

Frequency of pre-treatment may not increase the immune-related adverse events of RCC patients treated with nivolumab

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Abstract

Nivolumab has shown good prognosis in renal cell carcinoma (RCC) patients previously treated with targeted therapy. We aimed to study irAE (immune-related adverse event) due to nivolumab and numbers of previous treatment lines in RCC patients. Between October 2016 and November 2019, 114 patients were treated with nivolumab as second- and later-line therapy. Among them, 110 patients with complete data were evaluated in this retrospective observational study. The primary endpoint was the relation between irAE and numbers of previous targeted therapies. Secondary endpoints were the relation of irAE with the duration of nivolumab treatment and with best overall response. For the primary analysis, proportional odds logistic regression was used to assess the effect of the number of prior therapies on the grade of any irAE as the ordinal variable. For the secondary analysis, binomial logistic regression models adjusted for the covariates were prepared to confirm the association between the incidence of irAE and the number of courses, number of nivolumab treatments and best overall response. Overall, 69, 66, 33, 13, 9 and 9 patients were treated with sunitinib, axitinib, pazopanib, sorafenib, temsirolimus and everolimus, respectively, prior to nivolumab. In total, 60 adverse events (Grade 1, 21; Grade 2, 21; Grade 3, 14; Grade 4, 2; not evaluated, 2) were identified in the patients treated with nivolumab. Ordered logistic regression analysis showed that the adjusted odds ratios of numbers of prior treatment for grade of irAE were 1.12 (numbers of prior treatment: 2 to 1) and 1.31 (3 to 1). Odds ratios of the numbers of nivolumab treatments and best overall response for the incidence of irAE were not significant. No statistically significant relations were found between grade of irAE and numbers of treatments prior to nivolumab. Patients treated with nivolumab should be closely monitored for irAE regardless number of previous therapies.

Keywords: immune-related adverse event, nivolumab, renal cell carcinoma, targeted therapy

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The need to obtain informed consent from all patients included in this study was waived due to the retrospective study design.

The authors declare that they have no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Several cancers including renal cell carcinoma (RCC) with clear cell historic features have been well recognized to be candidates for treatment with immune checkpoint inhibitors.^[1–3] Nivolumab, a monoclonal anti-PD-1 (programmed death 1) antibody, improved overall survival in several cancers including RCC.^[1] Nivolumab blocks the interaction of PD-1 and its ligands and eventually restores antitumor immunity, which concomitantly may lead to a break in self-tolerance, manifesting as systemic or organ-specific autoimmunity.^[4] Indeed, 79% of adverse events were reported in patients who were treated with nivolumab as second- or third-line therapy.^[1] Although, the incidence rate did not seem to be significantly higher than that for everolimus, it was still high. In RCC, nivolumab was first reported as second- (72%) or third-line (28%) therapy after previous regimens of anti-angiogenic therapy,^[1] whereas De Giorgi et al reported that 79.3% of metastatic RCC patients receiving treatment with nivolumab on or after third-line treatment were accompanied by a 32% rate of adverse events of any grade in a real-world setting.^[5] Ishihara et al also reported that 37.3% of patients had received nivolumab on or after third-line therapy, and no statistically significant incidence of immune-related adverse events (irAE) occurred between second- and later-line nivolumab therapy.^[6] Knowledge of the grade of irAE experienced prior to nivolumab therapy and the efficacy of treatment is useful because severe irAE could be fatal in some patients.^[7] As long as nivolumab monotherapy is administered as second- or later-line

therapy in RCC patients, the number of prior therapies may affect irAE grade. However, there are few studies on the number of prior therapies and irAE of nivolumab as the primary endpoint. In an attempt to clarify this issue, we investigated the association of irAE grade with the number of prior lines of therapy by analyzing patient data sets with proportional odds logistic regression analysis in this study. In addition, many researchers showed a relation between anti-tumor efficacy and irAE in several cancers including RCC.^[8–12] Therefore, the associations of irAE with numbers of nivolumab treatments, and with best overall response, were also evaluated as secondary endpoints in this study.

2. Materials and methods

2.1. Patients and methods

This was a retrospective study conducted by reviewing the clinicopathological data of 114 Japanese patients with RCC who were treated with nivolumab as second- or later-line therapy between October 2016 and November 2019. The final pathologic diagnosis of RCC was made in routine clinical practice at 4 institutions belonging to the Tokai Urologic Oncology Research Seminar: Gifu University Graduate School of Medicine, Fujita Health University School of Medicine, Hamamatsu University School of Medicine and Nagoya City University Graduate School of Medical Sciences. One patient treated with chemotherapy and 3 patients with missing data on body mass index (BMI) and C-reactive protein (CRP) were excluded from this analysis, and thus the data of 110 patients treated with molecular-targeted therapy prior to nivolumab (tyrosine kinase inhibitors or mTOR inhibitors) were analyzed. This study was approved by the Medical Review Board of Gifu University, Graduate School of Medicine (No. 2019-169). The need to obtain informed consent from all patients included in this study was waived due to the retrospective study design.

2.2. Treatment with nivolumab and evaluation

In this cohort, nivolumab (3 mg/kg or a flat dose of 240 mg) was administered intravenously every 2 or more weeks to patients with advanced or metastatic RCC after 1 or more molecular-targeted agents until withdrawal of consent, unacceptable toxicity or disease progression occurred, at the discretion of the physician. The administration interval was also extended if necessary. Clinicopathological data including patient demographics (age, sex, BMI and performance status) and laboratory and radiological findings were extracted from the medical records for analysis. Data on irAE as recorded by each treating physician were also obtained from the medical records and classified according to the Common Terminology Criteria for Adverse Events v4.0. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors v1.1.^[13]

2.3. Statistical analysis

The characteristics of the patients are summarized using the median and interquartile range (IQR) for continuous variables and frequencies with percentages for categorical variables. For the primary analysis, we conducted proportional odds logistic regression to assess the effect of the number of prior therapies on the grade of any irAE as the ordinal variable. The proportional

odds logistic regression model, also known as the ordinal logistic regression model, is commonly used to analyze ordinal categorical variables as outcome variables. In this study, the adjusted odds ratio calculated from the ordinal logistic regression model was used to determine whether the number of prior therapies affected the grade of irAE. Statistical tests were performed for adjusted odds ratios, and an association was recognized when the p value was below the significance level. As potential confounders were considered to exist in the association between irAE and the number of prior therapies, proportional odds logistic regression analysis was performed adjusting for the variables that were considered general information and were reported to be partly associated with irAE or the prognosis of RCC.^[14–16] Age, sex, Karnofsky Performance Status, BMI, number of neutrophils and CRP were included in the model to reduce the potential confounders. For the secondary analysis, we used binomial logistic regression models adjusted for the above covariates to confirm the association between the incidence of irAE and the number of prior therapies, number of nivolumab treatments or best tumor response. The relation between each variable and the predicted probability of irAE obtained from the logistic model was represented graphically with 95% confidence interval. To correct for possible overfitting of the regression model, penalized maximum likelihood estimation was used to allow shrinkage for the effect of all variables. A 2-sided 5% significance level was used for all statistical inferences. R software version 3.6.2 (www.r-project.org) was used for all analyses.

3. Results

3.1. Patient characteristics and profile of immune-related adverse events of nivolumab

The characteristics of the 110 patients who received treatment with nivolumab are shown in Table 1. Overall, 69, 66, 33, 13, 9 and 9 patients were treated with sunitinib, axitinib, pazopanib, sorafenib, temsirolimus and everolimus, respectively, prior to nivolumab treatment. Among them, 66 (60%) patients had received 2 or more agents of molecular-targeted therapy. In total, 60 irAE were observed. Among them 21, 21, 14 and 2 were of grade 1, 2, 3 and 4, respectively. Two irAE were not evaluated by the Common Terminology Criteria for Adverse Events v4.0. In terms of number of therapies, 25, 24 and 11 irAE were identified in groups of 1, 2 and 3 or more numbers of prior lines of therapy, respectively (Table 2).

3.2. Candidates as risk factors of immune-related adverse events of nivolumab

Despite the lack of clear evidence, it is thought likely that later-line chemotherapy would increase the incidence of adverse events. To analyze whether the number of prior lines of therapy affects grade or incidence of irAE by nivolumab, proportional odds logistic regression analysis was performed. The adjusted odds ratios for grade of irAE were not significantly increased in the patients receiving 2 and 3 or more prior targeted therapies (Table 3). There was also no significant difference in the incidence of irAE for the other covariates (data not shown). The probabilities in each group were not significant. To analyze whether the duration of nivolumab treatment increases irAE incidence, we performed logistic regression analysis that included the number of nivolumab courses as an explanatory variable.

Table 1**Clinical characteristics of the patients.**

No. of prior therapies	1 (N=44)	2 (N=48)	≥3 (N=18)	Total (N=110)
Age (yr), median (IQR)	69.5 (63.75, 76.00)	72.0 (63.00, 79.00)	68.0 (64.25, 74.50)	69.5 (63.25, 76.00)
Sex (men), n (%)	38 (86.4%)	34 (70.8%)	12 (66.7%)	84 (76.4%)
BMI (kg/m ²), median (IQR)	21.1 (19.58, 24.00)	21.4 (20.00, 23.35)	20.9 (19.68, 22.77)	21.2 (19.68, 23.48)
KPS (<80%), n (%)	11 (25.0%)	14 (29.2%)	10 (55.6%)	35 (31.8%)
Lymphocytes (/ μ l), median (IQR)	1189.0 (889.00, 1508.00)	1180.5 (960.00, 1636.50)	1109.0 (880.00, 1580.50)	1175.5 (900.00, 1580.25)
Neutrophils (/ μ l), median (IQR)	3250.0 (2600.00, 4166.25)	4255.0 (3000.00, 4958.50)	3659.0 (2637.50, 4550.00)	3700.0 (2792.50, 4752.50)
CRP (mg/dl), median (IQR)	0.37 (0.17, 2.41)	0.74 (0.21, 2.52)	0.38 (0.16, 2.26)	0.47 (0.20, 2.43)
No. of courses	10.5 (5.50, 17.50)	13.5 (8.00, 23.50)	8.5 (2.75, 27.25)	12.0 (6.00, 21.75)
Best overall response, n (%)				
CR	2 (4.7%)	1 (2.2%)	0 (0.0%)	3 (2.8%)
PR	13 (30.2%)	20 (43.5%)	6 (33.3%)	39 (36.4%)
SD	18 (41.9%)	15 (32.6%)	5 (27.8%)	38 (35.5%)
PD	10 (23.3%)	10 (21.7%)	7 (38.9%)	27 (25.2%)

BMI = body mass index, CR = complete response, CRP = C-reactive protein, KPS = Karnofsky Performance Status, PD = progressive disease, PR = partial response, SD = stable disease.

There was no significant difference in the incidences of irAE by any variable. The predicted probability tended to decrease with the number of nivolumab treatments undergone (Table 4; Fig. 1).

3.3. irAE and tumor response

The association of irAE-incidence and the efficacy of nivolumab in several cancers had been reported. To assess whether irAE incidence correlates with tumor response, we performed logistic regression analysis. This secondary analysis showed no significant difference in tumor response (Table 5).

4. Discussion

Motzer et al first reported the efficacy of nivolumab for advanced or metastatic RCC after antiangiogenic therapy administered as mostly second-line therapy (72%).^[1] Recently, nivolumab has been widely used as third- or later-line therapy for advance or

metastatic RCC. Indeed, De Giorgi et al reported that 79.3% of RCC patients had received 2 or more systemic therapies prior to nivolumab.^[5] Ishihara et al also reported that 37.3% of patients had received nivolumab treatment as third- and later-line therapy.^[6] In the present study, 66 (60%) patients received more than 2 treatment regimens before nivolumab. This result was similar to those of previous reports.^[8]

Therapy with nivolumab for advanced RCC was approved in 2016 in Japan. Before nivolumab, 6 agents for targeted therapy (axitinib, sunitinib, sorafenib, pazopanib, everolimus and temsirolimus) had been approved, and thus, patients with advanced RCC frequently undergo multiple therapies during their clinical course in an attempt to achieve better clinical outcomes. In terms of irAE, Postow et al reported that any organ system can be affected by immune checkpoint inhibitors, and the wide range of potential events requires collaborative management by each specialist.^[4] Serious and fatal adverse events due to nivolumab were also reported; therefore, pre-evaluation of the incidence rate and grade of irAE in prior therapy was thought to be useful.^[7] However, because no data on the relation of irAE and the number of prior lines of therapy was available, we performed this analysis to assess the relation of prior molecular-targeted therapy numbers and irAE grade of nivolumab in a real-world setting. The incidence rates of irAE and involved organs in the

Table 2**Incidence of irAE by number of prior therapies.**

No. of prior therapies, n (%)	1 (N=44)	2 (N=48)	≥3 (N=18)	Total (N=110)
Total events	25 (56.8)	24 (50.0)	11 (61.1)	60 (54.5)
Pruritus/rash/skin disorders	6 (13.6)	4 (8.3)	0	10 (9.1)
Hyperthyroidism/hypothyroidism	5 (11.4)	3 (6.3)	0	8 (7.3)
Fatigue	3 (6.8)	1 (2.1)	1 (5.5)	5 (4.5)
Pulmonary fibrosis	2 (4.5)	3 (6.3)	1 (5.5)	6 (5.5)
Diarrhea	2 (4.5)	2 (4.2)	1 (5.5)	5 (4.5)
Hypoxia/dyspnea	1 (2.3)	1 (2.1)	2 (11.1)	4 (3.6)
Hepatobiliary disorders	1 (2.3)	1 (2.1)	1 (5.5)	3 (2.7)
Adrenal insufficiency	1 (2.3)	1 (2.1)	0	2 (1.8)
Anemia	1 (2.3)	1 (2.1)	0	2 (1.8)
Endocrine disorders	1 (2.3)	1 (2.1)	0	2 (1.8)
Nausea	1 (2.3)	0	1 (5.5)	2 (1.8)
Dysgeusia	1 (2.3)	0	0	1 (0.9)
Renal disorders	0	3 (6.3)	2 (11.1)	(3.6)
Pleural effusion	0	1 (2.1)	1 (5.5)	2 (1.8)
Arthritis	0	1 (2.1)	0	1 (0.9)
Glucose intolerance	0	1 (2.1)	0	1 (0.9)
Infections	0	0	1 (5.5)	1 (0.9)
Pain	0	0	1 (5.5)	1 (0.9)

irAE = immune-related adverse events.

Table 3**Proportional odds logistic regression with adjusted odds ratios for grade of irAE in RCC patients.**

Variable	Q1	Q3	OR	95% LCL	95% UCL	P value
Prior therapy, 2:1	–	–	1.12	0.6	2.1	.72
Prior therapy, >3:1	–	–	1.31	0.63	2.69	.47
Age	63	76	1.24	0.79	1.94	.35
Male	–	–	2.01	0.9	4.5	.09
BMI	19.75	23.55	0.98	0.66	1.47	.93
KPS <80%	–	–	1.53	0.75	3.12	.25
Lymphocytes	898	1548	0.84	0.6	1.19	.33
Neutrophils	2790	4700	0.96	0.72	1.28	.77
CRP	0.2	2.41	0.94	0.76	1.17	.59

BMI = body mass index, CRP = C-reactive protein, irAE = immune-related adverse event, KPS = Karnofsky Performance Status, LCL = lower confidence limit, OR = odds ratio for incidence of irAE obtained from proportional odds logistic regression model, Q1 = 25th percentile of variable, Q3 = 75th percentile of variable, RCC = renal cell carcinoma, UCL = upper confidence limit.

Table 4**Logistic regression with odds ratios for the incidence of irAE by number of courses and covariates.**

Variable	Q1	Q3	OR	95% LCL	95% UCL	P value
No. of courses	6	21	0.73	0.52	1.03	.07
Age	63	76	1.31	0.82	2.09	.26
Male	–	–	1.87	0.83	4.19	.13
BMI	19.75	23.55	1.03	0.67	1.56	.91
KPS <80%	–	–	1.24	0.59	2.58	.57
Lymphocytes	898	1548	0.94	0.66	1.32	.71
Neutrophils	2790	4700	0.9	0.68	1.21	.50
CRP	0.2	2.41	0.94	0.76	1.16	.56

BMI = body mass index, CRP = C-reactive protein, irAE = immune-related adverse event, KPS = Karnofsky Performance Status, LCL = lower confidence limit, OR = odds ratio for incidence of irAE obtained from logistic regression model, Q1 = 25th percentile of variable, Q3 = 75th percentile of variable, UCL = upper confidence limit.

present study were also comparable with those of previous reports.^[5,6] To analyze adjusted odds ratios for the grade of irAE and the number of prior lines of therapy, we used number of lymphocytes, which are thought to be functionally affected by nivolumab, in addition to general or other previously known prognostic factors for RCC. The analysis also showed no significant relation between grade of irAE and the number of prior lines of therapy. This result does not suggest, however, that there were no differences in grade between 1, 2 and 3 or more treatments prior to nivolumab; hence, all patients should be equally well monitored in all groups at any rate. In other words, nivolumab could be considered as a third- or later-line therapy similar to second-line therapy from the perspective of the consistency of the grade of irAE. According to recent articles, no significant differences in the incidences of irAE of both any grade and higher-grade (\geq grade 3) on second- and later-line treatment in RCC patients were found, and this is consistent with our

results.^[6] However, a meta-analysis of irAE of PD-1/PD-L1 inhibitor monotherapy in non-small cell lung cancer patients showed an increased incidence of both any-grade irAE and higher-grade irAE in first-line therapy compared to subsequent therapy.^[17] A decrease in irAE could be explained by more patients being treated with later-line therapy having a suppressed or compromised immune system due to increased tumor burden and prior treatment.^[18] This difference may be apparent when comparing first-line and later-line but not second-line and later-line therapies. Nevertheless, further analysis for irAE profiling of patients who are treated with nivolumab as later-line therapy will be needed in the era of immune checkpoint inhibitors. Although the grade of irAE in each group was not different, profiling of irAE in each group may indicate some differences (e.g., disorders of the skin and thyroid were not seen in the group with 3 or more prior lines of therapy). Hypothyroidism and hand-foot syndrome were reported as representative adverse events of tyrosine kinase in RCC.^[19] Patients in the later-line group may be well treated for or tolerate those adverse events, and hence, the incidence rate of some irAE tended to decrease in the group receiving later-line therapy.

Okada et al reported that IrAE occurred after a median of 4 cycles of nivolumab treatment in patients with melanoma.^[20] To investigate whether the duration of nivolumab therapy increases the incidence of irAE, we next analyzed odds ratios for the incidence of irAE and courses of nivolumab treatment, and no significant result was found. However, the incidence rate tended

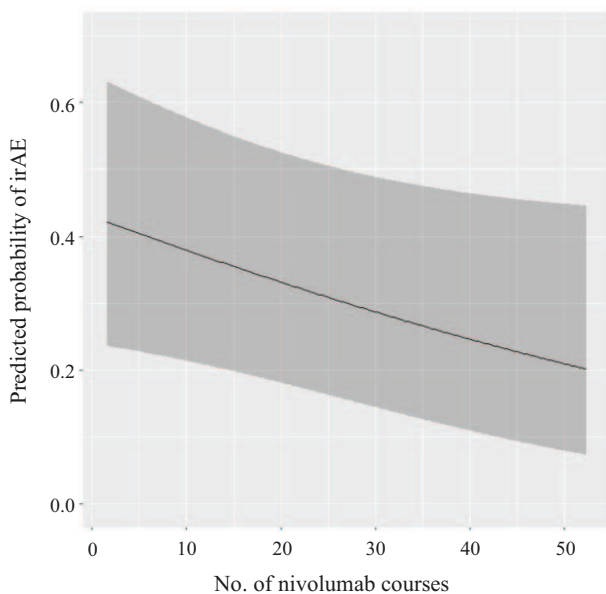


Figure 1. Association between irAE and number of nivolumab treatment courses. The probability of irAE was predicted by a logistic regression model adjusted for age, sex, number of lymphocytes, Karnofsky Performance Status, BMI, number of neutrophils and CRP. The solid line indicates the mean, and the gray area indicates the 95% confidence interval for each number of nivolumab courses.

Table 5**Logistic regression with odds ratios for the incidence of irAE by best overall response and covariates.**

Variable	Q1	Q3	OR	95% LCL	95% UCL	P value
Response, PD:CR	–	–	0.85	0.39	1.85	.68
Response, PR:CR	–	–	1.1	0.51	2.4	.81
Response, SD:CR	–	–	0.89	0.4	1.97	.78
Age	63	76	1.22	0.77	1.94	.44
Male	–	–	1.86	0.84	4.13	.06
BMI	19.75	23.55	1.06	0.7	1.6	.59
KPS <80%	–	–	1.32	0.64	2.72	.30
Lymphocytes	898	1548	0.89	0.64	1.25	.45
Neutrophils	2790	4700	0.91	0.69	1.22	.39
CRP	0.2	2.41	0.94	0.77	1.17	.74

BMI = body mass index, CR = complete response, CRP = C-reactive protein, KPS = Karnofsky Performance Status, LCL = lower confidence limit, OR = odds ratio for the incidence of irAE obtained from logistic regression model, PD = progressive disease, PR = partial response, Q1 = 25th percentile of variable, Q3 = 75th percentile of variable, SD = stable disease, UCL = upper confidence limit.

to decrease with the increasing number of nivolumab courses. A possible explanation for this result is that patients with irAE that were well managed or who were without irAE were capable of undergoing nivolumab treatment for a long period. Another explanation is that irAE may occur in the early phase of the treatment period. The onset time of irAE varies among different organs, and they mostly occur within less than 14 weeks except for adrenal insufficiency, hypopituitarism, type 1 diabetes mellitus and nephritis.^[18,21] These prior research may explain our result.

Several researchers reported the onset of irAE as a potential clinical biomarker for immune checkpoint inhibitor response.^[12,22,23] In the present study, a multivariable model using covariant factors produced no significant results in the relation between irAE and best overall response. In RCC, it was reported that the incidence of irAE was associated with prolonged overall survival.^[8] We did not collect data on the date of irAE onset, and thus the association of irAE with overall survival could not be analyzed to avoid lead-in time bias.^[24] As the incidence of irAE cannot be known before nivolumab is administered, it therefore cannot be a predictive factor. Further research into the relation between onset timing for irAE and the efficacy of immune checkpoint inhibitors including nivolumab is anticipated.

Our study has several limitations. First, the sample size was relatively small and may not have enough power to show statistical significance. However, this does not mean that there were no differences between the 3 groups. Second, all data were collected retrospectively, which might lead to information bias. The data on irAE and the response to nivolumab were recorded by each physician. This might cause wide variance in the diagnosis of irAE and best tumor response because of the retrospective nature of the study, but this is inherent in retrospective studies. Despite the foregoing limitations, we believe that our results show the possibility for a consistent incidence rate of irAE regardless of the numbers of prior treatments undergone by the patients.

In conclusion, although no significant results were found in the present study, the number of patients treated with nivolumab is increasing; therefore the data in this study should be assessed in terms of other studies conducted with a larger sample size. Nevertheless, the present study showed the possibility of irAE of nivolumab not increasing after third-line therapy in RCC patients, and this result suggests that nivolumab may be tolerated even though administered as later-line therapy. Nivolumab administered as or after third-line therapy for RCC patients may be considered safe similar to second-line therapy as long as the patients are monitored closely for irAE.

Author contributions

KM wrote the manuscript; TY, RS, HM and TK helped in its conception and design; KM, TIt, KT and RA collected and assembled the data; TIs analyzed the data as a biostatistician; and all authors read and approval the final manuscript.

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