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ORIGINAL ARTICLE

Clinical outcomes of second-line treatment following prior targeted therapy in patients with metastatic renal cell carcinoma: a comparison of axitinib and nivolumab

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Abstract

Background Sequential treatment starting with target therapy is still the standard care for metastatic renal cell carcinoma (mRCC), even in the era of immune checkpoint inhibitors. Our objective was to compare the clinical outcomes between axitinib and nivolumab as second-line therapy following prior targeted therapy in mRCC patients.

Methods We identified 41 patients treated with axitinib and 39 patients treated with nivolumab as a second-line regimen after targeted therapy, and retrospectively compared the treatment efficacy and safety in these patients.

Results The clinical benefit rate of axitinib was significantly higher than that of nivolumab (82.9% versus 56.4%; $p=0.014$) and patients who received axitinib tended to show longer progression-free survival (PFS) than those who received nivolumab (10.3 months versus 7.3 months; $p=0.067$). There was no difference in the overall survival (OS) of the two groups (both not reached; $p=0.581$). The incidence of grade ≥ 3 adverse events (AEs) was similar between the two groups, but one patient in the nivolumab group died due to an immune-related AE. In addition, a Cox proportional hazards model showed that the pre-treatment KPS, the baseline neutrophil-to-lymphocyte ratio (NLR), and an objective response in second-line therapy were significantly associated with PFS, while the pre-treatment KPS, the number of metastatic organs, and an objective response in second-line therapy significantly contributed to the predicted OS.

Conclusions Although the prognosis did not differ markedly between the two groups, axitinib resulted in a better tumor response rate. Further randomized prospective studies are needed for the ideal order of this sequential treatment.

Keywords Axitinib · Nivolumab · Metastatic renal cell carcinoma · Targeted therapy · Second-line therapy

Introduction

The prognosis of metastatic renal cell carcinoma (mRCC) has significantly improved with the development and widespread use of molecular targeted agents, including vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target of rapamycin (mTOR) pathway inhibitors [1, 2], and the sequential use of these agents has been the standard care for mRCC for the past decade. Axitinib, a VEGF receptor (VEGFR) targeted agent, has been approved as a second-line treatment after targeted therapy, since its clinical benefit was demonstrated in a randomized clinical study [3].

Recently, with the advent of immune checkpoint inhibitors (ICIs), the treatment strategy for mRCC has undergone further dramatic changes. Nivolumab, an anti-programmed death-1 (PD-1) monoclonal antibody that was shown to have a survival advantage in a randomized clinical trial, was also recommended as a subsequent therapy in patients previously treated with molecular targeted agent [4]. Furthermore, ICIs have been becoming a mainstay treatment for mRCC, even as first-line therapy [5]. However, conventional sequential therapy that starts with a targeted agent (e.g., sunitinib or pazopanib) is also categorized as recommended therapy [5]. Therefore, it is still important to identify the optimum drug to administer after targeted therapy.

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In addition to axitinib and nivolumab, cabozantinib, a novel VEGFR inhibitor that also targets MET and AXL, has been the preferred second-line therapy regimen [5, 6]. However, cabozantinib is only approved in limited areas, in which Japan is not included. Thus, a comparison of axitinib and nivolumab may still be of interest in clinical practice. Although a previous study using network meta-analysis model showed that nivolumab might be associated with more favorable outcomes than axitinib [7], there have been no randomized studies to directly compare the clinical efficacy of these two agents. Thus, it is unknown whether axitinib or nivolumab is better as a second-line regimen after targeted therapy.

In the present study, we retrospectively compared the clinical outcomes of patients who received axitinib or nivolumab as second-line treatment in sequential therapy following treatment with a targeted agent in a real-world setting.

Materials and methods

Patients

Patients with metastatic or unresectable RCC who had been treated with axitinib or nivolumab after receiving treatment with a molecular-targeted agent (sunitinib, pazopanib, sorafenib or temsirolimus) at Kobe University Hospital in Japan between August 2016 (the date on which nivolumab was approved in Japan) and June 2019 were included in this study. The study design was approved by the Research Ethics Committee of our institution (No. B190285), and was conducted in accordance with the Declaration of Helsinki.

Treatments and procedures

As a second-line therapy for metastatic or unresectable RCC, axitinib was administered orally in 4-week cycles at a dose of 10 mg per day, while nivolumab was administered by intravenous infusion at a dose of 3 mg/kg or 240 mg/body every 2 weeks. Both agents were administered until disease progression, unacceptable adverse events, withdrawal or death. Dose modification was permitted for both agents. We retrospectively collected the following data from the medical records of patients: patient demographics, histology, Karnofsky performance status (KPS), blood test results and adverse events (AEs). Patients were classified into favorable-, intermediate- and poor-risk groups according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification [8]. The neutrophil-to-lymphocyte ratio (NLR) was derived from the absolute neutrophil and lymphocyte counts in a full blood count at the induction of second-line therapy. In the present study, we used an NLR of 3 as the threshold value based on a previous systematic review that showed its clinical utility in predicting patient outcomes for various types of cancer [9]. Lactate dehydrogenase (LDH) elevation was defined as a value of > 222 U/L, which is considered to be the upper limit of normal in our hospital. The treatment response to axitinib or nivolumab was evaluated by computed tomography (CT) at least once every 12 weeks, and was classified according to the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1. The objective response rate (ORR) was defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) among all treated patients, while the clinical benefit rate was defined as the percentage of patients with confirmed CR, PR or stable disease (SD) among all treated patients.

Statistical analyses

The patients' characteristics were compared between the axitinib group and nivolumab group using a two-sample Student's *t* test and Fisher's exact test, as appropriate. We assessed the ORR, clinical benefit rate, progression-free survival (PFS), overall survival (OS) and the incidence of AEs of the axitinib and nivolumab treatment groups. Fisher's exact test was used to compare the ORR, clinical benefit rate and the incidence of AEs between two groups. The PFS and OS were estimated using the Kaplan–Meier method, and we assessed the predictive impact of several potential factors on PFS and OS in patients receiving second-line therapy using a Cox proportional hazards model. Variables with a $p < 0.05$ in the univariate analysis were used for creation of the multivariate model.

EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for all statistical analyses [10]. EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria); specifically, it is a modified version of R commander designed to add the statistical functions frequently used in biostatistics. Each test was two-sided, and p values of < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

In the present study, 80 patients with metastatic or unresectable RCC were identified (axitinib group, $n = 41$; nivolumab group, $n = 39$). The clinical characteristics of these patients are summarized in Table 1. The median observation periods of each group were 15.0 months and 12.1 months, respectively ($p = 0.205$). There were no significant differences in the pre-treatment characteristics,

Table 1 Patient and tumor characteristics

	Axitinib ($n=41$)	Nivolumab ($n=39$)	p value
Periods of observation, median (range), months	15.0 (1.5–39.2)	12.1 (0.4–33.6)	0.205
Age at the induction of second-line therapy, median (range), years	70 (46–88)	67 (39–87)	0.092
Sex, *n* (%)			0.597
Male	33 (80.5)	29 (74.4)	
Female	8 (19.5)	10 (25.6)	
Karnofsky performance status, *n* (%)			0.314
< 80%	13 (31.7)	8 (20.5)	
≥ 80%	28 (68.3)	31 (79.5)	
Prior nephrectomy, *n* (%)			0.757
Yes	34 (82.9)	34 (87.2)	
No	7 (17.1)	5 (12.8)	
Histology, *n* (%)			0.418
Clear cell	34 (82.9)	29 (74.4)	
Other or unknown	7 (17.1)	10 (25.6)	
IMDC classification at the induction of second-line therapy, *n* (%)			1.000
Favorable	3 (7.3)	2 (5.1)	
Intermediate	24 (58.5)	23 (59.0)	
Poor	14 (34.2)	14 (35.9)	
Number of metastatic organ, *n* (%)			1.000
Lymph node only	2 (4.9)	2 (5.1)	
1	21 (51.2)	19 (48.7)	
≥ 2	18 (43.9)	18 (46.2)	
First-line targeted therapy, *n* (%)			0.676
Sunitinib	18 (43.9)	20 (51.3)	
Pazopanib	19 (46.3)	18 (46.1)	
Sorafenib	2 (4.9)	1 (2.6)	
Temsirolimus	2 (4.9)	0 (0.0)	
PFS of first-line treatment, median (95% CI), months	12.7 (6.2–45.1)	13.3 (7.1–16.9)	0.283
Objective response in first-line therapy, *n* (%)			0.817
Yes	14 (34.1)	15 (38.5)	
No	27 (65.9)	24 (61.5)	
Discontinuation of first-line therapy due to AE, *n* (%)			0.070
Yes	20 (48.8)	11 (28.2)	
No	21 (51.2)	28 (71.8)	
NLR at the induction of second-line therapy, median (range)	2.5 (0.6–6.4)	3.0 (1.0–10.0)	0.103
CRP at the induction of second-line therapy, median (range), mg/dL	0.32 (0.02–10.24)	0.42 (0.01–19.96)	0.448
Elevated LDH at the induction of second-line therapy, *n* (%)			0.350
Yes	16 (39.0)	11 (28.2)	
No	25 (61.0)	28 (71.8)	

IMDC International Metastatic Renal Cell Carcinoma Database Consortium; *PFS* progression-free survival; *CI* confidence interval; *AE* adverse event; *NLR* neutrophil-to-lymphocyte ratio; *CRP* C-reactive protein; *LDH* lactate dehydrogenase

including KPS, history of prior nephrectomy, IMDC classification, drug of first-line targeted therapy, treatment outcomes of first-line therapy, or the parameters of systemic inflammation.

The treatment response and survival outcomes

The ORRs in the axitinib and nivolumab groups were 36.6% and 23.1%, respectively (odds ratio: 1.91, 95% CI 0.65–5.84;

Table 2 Treatment response in second-line therapy

	Axitinib ($n=41$)	Nivolumab ($n=39$)	p value
Objective response, n (%)	15 (36.6)	9 (23.1)	0.227
Clinical benefit, n (%)	34 (82.9)	22 (56.4)	0.014
Best response, n (%)			
CR	1 (2.4)	0 (0.0)	
PR	14 (34.1)	9 (23.1)	
SD	19 (46.3)	13 (33.3)	
PD	5 (12.2)	15 (38.5)	
Not evaluated	2 (4.9)	2 (5.1)	

CR complete response; *PR* partial response; *SD* stable disease; *PD* progressive disease

$p=0.227$), while the clinical benefit rates were 82.9% and 56.4%, respectively (odds ratio: 3.69, 95% CI 1.21–12.4; $p=0.014$) (Table 2).

As shown in Fig. 1a, the median PFS of patients treated with axitinib [10.3 months, 95% confidence interval (CI): 7.4 to not reached] tended to be longer than that in patients treated with nivolumab (7.3 months, 95% CI: 3.0–12.4); however, the difference was not statistically significant ($p=0.067$). The treatment effect of axitinib on PFS was consistently favorable (hazard ratio, < 1.0) across almost all prespecified subgroups (Fig. 2). In addition, there was no difference in OS between the two groups. In both groups, the median overall survival was not reached ($p=0.581$) (Fig. 1b).

At the end of the observation period, the numbers of patients receiving second-line therapy in the axitinib and nivolumab groups were 15 (36.6%) and 7 (17.9%), respectively. While 23 (56.1%) patients in the axitinib group (nivolumab: 21, pazopanib: 1 and everolimus: 1) and 20 (51.3%) patients in the nivolumab group (axitinib: 16, temsirolimus: 2, sunitinib: 1 and everolimus: 1) received third-line treatment, 1 (2.4%) patient in the axitinib group and 5 (12.8%) in the nivolumab group could not switch from second- to third-line therapy due to uncontrollable disease.

Next, we evaluated the association between the clinical characteristics and PFS. As shown in Table 3, male sex, pre-treatment KPS ≥ 80%, baseline NLR ≥ 3 and an objective response to second-line therapy were significantly associated with the PFS, with hazard ratios (HRs) of 0.38 (95% CI 0.18–0.82; $p=0.014$), 0.27 (95% CI 0.13–0.56; $p<0.001$), 2.19 (95% CI 1.10–4.36; $p=0.025$) and 0.09 (95% CI 0.03–0.27; $p<0.001$), respectively.

In the analysis of the relationship between the clinical characteristics and OS (Table 4), pre-treatment KPS ≥ 80%, > 2 metastatic organs and an objective response in second-line therapy were found to significantly contribute to predicted OS, with HRs of 0.04 (95% CI 0.01–0.15; $p<0.001$), 3.97 (95% CI 1.38–11.5; $p=0.011$) and 0.09 (95% CI 0.02–0.49; $p=0.005$), respectively. The type of the first-line agent and treatment outcomes of first-line treatment did not have a significant impact on either PFS or OS.

Safety

Treatment-related adverse events (AEs) are shown in Table 5. While AEs of any grade occurred more frequently in patients treated with axitinib than in those treated with nivolumab (90.2% and 56.4%, respectively; $p<0.001$), the two groups showed a similar incidence of grade ≥ 3

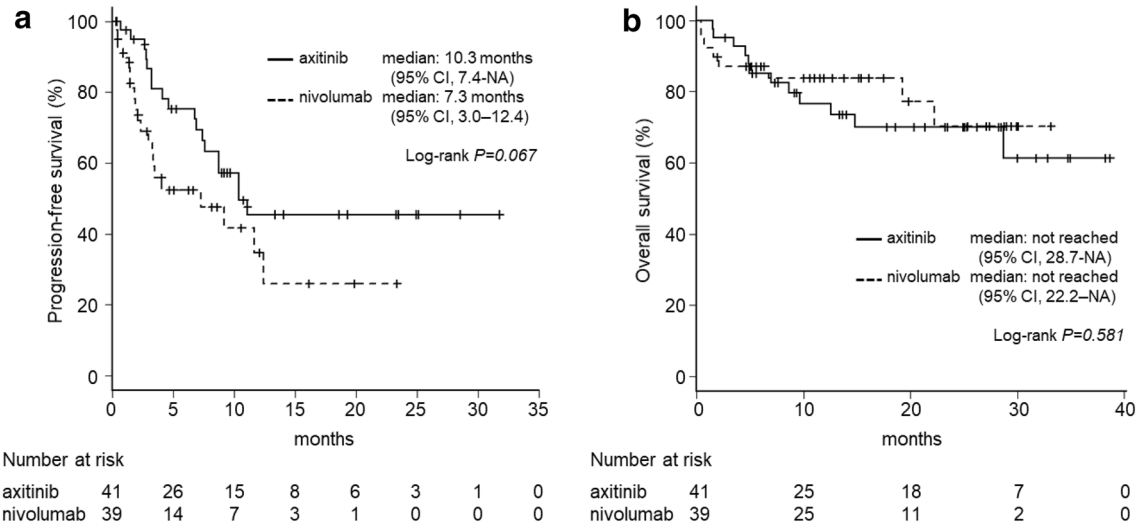

Fig. 1 Kaplan–Meier estimates of (**a**) the progression-free survival and (**b**) overall survival among mRCC patients treated with axitinib or nivolumab

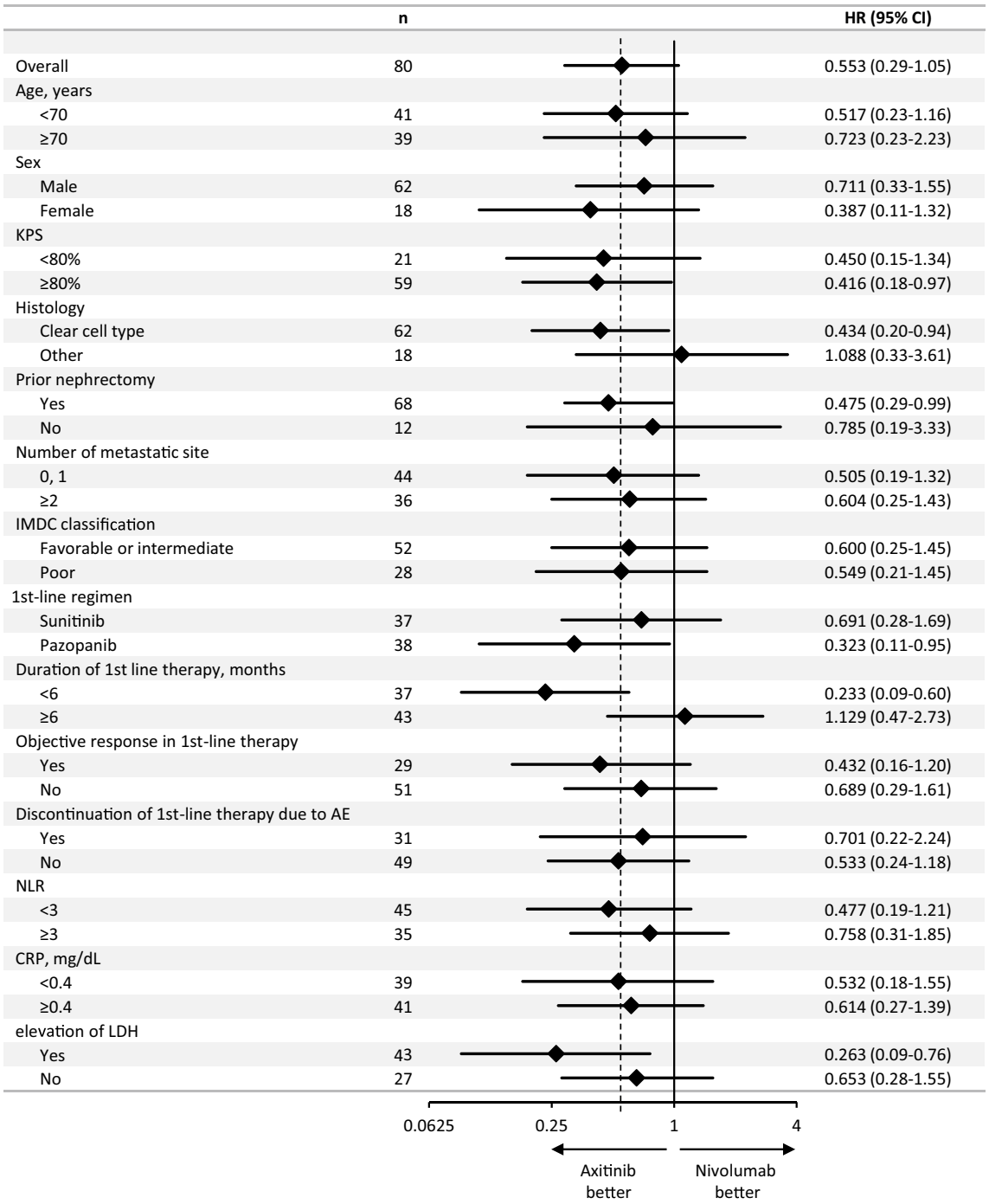

Fig. 2 Subgroup analysis of progression-free survival among mRCC patients with axitinib or nivolumab. *KPS* Karnofsky performance status, *IMDC* the International Metastatic Renal Cell Carcinoma Database Consortium, *NLR* neutrophil-to-lymphocyte ratio, *CRP* C-reactive protein, *LDH* lactate dehydrogenase

AEs. Although in almost all cases patients safely recovered from AEs, one patient in the nivolumab group died from pneumothorax due to interstitial pneumonia as an immune-related AE (irAE). Notably, all patients with nivolumab-induced adrenal insufficiency showed an objective response, and three of these patients kept the best response after the discontinuation of nivolumab with a median observation period of 14.6 months from the onset of the irAE. In addition, there was no significant difference in the rate of discontinuation due to AEs between the

Table 3 Univariate and multivariate analyses of factors associated with progression-free survival during second-line therapy

	Univariate		Multivariate	
$n=80$	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age, years (≥ 70 vs. < 70)	0.60 (0.31–1.17)	0.134	–	–
Sex (male vs. female)	0.33 (0.16–0.68)	0.003	0.38 (0.18–0.82)	0.014
Karnofsky performance status (≥ 80% vs. < 80%)	0.31 (0.16–0.59)	< 0.001	0.27 (0.13–0.56)	< 0.001
Prior nephrectomy (yes vs. no)	0.58 (0.26–1.26)	0.165	–	–
Histology (clear cell vs. others)	1.59 (0.79–3.20)	0.198	–	–
IMDC classification at the induction of second-line therapy (poor vs. favorable/intermediate)	2.84 (1.48–5.47)	0.002	1.22 (0.47–3.16)	0.683
Number of metastatic organs (≥ 2 vs. 0, 1)	1.73 (0.91–3.28)	0.094	–	–
First-line targeted therapy (sunitinib vs. pazopanib)	1.36 (0.69–2.65)	0.372	–	–
PFS in first-line treatment (≥ 1 year vs. < 1 year)	0.66 (0.33–1.33)	0.245	–	–
Objective response in first-line therapy (yes vs. no)	0.71 (0.36–1.40)	0.321	–	–
Discontinuation of first-line therapy due to AE (yes vs. no)	0.57 (0.29–1.14)	0.110	–	–
NLR at the induction of second-line therapy (≥ 3 vs. < 3)	2.17 (1.14–4.11)	0.018	2.19 (1.10–4.36)	0.025
Elevated LDH at the induction of second-line therapy (yes vs. no)	2.50 (1.31–4.80)	0.006	1.95 (0.93–4.09)	0.076
Second-line regimen (axitinib vs. nivolumab)	0.55 (0.29–1.05)	0.071	–	–
Objective response in second-line therapy (yes vs. no)	0.16 (0.04–0.33)	< 0.001	0.09 (0.03–0.27)	< 0.001

IMDC International Metastatic Renal Cell Carcinoma Database Consortium; *PFS* progression-free survival; *AE* adverse event; *NLR* neutrophil-to-lymphocyte ratio; *LDH* lactate dehydrogenase; *CI* confidence interval

Table 4 Univariate and multivariate analyses of factors associated with overall survival during second-line therapy

	Univariate		Multivariate	
$n=80$	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age, years (≥ 70 vs. < 70)	0.87 (0.36–2.12)	0.767	–	–
Sex (male vs. female)	0.61 (0.23–1.58)	0.305	–	–
Karnofsky performance status (≥ 80% vs. < 80%)	0.07 (0.02–0.19)	< 0.001	0.04 (0.01–0.15)	< 0.001
Prior nephrectomy (yes vs. no)	0.38 (0.14–1.04)	0.061	–	–
Histology (clear cell vs. others)	2.25 (0.89–5.66)	0.084	–	–
IMDC classification at the induction of second-line therapy (poor vs. favorable/intermediate)	8.55 (3.07–23.7)	< 0.001	1.96 (0.59–6.56)	0.275
Number of metastatic organs (≥ 2 vs. 0, 1)	4.01 (1.46–11.1)	0.007	3.97 (1.38–11.5)	0.011
First-line targeted therapy (sunitinib vs. pazopanib)	1.33 (0.51–3.45)	0.557	–	–
PFS in first-line treatment (≥ 1 year vs. < 1 year)	0.61 (0.24–1.60)	0.320	–	–
Objective response in fist-line therapy (yes vs. no)	0.37 (0.12–1.10)	0.074	–	–
Discontinuation of fist-line therapy due to AE (yes vs. no)	0.23 (0.07–0.79)	0.019	0.29 (0.08–1.04)	0.057
NLR at the induction of second-line therapy (≥ 3 vs. < 3)	5.15 (1.86–14.3)	0.002	1.80 (0.52–6.26)	0.358
Elevated LDH at the induction of second-line therapy (yes vs. no)	3.45 (1.40–8.50)	0.007	0.69 (0.21–2.32)	0.552
Second-line regimen (axitinib vs. nivolumab)	1.29 (0.53–3.15)	0.582	–	–
Objective response in second-line therapy (yes vs. no)	0.21 (0.05–0.92)	0.038	0.09 (0.02–0.49)	0.005

IMDC International Metastatic Renal Cell Carcinoma Database Consortium; *PFS* progression-free survival; *AE* adverse event; *NLR* neutrophil-to-lymphocyte ratio; *LDH* lactate dehydrogenase; *CI* confidence interval

axitinib and nivolumab groups (17.1% and 25.6%, respectively; $p=0.418$). However, in the nivolumab group, six (15.4%) patients did not re-start any systemic therapy after discontinuation of second-line treatment due to irAE.

Table 5 Adverse events of second-line treatment

n (%)	Axitinib (*n* = 41)	Nivolumab (*n* = 39)	*p* value
Any grade	37 (90.2)	22 (56.4)	< 0.001
Grade 3 or 4	16 (39.0)	12 (30.8)	0.488
Grade ≥ 3			
Axitinib			
Hand–foot syndrome	5 (12.1)		
Fatigue	4 (9.8)		
Diarrhea	3 (7.3)		
Renal dysfunction	3 (7.3)		
Hypertension	2 (4.9)		
Proteinuria	2 (4.9)		
Thrombopenia	1 (2.4)		
Adrenal dysfunction	1 (2.4)		
Intestinal necrosis	1 (2.4)		
Nivolumab			
Adrenal dysfunction	4 (10.3)		
Diarrhea	2 (5.1)		
Interstitial pneumonia	2 (5.1)		
Polymyositis	1 (2.6)		
Pruritus	1 (2.6)		
Hyperthyroidism	1 (2.6)		
Gastrointestinal bleeding	1 (2.6)		
Discontinuation of the second-line therapy due to AEs	7 (17.1)	10 (25.6)	0.418

AEs adverse events

Discussion

In the present study, we retrospectively compared the clinical outcomes of mRCC patients who received axitinib or nivolumab after treatment with one targeted therapy, and showed that axitinib demonstrated a more favorable disease control than nivolumab. To our knowledge, this is the first direct comparison of these two agents.

Recently, the mainstay of sequential therapy for mRCC has been shifting from targeted drugs to ICIs. In the randomized clinical trial setting, the combinations of ICIs or ICI plus targeted therapy have been shown to have a survival advantage in comparison to sunitinib, which has been the standard of care in first-line treatment for previously untreated advanced RCC for the past decade [11–13]. According to these data, ICI-based regimens have been most recommended as first-line therapy for these patients in the recent guidelines for RCC [5].

However, while AEs due to targeted therapy are generally non-serious and manageable by treatment interruption or dose reduction [14], ICI-based therapy is often associated with the development of high-grade and irreversible irAEs [15]. In addition, ICI-based therapy generally needs higher cost than targeted agents [16]. Therefore sequential therapy starting with a conventional targeted therapy has still been widely selected in clinical practice, and this has also been categorized as a recommended regimen [5]. Thus, it is important to identify the optimum regimen to administer after first-line targeted therapy.

In the present study, we showed that axitinib was associated with a favorable tumor response; axitinib was associated with a significantly higher clinical benefit rate than nivolumab. This would probably have resulted in relatively longer PFS of axitinib in comparison to nivolumab. Consistent with these findings, in several previous reports, the clinical benefit rate in patients receiving second-line axitinib was ≥ 70% [17–20], while approximately 50% of patients treated with nivolumab showed a clinical benefit [21, 22]. In addition, in our cases, while five (12.8%) patients in the nivolumab group could not shift from second-line to third-line therapy due to uncontrollable disease, only one (2.4%) patient in the axitinib group could not receive third-line therapy. These findings suggest that patients receiving axitinib treatment may be expected to show greater disease control in comparison to those receiving nivolumab. Based on these findings, in our recent strategy of sequential treatment starting with targeted therapy, we use axitinib but not nivolumab as subsequent therapy for patients with rapid progression after the failure of first-line treatment, expecting the disease to be controlled by axitinib.

One concern is cross-resistance between first-line VEGF inhibitors and subsequent axitinib. Several previous reports have shown that an objective response to first-line treatment with sunitinib was significantly associated with longer OS in patients receiving axitinib as a second-line treatment [18, 19]. In addition, Heng et al. reported that patients with primary refractory disease, in whom PD was the best response, in prior anti-VEGF therapy had significantly poor prognosis in subsequent anti-VEGF therapy [23]. On the other hand, Guida et al. also reported that axitinib showed a comparable efficacy to that of everolimus, an mTOR inhibitor, even in patients who had a poor response to prior targeted therapy [18]. In our subgroup analysis with a shorter response duration of the first-line targeted therapy, the PFS in axitinib was longer than that of nivolumab. In addition, a poor KPS and high NLR, which have been demonstrated as prognostic factors for RCC [24, 25], but not a type of agent, were significantly associated with a poor prognosis for the second-line therapy. These data suggest that poor outcomes of subsequent axitinib treatment in patients with a poor response to first-line targeted therapy may indicate the aggressiveness of the disease rather than cross-resistance, and that a more potent ICI-based regimen may be appropriate as a first-line treatment for these patients. Especially, further studies are called for to identify biomarkers predicting a primary refractory disease to first-line targeted therapy.

The main advantage of nivolumab has been shown to be its durable response. David et al. reported that RCC patients with an objective response to nivolumab showed a median response duration of 12.9 months [26], and a phase II trial of nivolumab for metastatic RCC demonstrated that the median duration of the response in patients with an objective response was not reached in the 2 mg/kg groups and was 22.3 months in the 10 mg/kg group [27]. Interestingly, Osa et al. demonstrated that the prolonged binding of nivolumab on T cells was observed for more than 20 weeks even after the cessation of nivolumab in non-small cell lung cancer patients treated with nivolumab [28]. In the present study, with our limited number of cases and relatively short observation period, there was no significant difference in the duration of the response between the axitinib and nivolumab groups (median duration not reached for both, data not shown). However, in our patients with nivolumab-induced adrenal insufficiency, a partial response was maintained, even after the cessation of nivolumab, for a median duration of 14.6 months.

In addition, the clinical data demonstrating the favorable efficacy of subsequent targeted therapy after ICI-based therapy have recently been accumulated. Auvray et al. reported a clinical benefit rate of 75% and a median PFS of 8.0 months in RCC patients receiving second-line targeted therapy after primary nivolumab plus ipilimumab, an anti CTLA-4 monoclonal antibody [29]. Nadal et al. showed a clinical benefit rate of 79% and a median PFS of 8.4 months in RCC patients treated with VEGFR inhibitor after PD-1 inhibitor [30]. In the present study, the nivolumab group showed comparable OS to the axitinib group, despite the nivolumab group showing shorter PFS, suggesting that third-line and beyond targeted therapy may be more effective in patients treated with nivolumab than in those treated with axitinib.

The present study was associated with several limitations. This was a retrospective study with a relatively small number of patients and short observation period. Of particular note, the OS was not fully evaluated. In addition, our data might have been biased by the reason for the discontinuation of first-line therapy. In our cohort, the patients who received axitinib have been more likely to halt first-line treatment due to AEs rather than disease progression, although the difference did not reach statistical significance. Furthermore, unevaluated confounders and missing values may have affected our findings.

In conclusion, although the prognosis did not differ between the patients who received axitinib or nivolumab as second-line treatment in sequential therapy starting with targeted therapy, the clinical benefit rate in the axitinib group was significantly higher than that in the nivolumab group. In addition to the durable response of nivolumab, the greater disease control by axitinib shown in our study should be considered in the selection of second-line agent. However, the ideal order of this sequential therapy is still unclear and further randomized prospective studies are needed.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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