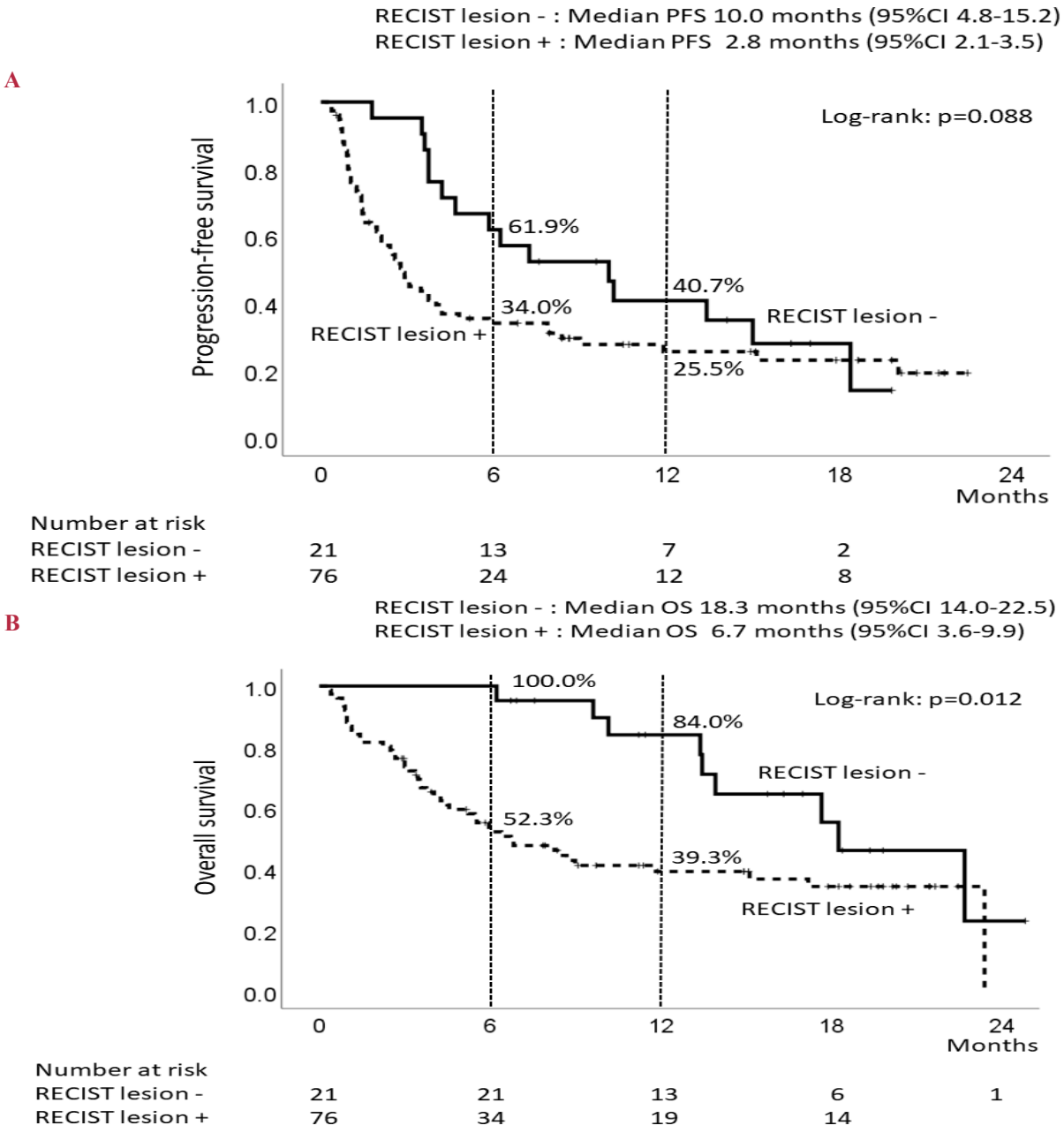

Figure2: Kaplan–Meier curves of progression-free survival (PFS) **(A)**, and overall survival (OS) **(B)** in each patient with or without lesions evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria

and recurrent UC patients who were treated with pembrolizumab after progression of platinum-based chemotherapy at our and related hospitals from January 2018 to October 2019. The recurrence of UC and the timing of pembrolizumab administration were determined by the doctors in charge.

Pembrolizumab was administered at a dose of 200 mg every three weeks until discontinuation due to disease progression or unacceptable AEs. We obtained medical records, and clinical features were recorded, including age, sex, smoking status, primary tumor site, histology, metastatic organs, duration since previous chemotherapy, and ECOG-PS. Treatment efficacy was assessed according to RECIST version 1.1,[4] wherein non-measurable lesions, such as small lesions or bone metastasis, with a 20% (and over 5 mm) increase in total diameter size or a new lesion were defined as progressive disease (PD); lesions with a 30% decrease in total diameter size were defined as partial response (PR); and the disappearance of all measurable lesions indicated complete response (CR). The objective response rate (ORR) was defined as the proportion of PR and CR, and disease control rate (DCR) was defined as the proportion of PR, CR, and stable disease (SD). Progression-free survival (PFS) was calculated from the commencement of pembrolizumab to radiographic or clinical disease progression or death. The durable response rate (DRR) and duration of response (DOR) from the commencement of pembrolizumab to radiographic or clinical disease progression or death of CR and PR patients were also calculated. OS was calculated from the commencement of pembrolizumab to death or the time of last follow-up. Pseudoprogression (PP) was defined as a response to treatment after an initial increase in the volume of cancer lesions or with the appearance of new lesions subsequently followed by disease stabilization or a disease response before confirming the progression with a second assessment using imaging evaluation.[5] Hyperprogression (HP) was defined as rapid tumor progression after the initiation of pembrolizumab.[6] Toxicity, including immune-related adverse events (irAE), was assessed according to the Common Terminology Criteria for Adverse Events version 4.0.[7]

The categorical variables used for calculating the incidence and percentage of each factor as well as the continuous variables were summarized as their median and range. When making comparisons, the chi-square test was used for categorial variables, while the Mann-Whitney U test was used for continuous variables. PFS and OS were estimated using Kaplan–Meier methods, and the differences were evaluated using the log-rank test. Cox proportional hazards models were used to identify the prognostic factors for OS. All data analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL), taking p-value < 0.05 as statistically significant.

RESULTS

The study included 97 patients with advanced UC who were treated with pembrolizumab after platinum-based chemotherapy at Kanazawa University and seven related hospitals. The characteristics of the patients are presented in Table 1. Twenty-one (22%) patients had no measurable lesions by RECIST (6 cases of small lymph node metastasis only; 8 cases of unmeasured primary and lymph node metastasis; and 7 cases of small visceral metastasis, including unmeasured bone metastasis). Nineteen (20%) patients were ECOG-PS 2–4.

The median follow-up period after pembrolizumab commencement was 7.8 months (range 0.4–24.8 months). The number of deaths during follow-up were 55 (57%) patients. The causes of death were UC in 47 (85%) patients, AEs in four (7%) patients, acute myeloid leukemia (AML) in two (4%) patients, suicide in one (2%) patient, and unknown cause in one (2%) patient, respectively. The best response was CR in nine (9%) patients, PR in 16 (17%) patients, SD in 26 (27%) patients, and PD in 46 (47%) patients. Therefore, the ORR was 26% and DCR was 49%. The median PFS and OS were 3.7 months (95% confidence interval (CI): 2.8–4.7) and 11.8 months (95%CI: 6.7–17.0), respectively (**Figure 1A, B**). At 12 months after pembrolizumab commencement, the DRR was 79%. At the time of last follow-up, 16 out of 25 (64%) patients with a response continued to show a response. The median DOR was not reached (**Figure 1C**). PP was observed in three (3%) patients and HP was observed in nine (9%) patients. The median OS of patients with HP was 28 days (range 10–43 days).

We investigated variables that predict shorter OS. In univariate and multivariate analysis, PS 2–4 lesions by RECIST were identified as factors associated with short OS (**Table 2**). The PFS of patients without lesions by RECIST was longer than that of patients with lesions by RECIST; however, it was not statistically significant (p = .088) (**Figure 2A**). The median OS of 18.3 months in patients without lesions by RECIST was significantly longer than the median OS of 6.7 months in patients with lesions by RECIST (p = .012) (**Figure 2B**). The best response of patients with and without lesions by RECIST were CR 4 cases (5%), PR 13 cases (17%), SD 17 cases (22%), and PD 42 cases (56%) versus CR 5 cases (24%), PR 3 cases (14%), SD 9 cases (43%), and PD 42 cases (19%), respectively (p = .004).

Severe AEs (including grade 3–5 AEs) were observed in 18 (19%) patients. Interstitial pneumonia was the most frequent grade 3–5 AE in this study. Other types of pneumonia included one pneumocystis pneumonia and one bronchial pneumonia. Five (5%) patients died after pembrolizumab treatment because of AEs. Two (2%) patients died of interstitial pneumonia, one (1%) of pneumocystis pneumonia, one (1%) of ulcerative colitis, and one (1%) of AML, respectively. Two (2%) patients with persistent bone marrow suppression caused by previous chemotherapy suffered with AML after two and four administrations of pembrolizumab, respectively.

DISCUSSION

We report the clinical outcome after pembrolizumab in Japanese patients with advanced UC. The most significant difference in patient background between this real-world study and KEYNOTE045 arises from the fact that patients with poor PS and no measurable lesions, as defined by RECIST, cannot be included in clinical trials. There have been some reports of poor prognosis in patients with poor PS;[1,8] however, to the best of our knowledge, we could not find a report that examined the prognosis of patients without lesions by RECIST treated by immune checkpoint inhibitors. Non-measurable lesions defined by RECIST are small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-meas-

urable lesions.[4] Lesions considered truly non-measurable included: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.[4] In this study, all the cases, which had only non-measurable lesions defined by RECIST, had only small lesions. The median PFS and OS were 3.7 months and 11.8 months, respectively, and the ORR was 26%. These outcomes were slightly better than the KEYNOTE-045 trial.[3] This might be because of the patients' backgrounds. Poor prognostic factors after systemic treatment for advanced UC are poor PS and visceral metastases,[9-12] especially liver metastases.[13] In the KEYNOTE-045 trial, the proportion of PS 0–1, PS 2, and PS 3–4 participants were 97.1%, 2.9%, and 0%, respectively.[3] In our study, the proportion of patients with PS 2–4 was 20%. The evaluation of risk factors for OS revealed poor PS and badly affected OS. The median OS of patients with PS 0–1 and PS 2–4 was 17.7 months and 1.4 months, respectively (data not shown). The inclusion criteria for KEYNOTE-045 trial for cancer status determined at least one measurable lesion evaluated by RECIST version 1.1.[3] In our study, 21 cases (22%) did not have lesions per RECIST. The visceral metastases and liver metastases, which were reported as poor prognostic factors,[9-13] were 62% and 18% in our study, compared to 89% and 34% in KEYNOTE-045.[3] In our study, patients with good PS 0–1 and without measurable lesions by RECIST, which were good prognostic factors for OS (**Table 2**), would contribute to the improved outcomes of our study. In clinical practice, we often determine that the lesion has metastasized due to its growth over time. In particular, with regard to the evaluation of lymph node metastasis, RECIST does not result in the evaluation of metastasis until the lymph nodes are more than 15 mm in short diameter. In actual clinical practice, we rarely wait to treat lymph node metastases until they grow to that size. In fact, in this study, most of the patients without RECIST-evaluated lesions had small lymph node and visceral metastases. In the present study, treatment was initiated before the size of the lesion was assessed as metastatic by RECIST, and the period of earlier intervention can be considered as the time until the lesion grew to a measurable size by RECIST, which may be counted as a prolonged prognosis. However, since the median difference was about 12 months (**Figure 2B**), it is conceivable that early intervention may have had a greater therapeutic effect. Basic research reported that PD-1-positive CD8-positive T-cell infiltration was higher in early-stage tumors with smaller size, and the efficacy of anti-PD-1 antibody was higher, suggesting the usefulness of early therapeutic intervention with immunotherapeutic agents.[14] In fact, in this study, ORR was better in the group of patients without RECIST-evaluated lesions. Although this study showed a high short-term efficacy for small lesions, the results of Kaplan–Meier analysis showed that treatment efficacy and survival approached the long-term (**Figure 2A, B**). The durable effect of long-term treatment may depend more on the immunity of the individual than on the size of the lesion. The long-term effects of the treatment need to be examined with an extended observation period.

After treatment with immune checkpoint inhibitors, atypical patterns of response, such as PP and HP, were reported. The PP is characterized by a transient increase followed by a decrease in tumor size.[5] The histopathological findings of the lesion biopsies revealed the presence of inflammatory infiltration or necrosis; therefore, PP is possibly associated with the infiltration of active T cells and other immune cells at the lesion.[15] Rosenberg et al reported that PP was observed in 20 (6%) out of 310 patients with advanced UC who were treated with atezolizumab after progression of platinum-based chemotherapy.[16] Sharma et al reported that PP was observed in 24 (9%) out of 265 patients with advanced UC who were treated with nivolumab after progression of platinum-based chemotherapy.[17] In our study, we observed PP in three (3%) patients. HP was defined as a rapid increase in tumor growth rate.[18] There were few reports of HP of UC. Hwang et al reported that HP in patients with UC treated with PD-1/PD-L1 inhibitors was observed in 12 (11.9%) out of 101 patients.[19] Higher CRP, neutrophil count, and volume of target lesions were reported to be associated with increased risks of HP.[20] In our study, 9 patients progressed rapidly after pembrolizumab treatment, and these patients were defined as HP. All patients had multiple lesions with poor ECOG PS. Eight patients were PS 2-4, and the other, who was PS 1, had liver, brain, peritoneal, and lymph node metastases without removal of the primary lesion. The median OS of these 9 patients was 29 days (range 11–43 days). All patients died before the first scheduled imaging evaluation; therefore, there were no imaging data to evaluate the actual progressions of the cancer, and it was difficult to distinguish these cases as HP or natural course.

In our study, 51 (53%) patients experienced AEs, including 18 (19%) patients with severe AEs (grade 3 or more), and 5 (5%) with death (grade 5). The frequency of AEs in our study was higher than that in the KEYNOTE-045 trial.[3] The median age in our study was higher than the median age of patients in the KEYNOTE-045 trial (73 vs 67 years, respectively),3 which might affect the proportion of AEs.[21] Interstitial pneumonia was observed in 10 patients (10%) in all grade and 8 patients (8%) in grade 3–5. In our study, 5 patients died after pembrolizumab treatment. One of the deaths was due to Pneumocystis jirovecii pneumonia. Cases with Pneumocystis jirovecii pneumonia caused by immunosuppression for immune checkpoint-related toxicity have been reported.[22] Therapy-related myelodysplastic syndrome or AML with chemotherapy for solid cancer is well known;[23] however, a report of AML after an immune checkpoint inhibitor was not found. The two cases of AML after pembrolizumab treatment each received 26 and 27 courses of platinum-based chemotherapy before pembrolizumab commencement and suffered chronic bone marrow suppression at the commencement of pembrolizumab; therefore, it was unclear whether the onsets of AML were the natural course after long-term chemotherapy or irAE.

The limitations of our study are its retrospective design, small cohort, and short follow-up period. Our study revealed the features of pembrolizumab treatment for advanced UC current clinical practice in Japan. We could discuss the difference between clinical trial and real clinical practice; therefore, we also investigated the cohort whose background was incompatible with a clin-

ical trial, such as patients with poor PS and low volume or unmeasurable cancer status as evaluated by RECIST.

CONCLUSIONS

In conclusion, we demonstrated that good PS 0–1 and no measurable lesions, especially small lesions, by RECIST were favorable prognostic factors in patients with advanced UC treated by pembrolizumab. A favorable response to immunotherapeutic agents was observed when the lesions were small. HP was observed mostly in poor PS patients with high volume lesions. Atypical AEs, such as, Pneumocystis pneumonia and AML, were observed in our cohort. This was a small size pilot study; therefore, a larger study population and long-term follow-up data are needed to clarify our outcomes.

ACKNOWLEDGEMENTS

The authors would like to thank the following individuals and institutions that participated in this study for their invaluable help with data collection: Hiroaki Iwamoto, Hiroshi Yaegashi, and Masashi Iijima of the Department of Integrative Cancer Therapy and Urology in Kanazawa University Graduate School of Medical Science Kanazawa, Kanazawa, Japan; Yuuta Takezawa and Kazuaki Machioka of the Department of Urology, Toyama Prefectural Central Hospital, Toyama, Japan; Jirou Sakamoto of the Department of Urology, Kouseiren Takaoka Hospital, Takaoka, Toyama, Japan; Kazuhiko Shibata of the Department of Medical Oncology, Kouseiren Takaoka Hospital, Takaoka, Toyama, Japan; Satoko Urata, Mitsuo Ofude, and Takao Nakashima of the Department of Urology, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa, Japan; Hiderou Minami and Osamu Ueki of the Department of Urology, Noto General Hospital, Nanao, Ishikawa, Japan; Masaharu Nakai and Kazunori Kobashi of the Department of Urology, Kaga Medical Center, Kaga, Ishikawa, Japan; Masato Yagisawa, Masashi Takeda, and Hidekazu Yamamoto of the Department of Urology, Fukui-ken Saiseikai Hospital, Fukui, Japan; Atsuya Takimoto, Ryou Satou, Sotaro Miwa, and Kiyoshi Koshida of the National Hospital Organization Kanazawa Medical Center, Kanazawa, Japan.

CONFLICT OF INTEREST

The authors have stated that they have no conflicts of interest.

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