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Original Article

Analyses of Nivolumab Exposure and Clinical Safety Between 3-mg/kg Dosing and 240-mg Flat Dosing in Asian Patients with Advanced Renal Cell Carcinoma in the Real-World Clinical Setting

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ABSTRACT

We aimed to identify the clinical characteristics related to increased nivolumab exposure in Japanese patients with renal cell carcinoma (RCC) in real-world clinical setting. Eleven patients were treated with the originally approved nivolumab dosing regimen of 3 mg/kg every 2 weeks (Q2W) (3-mg/kg group) and 8 patients with a flat dose of 240 mg Q2W (flat dosing group). Trough concentrations (C_{min}) until the fifth cycle were measured by sandwich enzyme-linked immunosorbent assay using anti-nivolumab monoclonal antibody established by the Autonomously Diversifying Library system. Mean C_{min} at four cycles of nivolumab were significantly higher in the flat dosing group than in the 3-mg/kg group. In an analysis of covariates related to nivolumab concentration, serum albumin (Alb) was significantly lower in the 3-mg/kg group than in the flat dose group. C_{min} correlated significantly with serum Alb at all cycles. In conclusion, serum Alb was a potential clinically relevant covariate for nivolumab pharmacokinetics in Japanese RCC patients. Further studies should verify whether serum Alb affects nivolumab efficacy and toxicity.

Introduction

Nivolumab is a monoclonal antibody that blocks programmed death-1 and acts as an immune checkpoint inhibitor. This agent is a standard-of-care option for patients with metastatic renal cell carcinoma (mRCC) following failure of prior targeted agents [1]. Regarding the regimen of nivolumab for the treatment of mRCC, a weight-based dosing schedule at 3 mg/kg every 2 weeks (Q2W) was approved by The U.S. Food and Drug Administration in 2015 and by the Japanese Ministry of Health, Labor, and Welfare in 2016. From population pharmacokinetic (PPK) model analyses, the pharmacokinetics (PK) of nivolumab was linear with dose-proportional exposure over a dose range of 0.1-10 mg/kg and was similar in patients across tumor types including RCC [2]. Subsequently, an exposure assessment using PPK analysis comparing the originally approved 3-mg/kg Q2W dosing with flat dosing of 240 mg Q2W showed that exposure, safety, and efficacy of nivolumab were similar for both dosing regimens [5]. Based on these results, the Japanese Ministry of Health, Labor, and Welfare approved a flat dose of 240 mg Q2W in 2018. Thereafter, the clinical dosing regimen of nivolumab has changed from the weight-based dosing of 3 mg/kg Q2W to the flat dosing of 240 mg Q2W. However, the previous exposure analysis was based on the data of phase 1, 2, and 3 clinical trials [5]. There are some issues concerning the validity of those results for Japanese patients in real-world clinical settings because of the strict selection criteria, small Asian cohort included in the analysis, and lower body weight of Asian cohort compared to Western cohort.

The aim of the present study was to evaluate the efficacy and safety of the flat dosing regimen in Japanese RCC patients in clinical settings and to identify clinical characteristics related to increased nivolumab exposure.

Materials and Methods

Patients

This study was a retrospective study by reviewing medical records at the Department of Urology, Iwate Medical University, during the period of January 2018 to November 2019. Nineteen consecutive patients who had a confirmed diagnosis of metastatic or unresectable RCC and received nivolumab therapy were enrolled in the study. All participants had targeted therapies prior to nivolumab therapy. In the present study, 11 patients were treated with the originally approved dosing regimen of 3 mg/kg Q2W (prior to August 2018) and 8 patients with the later approved flat dosing of 240 mg Q2W (after September 2018). Treatments for participants were

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planned according to standard of care in accordance with respective treatment guidelines. From the medical records, clinical data including demographics, medical history, nivolumab dose, treatment duration, reason for discontinuation, and progression-free survival were collected. Tumor assessments were conducted at baseline, week 12, and every 12 weeks thereafter. Symptom severity was evaluated at each cycle of nivolumab therapy.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The institutional review board of our institution approved the present study (approval number: H29-18). Informed consent was waived by the institutional review board.

Sample Collection and Laboratory Tests

Plasma sampling for assay of blood nivolumab concentration was performed before nivolumab administration from the first to fifth cycle of nivolumab treatment as part of routine care in all patients treated with nivolumab at our hospital. At the same time point, bone marrow function (red blood cells, platelets, and white blood cells), renal function (serum creatinine), and other laboratory tests were conducted. In the current study, data from routine clinical care including nivolumab plasma concentrations were used, with authorization from the institute. Baseline nivolumab concentration was measured before administration of cycle 1. Trough concentrations (C_{min}) were measured before administration of cycles 2, 3, 4, and 5 and were denoted $C_{min}1$, $C_{min}2$, $C_{min}3$, and $C_{min}4$, respectively (Figure 1).

Sandwich Enzyme-Linked Immunosorbent Assay (ELISA) for Blood Nivolumab Concentration

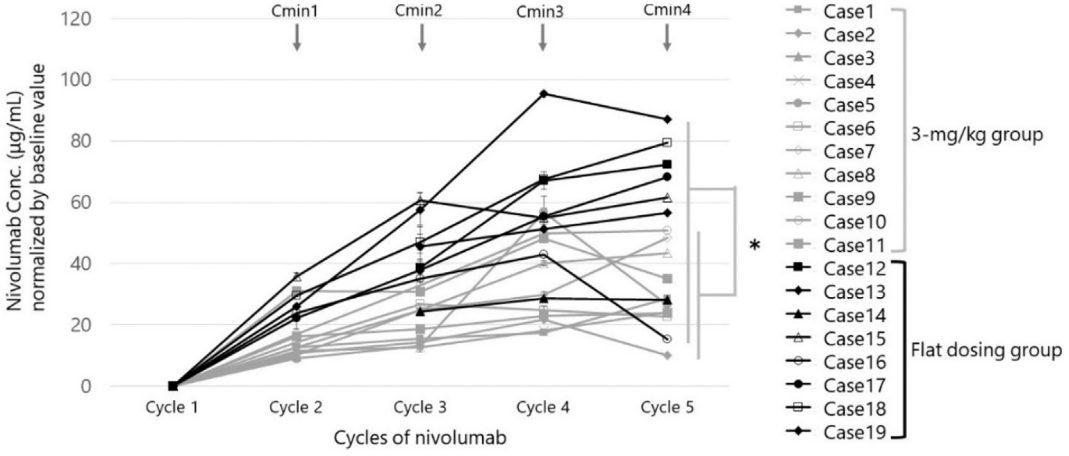
Using the Autonomously Diversifying Library (ADLib) system [3,4], we established two anti-nivolumab monoclonal antibodies (mAbs): mouse Fc chimeric mAb for capture and human IgG1 mAb for detection using sandwich ELISA. Ninety-six-well microtiter plates (Nunc MaxiSorp, Thermo Fisher Scientific, MA, USA) were coated with streptavidin at 2.5 μg/ml in Dulbecco's phosphate-buffered saline (PBS) and incubated overnight at 4°C. After washing the plates with PBS-Tween, the capture antibody (biotinylated anti-nivolumab mouse Fc chimeric mAb) at 2.5 μg/ml in Dulbecco's PBS was added to each well and incubated at 25°C for 1 hour. The plates were washed and blocked with Blocking Reagent-N102 (NOF Corporation, Tokyo, Japan) at 25°C for 1 hour. Serial dilutions of nivolumab from 500 to 7.8 ng/ml were prepared for the standard curve, and test samples were diluted in sample diluent (1% BSA, 0.05% Tween-20, 0.05% ProClin 300 in PBS). After washing the plates, the standard and diluted samples were added and incubated at 25°C for 1 hour. The plates were washed, and the detection antibody (horseradish peroxidase–conjugated anti-nivolumab human IgG1 mAb) was then added and incubated at 25°C for 45 minutes. The plates were washed, and TMB substrate (Nacalai Tesque, Kyoto, Japan) was added and incubated at 25°C for 10 minutes. Finally, to stop color development, 2 N sulfuric acid was added, and absorbance at 450 nm was measured using a microplate reader (Infinite m1000, TECAN, Switzerland). Data analysis was performed using GraphPad Prism software (GraphPad, CA, USA).

Clinical Outcome

Outcome measures included progression-free survival (PFS), overall survival (OS), and occurrence of immune-related adverse events (irAEs). Tumor response was evaluated by Response Evaluation Criteria version 1.1. Hematological and nonhematological irAEs were graded according to the National Cancer Center Common Toxicity Criteria for Adverse Events version 5.0. Associations between C_{min} and clinical covariates including body weight (BW), estimated glomerular filtration rate (eGFR), serum lactate dehydrogenase (LDH), and serum albumin (Alb) were explored [2].

Data Analyses

Fisher's exact test and *t* test were used to compare patient characteristics. Laboratory data and trough concentrations were compared using *t* test. Correlation between C_{min} and dose of nivolumab or Alb, which was evaluated as an outcome-related clinical factor, was examined by Pearson correlation analysis. PFS and OS were estimated by the Kaplan-Meier method. Univariate analyses were performed by the log-rank test. Clinical response and adverse events were analyzed using Fisher's exact test. All statistical analyses were conducted using JMP 14.3.0 (SAS Institute, Cary, NC).



Dosing group	Cmin1		Cmin2		Cmin3		Cmin4	
	Mean ± SD (μg/mL)	p value	Mean ± SD (μg/mL)	p value	Mean ± SD (μg/mL)	p value	Mean ± SD (μg/mL)	p value
3-mg/kg group	14.2 ± 1.9	<0.01	21.5 ± 2.4	<0.01	33.0 ± 4.6	0.01	31.4 ± 4.1	0.02
Flat dosing group	27.5 ± 2.4		43.3 ± 4.2		57.9 ± 7.0		58.6 ± 8.8	

Figure 1. Trough concentrations at cycles 2-5 of nivolumab in all subjects. *P* values: flat dosing group versus 3-mg/kg group by *t* test. Mean C_{min} were significantly higher in the flat dosing group than in the 3-mg/kg group for cycles 2 to 5.

Results

Patient Characteristics

The subjects comprised 15 men and 4 women with median age of 68 (range 37-83) years. Seventeen patients had Karnofsky performance status rating of 80% to 100% (mean 91.6% ± 2.6%) at the start of nivolumab treatment. According to the International Metastatic RCC Database Consortium risk criteria,13 patients (68.4%) were classified as intermediate risk and 3 patients (15.8%) as poor risk. The most common sites of metastases were lung (12 patients, 63.2%) and lymph node (10 patients, 52.6%). Mean BW before nivolumab treatment was 63.4 ± 3.0 kg, and mean eGFR was 49.6 ± 4.7 ml/min/1.73 m^2.

Comparison of Patient Characteristics Between 3-mg/kg Group and Flat Dosing Group

To examine the change in nivolumab exposure related to the dosing regimen of nivolumab, we compared patients treated with 3 mg/kg ($n = 11$) and those treated with flat dose of 240 mg ($n = 8$). Patient characteristics of the two groups are summarized in Table 1. Patient background did not differ significantly between the two groups. The mean dose of nivolumab was significantly higher in the flat dosing group than in the 3-mg/kg group (240.0 ± 0.0 mg vs 181.8 ± 12.0 mg, respectively, $P < .001$). For patients in the flat-dosing group, the 240 mg dose was significantly higher than when the dose was calculated according to 3 mg/kg (176.2 ± 23.7 mg, $P < .001$).

Trough Concentrations in 3-mg/kg Group and Flat Dosing Group

Changes of trough concentration up to cycle 5 (C_{min}1-4) in each patient are summarized in Figure 1. Baseline concentration (before administration of cycle 1) was 0 μg/ml in all patients. Mean C_{min} of nivolumab were significantly higher in the flat dosing group than in the 3-mg/kg group (C_{min}1: 27.5 ± 2.4 vs 14.2 ± 1.9 μg/ml, respectively, $P < .01$; C_{min}2: 43.3 ± 4.2 vs 21.5 ± 2.4 μg/ml, respectively, $P < .01$; C_{min}3: 57.9 ± 7.0 vs 33.0 ± 4.6 μg/ml, respectively, $P = .01$; C_{min}4: 58.6 ± 8.8 vs 31.4 ± 4.1 μg/ml, respectively, $P = .02$). Among all patients, C_{min} correlated with the dose administered after the third cycle of nivolumab (C_{min}1: $r = 0.45$, $P = .08$; C_{min}2: $r = 0.68$, $P < .01$; C_{min}3: $r = 0.54$, $P = .02$; C_{min}4: $r = 0.55$; $P = .02$). In both groups, trough concentration increased significantly by cycle 4 and reached steady state at cycle 5 (3-mg/kg group: baseline vs C_{min}1; $P < .01$, C_{min}1 vs C_{min}2; $P < .01$, C_{min}2 vs C_{min}3; $P = .02$, C_{min}3 vs C_{min}4; $P = .71$; flat dosing group: baseline vs C_{min}1; $P < .01$, C_{min}1 vs C_{min}2; $P < .01$, C_{min}2 vs C_{min}3; $P = .02$, C_{min}3 vs C_{min}4; $P = .89$).

Efficacy and Safety in 3-mg/kg Group and Flat Dosing Group

Median follow-up period was 11 (range 1.4-21.6) months. The median PFS in all patients was not reached (range 1.0-21.6), and the estimated median OS was not reached (range 1.4-21.6). The PFS rate tended to be higher in the flat dosing group than in the 3-mg/kg group [PFS rate at 12 months: 87.5% (95% CI, 46.3-98.3) vs 53.0% (95% CI, 25.0-79.2), respectively]. The OS rate tended to be higher in the flat dosing group than in the 3-mg/kg group [OS rate at 12 months: 100% (95% CI, not detected) vs 80.8% (95% CI, 47.2-95.2), respectively].

According to best overall response in all patients, partial response (PR) was 37%, and stable disease (SD) was 37%. Rate of PR was not significantly different between the flat dosing group and the 3-mg/kg group [25.0% (95% CI, 7.1-59.1) vs 45.5% (95% CI, 21.3-72.0), respectively, $P = .63$].

Twelve of all patients had any grade of irAEs. The most common grade 3 or 4 irAEs (grade 3/4 irAEs) were adrenal insufficiency (28%), hypothyroidism (5%), and skin rash (5%). In the 3-mg/kg group, diarrhea occurred in three patients (27.3%), and increased aspartate aminotransferase or aspartate aminotransferase, pneumonitis, and colitis in one patient (9.1%) each, all of which were grades 1-2. Adrenal insufficiency occurred in four patients (36.4%), and skin rash and hypothyroidism in one patient (9.1%) each, all of which were grades 3-4. In the flat dosing group, increased aspartate aminotransferase or aspartate aminotransferase occurred in two patients (25.0%), and skin rash and diarrhea in one patient (12.5%) each, all of which were grades 1-2. No grades 3-4 adverse events occurred in the flat dosing group. The flat dosing group and the 3-mg/kg group did not differ significantly in the rate of any grade irAEs [50.0% (95% CI, 21.5-78.5) vs 72.7% (95% CI, 43.4-90.3), respectively, $P = .38$] or grade 3/4 irAEs [12.5% (95% CI, 2.2-47.1) vs 54.6% (95% CI, 28.0-78.7), respectively, $P = .15$].

Serum Albumin as Clinical Factor Explaining Difference in Nivolumab Trough Concentration

Previous PPK analysis showed that BW, eGFR, serum LDH, and serum Alb were clinical covariates related to nivolumab clearance [2]. To identify the clinical factors that explain the difference in trough concentration of nivolumab, we compared the above covariates between the two dosing regimen groups (Table 2). Mean serum Alb was significantly higher in the flat dose group than the 3-mg/kg group (4.0 ± 0.1 vs 3.3 ± 0.1 g/dl, respectively, $P < .01$). BW, eGFR, and serum LDH were not significantly different between the flat dosing group and 3-mg/kg group (BW: 67.4 ± 4.5 vs 60.6 ± 4.0 kg, respectively, $P = .27$; eGFR: 59.6 ± 7.7 vs 42.3 ± 5.1 ml/min/1.73 m^2, respectively, $P = .09$; serum LDH: 175.4 ± 10.7 vs 222.3 ± 24.2 IU/l, respectively, $P = .10$).

Table 1
Patient Characteristics of Two Dosing Groups

Patient Characteristics	3-mg/kg Group $n = 11$	Flat Dosing Group $n = 8$	*P* Value
Mean age ± SD (years)	67.5 ± 3.2	58.4 ± 4.8	.13
Sex: male, *n* (%)	8 (72.7)	7 (87.5)	.60
IMDC risk, *n* (%)			
Favorable	1 (9.1)	2 (25.0)	
Intermediate	7 (63.6)	6 (75.0)	
Poor	3 (27.3)	0 (0)	.22
Histological subtype: clear cell, *n* (%)	9 (81.8)	6 (75.0)	1.00
Sites of metastases, *n* (%)			
Lung	8 (72.7)	4 (50.0)	.38
Lymph node	5 (45.5)	5 (62.5)	.65
Bone	3 (27.3)	2 (25.0)	1.00
Liver	4 (36.4)	0 (0)	.10
Number of targeted therapies before nivolumab treatment, *n* (%)			
1			
	8 (72.7)	8 (100)	.23
Dose of nivolumab, mean ± SD (mg)	181.8 ± 12.0	240.0 ± 0	<.001

IMDC; the International Metastatic RCC Database Consortium.

Table 2
Clinical Factors of the Two Dosing Groups

Clinical Factor	3-mg/kg Group $n = 11$	Flat Dosing Group $n = 8$	*P* Value
BW, mean ± SD (kg)	60.6 ± 4.0	67.4 ± 4.5	.27
eGFR, mean ± SD (ml/min/1.73 m^2)	42.3 ± 5.1	59.6 ± 7.7	.09
LDH, mean ± SD (IU/l)	222.3 ± 24.2	175.4 ± 10.7	.10
Alb, mean ± SD (g/dl)	3.3 ± 0.1	4.0 ± 0.1	.001

We also conducted correlation analysis between trough nivolumab concentration and serum Alb level at each cycle of nivolumab treatment (Figure 2). C_{min} correlated significantly with serum Alb at each cycle (C_{min}1-lb_{2W}: $r = 0.54$, $P = .03$; C_{min}2-Alb_{4W}: $r = 0.57$, $P = .01$; C_{min}3-Alb_{6W}: $r = 0.47$, $P = .04$; C_{min}4-Alb_{8W}: $r = 0.58$, $P = .01$).

Discussion

In the present study, we explored the clinical characteristics related to increased nivolumab exposure in Japanese RCC patients. Using monoclonal antibodies generated by the ADLib system (Chiome Bioscience Inc., Tokyo, Japan), we measured blood concentrations of nivolumab by sandwich ELISA.

Therapeutic monoclonal antibodies are often dosed based on body weight of patients. The current dosing regimen of nivolumab used in Japan is a flat dose of 240 mg Q2W, and the efficacy and safety of this dosing regimen have been verified by sensitivity analyses using the data of previous clinical trials [5]. In a large phase 1b dose escalation study, nivolumab was tolerated up to 10 mg/kg across tumor types including RCC, with no maximum tolerated dose identified [6]. The antitumor activity based on objective response rate approached a plateau at 3 mg/kg, with no increased benefit at doses over 3 mg/kg [6]. The exposure-response analyses of efficacy and safety showed that nivolumab exposure was not a significant predictor of prolongation of OS or a risk of AE leading to drug discontinuation or death in patients with advanced solid tumors [5]. However, previous clinical trials use strict criteria for subject selection, and Asian cohort was small and had lower body weight compared to Western cohort. Compared to the cohort of the PPK analysis [2], our study group had much lower mean body weight (63.4 ± 3.0 vs 79.1 ± 19.3 kg, respectively) and lower eGFR (49.6 ± 4.7 vs 78.5 ± 21.6 ml/min/1.73 m^2, respectively). In our institute, 11 patients were treated with 3-mg/kg dosing regimen before approval of the flat dosing regimen in 2018, and 8 patients were treated with the flat dosing regimen after the approval. The mean dose of nivolumab was significantly higher in the flat dosing group than in the 3-mg/kg group. In the flat dosing group, the administered dose was significantly higher than the dose calculated from 3 mg/kg. Based on these results, we assumed that Japanese RCC patients treated with the flat dosing regimen probably have increased nivolumab exposure compared to Western population. To verify nivolumab exposure in Asian cohort, we performed an analysis to compare 3 mg/kg Q2W with the flat dose of 240 mg Q2W.

Trough concentrations at cycles 2-5 of nivolumab were significantly higher in the flat dosing group than in the 3-mg/kg group. In both groups, the trough concentration reached steady state after cycle 4. Correlation analysis showed a significant relation between C_{min} and administered dose in our study group. However, in the flat dosing group, variation of nivolumab concentration tended to be larger as the treatment cycle progressed [average C_{min} (95% CI): C_{min}1; 27.5 (20.8-34.2) μg/ml, C_{min}2; 43.3 (33.3-53.4), C_{min}3: 57.9 (41.4-74.4), C_{min}4: 58.6 (37.8-79.4)]. Previous PPK analysis suggested that individual covariates (BW, PS, sex, eGFR, serum Alb, and LDH) had some effects on the pharmacokinetics of nivolumab [2]. We hypothesized that the difference in trough concentration among patients in the same dosing regimen group may depend not only on nivolumab dosage but also on nivolumab clearance.

Therefore, our study focused on differences in clinical factors that have been reported to be covariates related to nivolumab clearance [2]. Between the two dosing regimen groups, body weight, eGFR, and serum LDH were similar, but mean serum Alb was significantly higher in the flat dosing

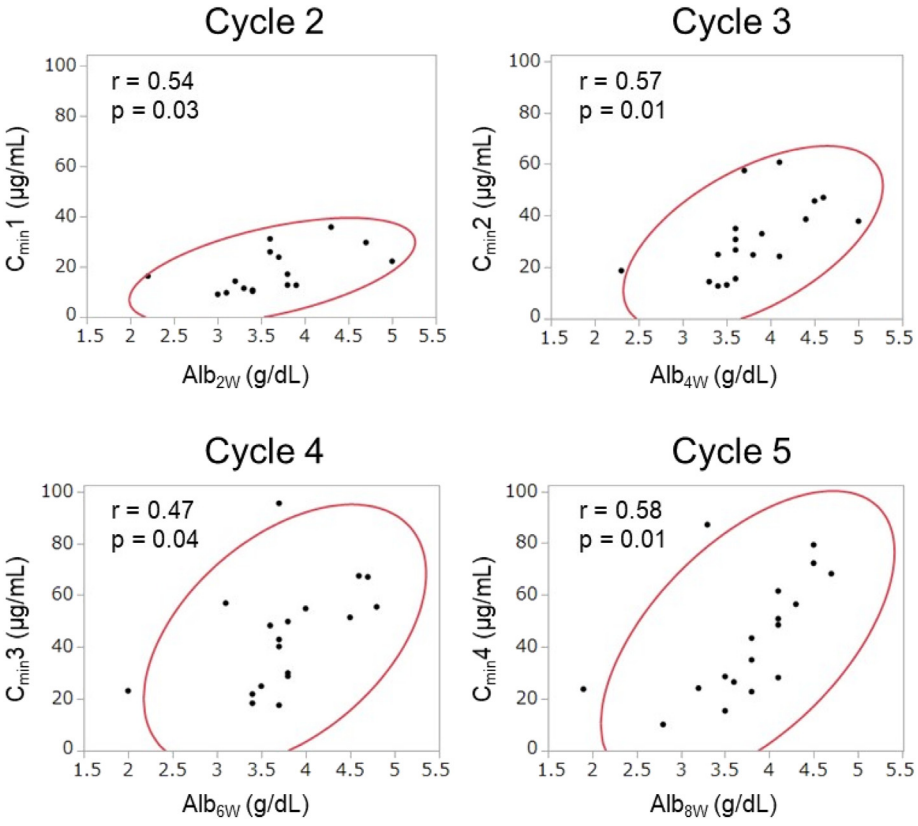


Figure 2. Correlation analysis between trough concentration and serum Alb at each cycle of nivolumab treatment. C_{min} correlated significantly with serum Alb at each cycle.

group than in the 3-mg/kg group. Correlation analysis revealed a significant relation between trough concentration and serum Alb. The previous sensitivity analysis showed that serum Alb had a significant effect on clearance of nivolumab [2]. Generally, low serum Alb is an indicator of cachexia level and hypercatabolic state [7,8]. Previous report indicated that cancer patients had higher rates of whole-body protein turnover [9]. Turner et al. [10] suggested that catabolic drivers accompanying skeletal muscle loss constitute a primary elimination pathway of humanized IgG4 mAb. Further studies are warranted to evaluate the potential effects of the prognostic factors of RCC on blood nivolumab concentration.

Both PFS and OS tended to be longer in the flat dosing group than in the 3-mg/kg group. The PR rate was similar in the two dosing groups. Similar to the efficacy results, difference in dosing regimen was not associated with increased toxicity. These results were consistent with previous report [5]. Thus, the difference in nivolumab concentration between two dosing regiments does not correlate with efficacy or AEs. These results raise the question of whether higher nivolumab concentrations obtained by 240-mg dosing Q2W is needed for Japanese RCC patients.

We also found that higher Alb levels were related to higher nivolumab concentrations. This finding has clinical significance. Administration of nivolumab every 2 weeks for many years is not feasible in real-world clinical practice. However, there are no studies so far that indicate when to stop or decrease the frequency of nivolumab. Our result may suggest that modifying the interval of nivolumab in patients with higher Alb levels is a therapeutic option. Modified schedule of nivolumab dosing would have additional advantages of reducing medical costs and patient burden of hospital visit and treatment.

Our study had several limitations. It was a retrospective study with a small number of cases and potential selection bias. The follow-up period was too short. Consequently, the study was not sufficiently powered for analyzing efficacy and safety of nivolumab treatment. Nevertheless, we propose that increase and maintenance of a therapeutic trough nivolumab concentration may indicate decrease in nivolumab clearance through ameliorated cachexia, and improvement in disease state.

In conclusion, our study in Japanese RCC patients found no clinically relevant difference in nivolumab exposure that may affect efficacy and safety between the initially approved 3-mg/kg dosing regimen and the current 240-mg flat dosing regimen. In addition, analyses revealed that trough concentration was associated with not only nivolumab dose but also serum Alb level, which is a prognostic factor reflecting clinical status. Further studies with longer follow-up are warranted to verify whether wasting of nivolumab dose by cancer cachexia affects the prognosis of RCC in the clinical setting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors' Contributions

Conception and design: R. Kato, D. Ikarashi, W. Obara.

Development of methodology: R. Kato.

Acquisition of data (acquired and managed patients,): R. Kato, T. Matsuura, Y. Kato, M. Kanehira, R. Takata. W. Obara.

Establishment of anti-nivolumab mAb and measurement of trough concentration of nivolumab: R. Tokuyama, K. Tamai, N. Harigai, Y. Nakazaki.

Analysis and interpretation of data (statistical analysis, biostatistics, computational analysis): R. Kato, R. Tokuyama.

Writing, review, and/or revision of the manuscript: R. Kato, W. Obara.

Administrative, technical, or material support (reporting or organizing. data, constructing databases): R. Kato, D. Ikarashi.

Study supervision: Y. Kato, M. Kanehira, R. Takata.

References

[1] R.J. Motzer, B. Escudier, D.F. McDermott, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (2015) 1803–1813.
[2] G. Bajaj, X. Wang, S. Agrawal, et al., Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors, CPT Pharmacometrics Syst. Pharmacol. 6 (2017) 58–66.
[3] H. Seo, S. Hashimoto, K. Tsuchiya, et al., An ex vivo method for rapid generation of monoclonal antibodies (ADLib system), Nat. Protoc. 1 (2006) 1502–1506.
[4] H. Seo, M. Masuoka, H. Murofushi, et al., Rapid generation of specific antibodies by enhanced homologous recombination, Nat. Biotechnol. 23 (2005) 731–735.
[5] X. Zhao, S. Suryawanshi, M. Hruska, et al., Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors, Ann. Oncol. 28 (2017) 2002–2008.
[6] S. Agrawal, Y. Feng, A. Roy, et al., Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy, J Immunother Cancer 4 (2016) 72.
[7] W.J. Evans, J.E. Morley, J. Argiles, et al., Cachexia: a new definition, Clin. Nutr. 27 (2008) 793–799.
[8] D.C. McMillan, The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer, Cancer Treat. Rev. 39 (2013) 534–540.
[9] K.C. Fearon, D.T. Hansell, T. Preston, et al., Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer, Cancer Res. 48 (1988) 2590–2595.
[10] D.C. Turner, A.G. Kondic, K.M. Anderson, et al., Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance, Clin. Cancer Res. 24 (2018) 5841–5849.