Therapeutic outcome of combination therapy using immune-checkpoint inhibitors and tyrosine kinase inhibitors for metastatic non-clear-cell renal cell carcinoma

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ABSTRACT

INTRODUCTION: We aimed to clarify the therapeutic outcome of combination therapy using immune-checkpoint inhibitors (ICIs) and/or tyrosine kinase inhibitors (TKIs) for metastatic non-clear-cell renal cell carcinoma (nccRCC).

METHODS: We have been retrospectively investigating the therapeutic efficacy and prognosis in 36 patients with metastatic nccRCC undergoing combination therapy using two ICIs, ipilimumab plus nivolumab (ICI-ICI), and ICI plus TKI (ICI-TKI), at Kobe University and affiliated institutions since 2018. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse event (AE) were compared.

RESULTS: The first-line regimen was ICI-ICI in 26 cases and ICI-TKI in 10 cases. The ORRs in the ICI-ICI and ICI-TKI groups were 34.6 and 30.0%, respectively (p=0.9433). The 50% PFS for the ICI-TKI group was 9.7 months, significantly longer than that for the ICI-ICI group (4.6 months, p=0.0499), and there was no significant difference in OS between groups (p=0.3984). There was no significant difference in the occurrence rate of AE for below grade 2 (p=0.8535), nor above grade 3 (p=0.3786) between the ICI-ICI and ICI-TKI groups.

CONCLUSIONS: From our analysis of real-world data, a better outcome of PFS was expected in the ICI-TKI group compared with that in the ICI-ICI group, while there was no significant difference in OS or ORR.

INTRODUCTION

Non-clear-cell renal cell carcinoma (nccRCC) is a heterogeneous subgroup of RCC, which represents 15–30% of renal tumors,[1] and the prognosis of metastatic nccRCC was reported to be worse compared with that of metastatic ccRCC in the cytokine era.[2] The introduction of molecular targeted agents, including tyrosine kinase inhibitors (TKIs) and immune-checkpoint inhibitors (ICIs), has led to the dramatic change in the treatment of metastatic RCC (mRCC).[3,4] Regimens combining these drugs have been introduced one after another, and the prognosis of patients with mRCC has remarkably improved.

Combination regimens can be broadly classified into two types: regimens combining two ICIs (ipilimumab and nivolumab) (ICI-ICI) and those combining a TKI with ICI (ICI-TKI). Four regimens have been introduced: avelumab+axitinib, pembrolizumab+axitinib, nibolumab+cabozantinib, and pembrolizumab+lenvatinib. While these regimens have been shown to improve treatment efficacy and prognosis by randomized control trials (RCTs) for mRCC with clear-cell histology,[5-9] patients with nccRCC have been excluded from these trials. Therefore, the benefit of various combination regimens for nccRCC remains unclear.

We previously demonstrated the therapeutic efficacy of ICI-ICI therapy as a first-line option for metastatic nccRCC compared with that of TKI monotherapy.[10] The aim of this study

was to evaluate the therapeutic efficacy and survival benefit of combination therapy using ICI-ICI therapy or ICI-TKI therapy and to compare them.

METHODS

Patients

The 38 cases of patients with metastatic nccRCC who were treated with combination regimens consisting of ICIs and/or TKIs as first-line therapy at Kobe University Hospital or an affiliated institute in Hyogo Prefecture in Japan from January 2018 to June 2022 were retrospectively reviewed on the basis of their related clinicopathologic data derived from medical records. Ethical approval was given by the Ethical Committee of Kobe University (autholization number: B230087).

Patients who were treated with ipilimumab+nivolumab, and those treated with avelumab+axitinib, pembrolizumab+axitinib, nibolumab+cabozantinib, and pembrolizumab+lenvatinib were defined as the ICI-ICI group and ICI-TKI group, respectively. Baseline clinical data, including age, sex, pathologic finding, Karnofsky performance status (KPS), metastasis status, choice of first-line regimen, and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)[11] risk were collected by reviewing medical records, and the distribution of these parameters in each group was compared. Treatment outcomes, including objective response (OR) and its rate (ORR) assessed using RECIST 1.1,[12] progression-free survival (PFS), and overall survival (OS) rates, as well as adverse events (AEs) were evaluated in each group.

Statistical analysis

The differences in the distribution of categorical variables between the two groups were analyzed using a Chi-squared test. The PFS and OS rates were determined using the Kaplan-Meier method, and the differences between the two groups were analyzed using log-rank testing. All statistical analyses were conducted using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, U.S.), and p-values less than 0.05 were considered statistically significant.

RESULTS

The clinicopathologic characteristics are listed in Table 1. The median age was 70 (range 30–83) years, and the median observation period was 12.6 (range 2–53.7) months. The first-line regimens were ICI-ICI regimens in 26 cases and ICI-TKI in 10 cases. The rate of patients with liver metastasis was significantly higher and that

Table 1. Comparison between ICI and/or TKI groups for patients with metastatic non-clear-cell RCC

	ICI-ICI (n=26) n (%)	ICI-TKI (n=10) n (%)	p	Total (n=36) n (%)
Age				
≥70	15 (57.7)	4 (40.0)	0.3409	19 (52.8)
≤69	11 (42.3)	6 (60.0)		17 (47.2)
Sex				
Male	19 (73.1)	8 (80.0)	0.6674	27 (75.0)
Female	7 (26.9)	2 (20.0)		9 (25.0)
Histologic type				
Papillary	14 (53.8)	5 (50.0)		19 (52.8)
Chromophobe	1 (3.9)	1 (10.0)		2 5.6)
Unclassified	3 (11.5)	0 (0)		3 (8.3)
Translocated	2 (7.7)	0 (0)		2 (5.6)
Bellini duct	1 (3.9)	0 (0)		1 (2.8)
Tubulocystic	1 (3.9)	0 (0)		1 (2.8)
ACD-associated	0 (0)	2 (0)		2 (5.6)
Sarcomatoid	4 (15.4)	2 (0)		6 (16.7)
KPS				
≥80%	20 (76.9)	8 (80.0)	0.8423	28 (77.8)
<80%	6 (23.1)	2 (20.0)		8 (22.2)
No. of metastatic organs				
1	8 (30.8)	4 (40.0)	0.5987	12 (33.3)
≥2	18 (69.2)	6 (60.0)		24 (66.7)
Metastatic disease sites				
Lung	13 (50.0)	3 (30.0)	0.2794	16 (44.4)
Bone	10 (38.5)	1 (10.0)	0.0968	11 (30.6)
Lymph node	18 (69.2)	4 (40.0)	0.0171	22 (61.1)
Adrenal gland	3 (11.5)	0 (0)	0.2619	3 (8.3)
Liver	1 (3.9)	6 (60.0)	0.0001	7 (19.4)
Brain	1 (3.9)	0 (0)	0.5294	1 (2.8)
IMDC risk				
Favorable	0 (0)	1 (10.0)	0.1020	1 (2.8)
Intermediate	10 (38.5)	4 (40.0)		14 (38.9)
Poor	16 (61.5)	5 (50.0)	0.5294	21 (58.3)

ACD: acquired cystic disease; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ICI: immune-checkpoint inhibitors; KPS: Karnofsky performance status; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor.

Table 1 (cont'd). Comparison between ICI and/or TKI groups for patients with metastatic non-clear-cell RCC

	ICI-ICI (n=26) n (%)	ICI-TKI (n=10) n (%)	p	Total (n=36) n (%)
Prior nephrectomy				
Radical	6 (23.1)	4 (40.0)	0.3099	10 (27.8)
Cytoreductive	8 (30.8)	2 (20.0)		10 (27.8)
Bone	12 (46.2)	4 (40.0)	0.7393	16 (44.4)
First-line regimen				
Ipilimumab+nivolumab	26 (100.0)	0 (0)		26 (72.2)
Avelumab axitinib	0 (0)	3 (30.0)		3 (8.3)
Pembrolizumab+axitinib	0 (0)	1 (10.0)		1 (2.8)
Nivolumab+cabozantinib	0 (0)	4 (40.0)		4 (11.1)
Pembrolizumab+envatinib	0 (0)	2 (20.0)		2 (5.6)

ACD: acquired cystic disease; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ICI: immune-checkpoint inhibitors; KPS: Karnofsky performance status; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor.

Table 2. Objective response of first-line therapy in each regimen

	First-line combination regimen	
	ICI-ICI	ICI-TKI
Objective response	(n=26), n (%)	(n=10), n (%)
CR	3 (11.5)	0 (0)
PR	6 (23.1)	3 (30.0)
SD	8 (30.8)	4 (40.0)
PD	9 (34.6)	3 (30.0)

p-values: CR: 0.2619; CR+PR: 0.7925; PD: 0.7925. CR: complete response; ICI: immune-checkpoint inhibitor; PD: progressive disease; PR: partial response; SD: stable disease; TKI: tyrosine kinase inhibitor.

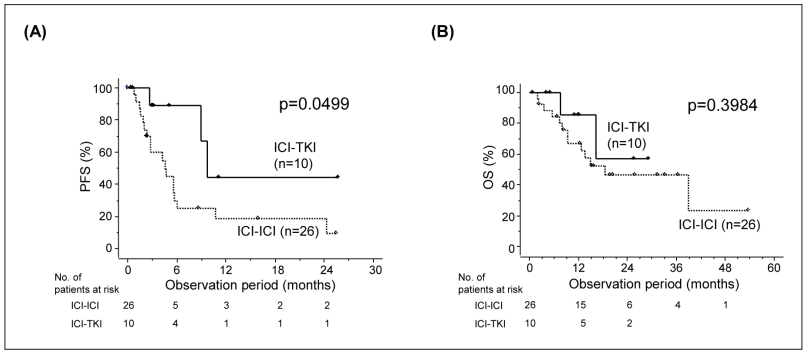

Figure 1. (A) Progression-free survival (PFS); and (B) overall survival (OS) stratified using first-line regimens in all patients with metastatic renal cell carcinoma. ICI: immune-checkpoint inhibitors; TKI: tyrosine kinase inhibitor.

with lymph node metastasis was significantly lower in the ICI-TKI group than those in the ICI-ICI group. There was no significant difference in patients' background between these two groups. The ORRs were 34.6 and 30.0% (p=0.9443) and disease control rates were 65.4 and 80% in the ICI-ICI and ICI-TKI groups, respectively (Table 2). The 50% PFS in the ICI-TKI group was significantly longer than that in the ICI-ICI group (9.7 months and 4.6 months, p=0.0499). There was no significant difference in OS between these groups (p=0.3984) (Figure 1).

All AEs of first-line systemic therapy are listed in Table 3. There was no significant difference in the frequency of occurrence between the ICI-ICI and ICI-TKI groups for any AEs below grade 2 (p=0.8535) or above grade 3 (p=0.3786). In 14 cases in the ICI-ICI group (53.8%) and eight cases in the ICI-TKI group (80.0%), first-line therapy was not interrupted due to AEs (p=0.1494). Nine cases in the ICI-ICI group (34.6%) and one case in the ICI-TKI group (10%) underwent high-dose steroidal therapy for the treatment to AE (p=0.1397). In six cases in the ICI-ICI group (23.1%) and in none in ICI-TKI group (0%), first-line therapy was terminated due to AEs (p=0.0961).

DISCUSSION

We retrospectively investigated the efficacy and safety of combination therapy, including ICI-ICI and ICI-TKI, as first-line therapy. ICI-TKI therapy revealed no significant difference in OS and ORR but significantly longer PFS compared with ICI-ICI therapy. Although several RCTs have demonstrated the therapeutic efficacy and improved prognosis of various combination immunotherapies for mRCC,[5-9] they did not include nccRCC; thus, no evidence of efficacy for nccRCC was available.

Subsequently, several retrospective studies have reported the efficacy of ICI-ICI therapy for nccRCC.[13-15] A study on ICI-ICI therapy for nccRCC reported that the ORR was 33.3%, while 50% of patients had progressive disease as the best response.[14] Our previous study revealed similar ORRs in patients with nccRCC treated with ICI-ICI and was better than when treated with TKI as first-line therapy.[10] Another study demonstrated a lower ORR for nccRCC.[16] The distribution of histologic types was different among these studies, which might lead to a difference in outcome. Since nccRCC is a mixture of multiple pathologic types with very different prognoses and drug sensitivities, we should be careful when evaluating the results of various studies.

ICI-ICI therapy is associated with a high incidence of serious immune-related AEs, and many patients fail to respond to ICI-ICI therapy, while some achieve a dura-

ble response. Studies reported that the ICI-ICI regimen presented lower ORRs in patients with nccRCC than ccRCC.[16,17] ICI-TKI therapy may be expected to have a higher response rate than ICI-ICI therapy according to the data of previous RCTs for each regimen.[5-9] Some TKIs have been reported to be effective for nccRCC. For example, cabozantinib showed a better outcome for papillary RCC compared with other TKIs.[18] Among ICI-TKI regimens, nivolumab-cabozantinib provides 47.5% ORR for nccRCC, which consisted of 80% papillary RCC.[19]

In this study, we investigated patients who received ICI-TKI therapy in addition to those who received ICI-ICI therapy and compared the efficacy of these regimens in nccRCC patients. ICI-TKI therapy resulted in similar ORRs but longer PFS compared with ICI-ICI therapy. In fact, ICI-TKI therapy is expected to be effective in the treatment of refractory advanced nccRCC despite the significantly higher frequency of patients with liver metastasis, which is considered to be a poor efficacy and prognostic factor.[20] Although various AEs were observed, there was no significant difference in the frequency of AEs between these two regimens, suggesting the results are acceptable in terms of safety; however, there was no significant difference in OS between the two groups, while longer PFS was observed in the ICI-TKI group.

The rate of complete response is lower with ICI-TKI than with ICI-ICI, and it is difficult to obtain a durable response,[5-9] which may explain why the difference in PFS was not reflected in OS. ICI-ICI does not include TKI in the first-line treatment, and the efficacy of TKI in the subsequent therapy has been reported,[18] whereas in ICI-TKI, the choice of TKI in the subsequent therapy is limited by the first-line regimen, affecting efficacy,[21,22] which may have led to the OS results in this study. To take advantage of the high response rate and long PFS, especially when ICI-TKI is selected, appropriate consideration of local therapy, such as radiation therapy and surgical intervention (including the resection of metastases and deferred cytoreductive nephrectomy) during the response period, may be important to further improve prognosis.

Limitations

There were several limitations in this study. It was a small, retrospective study based on the analysis of real-world data, and various histologic types were mixed. Since nccRCC consists of various histologic types with different genetic backgrounds and molecular features, more accumulation of precise pathologic diagnosis by immunohistologic and/or genetic analyses is required to establish personalized treatment for nccRCC.[23]

Four different types of regimens were mixed within the ICI-TKI group. The decision for the therapeutic strategy, including the choice of regimen, is made by individual physicians. The efficacy of treatment may differ even for the same histologic type, and there have been reports on combination therapy being successfully applied to histologic types that are considered refractory to treatment, such as chromophobe RCC[24] and collecting duct carcinoma.[25] In addition to the various clinical trials underway for nccRCC,[26] further study with a larger volume and longer followup period should be conducted to confirm the results of this study.

Table 3. Summary of adverse events

	ICI-ICI (n=26)		ICI-TKI (n=10)	
	All grades, n (%)	Grade 3–4, n (%)	All grades, n (%)	Grade 3–4, n (%)
Any event	19 (73.1)	12 (46.2)	7 (70.0)	3 (30.0)
Liver dysfunction	4 (15.4)	4 (15.4)	2 (20.0)	1 (10.0)
Renal dysfunction	1 (3.8)	1 (3.8)		
Pneumonitis	1 (3.8)	1 (3.8)		
Hypertension			3 (30.0)	
Myositis	1 (3.8)	1 (3.8)		
Skin toxicity	5 (19.2)	2 (7.7)	4 (40.0)	2 (20.0)
Dysgeusia			1 (10.0)	
Oral mucositis			1 (10.0)	
Appetite loss			1 (10.0)	
Colitis, diarrhea		1 (3.8)	3 (30.0)	
Cholangitis	1 (3.8)	1 (3.8)		
Hypopituitarism	2 (7.7)	1 (3.8)		
Adrenal insufficiency	2 (7.7)	1 (3.8)		
Hypothyroidism, thyroiditis	7 (26.9)	1 (3.8)	1 (10.0)	
Diabetes mellitus type 1		1 (3.8)		
Malaise	4 (15.4)		2 (20.0)	

ICI: immune-checkpoint inhibitor; TKI: tyrosine kinase inhibitor.

CONCLUSIONS

We demonstrated the efficacy of ICI-TKI therapy compared with ICI-ICI therapy for metastatic nccRCC. A better PFS outcome was expected in the ICI-TKI group compared to that in the ICI-ICI group, while there was no significant difference in OS. Multidisciplinary treat-

ments with local therapy, including surgery and radiation therapy, might further improve the therapeutic outcomes for these regimens.

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