Early Experiences with Nivolumab in Patients with Metastatic Renal Cell Carcinoma and Failed Target Therapy

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Purpose: The efficacy of nivolumab in metastatic renal cell carcinoma (mRCC) has been proven. However, the nivolumab experience in Korean patients with mRCC is still poorly reported. We report initial experiences with the efficacy and safety of nivolumab in patients with mRCC.

Materials and Methods: We retrospectively reviewed records for 25 patients with mRCC who had failed targeted therapy and were treated by nivolumab (2 mg/kg, every 2 weeks) at a single institution. The primary endpoint was objective response rate (ORR), and secondary endpoints were progression-free survival (PFS), safety profiles, and ORR in a programmed cell death receptor ligand 1 (PD-L1) expression subgroup.

Results: The median age was 60 years and 16 patients (64%) were male. Objective responses were achieved in 8 patients (32.0%) (complete response, 1; partial response, 7). Median PFS was 3.0 months (95% confidence interval, 1.46-4.53). Treatment-related adverse events (AEs) of any grade were observed in 19 patients (76.0%) with 6 (24.0%) experiencing grade 3 to 4 treatment-related AEs. In subgroups by PD-L1 expression levels classified as 1% or greater and less than 1%, ORR was 50% and 0%, respectively.

Conclusions: This study showed the efficacy and safety of initial experiences with nivolumab in Korean patients with mRCC who had failed targeted therapy. Our results were comparable to recent clinical trials on nivolumab in mRCC. (Korean J Urol Oncol 2019;17:96-102)

Key Words: Metastasis • Monoclonal antibody • Programmed cell death 1 ligand 1 • Renal cell carcinoma • Treatment outcome

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INTRODUCTION

Every year, 338,000 renal cell carcinoma (RCC) patients are diagnosed worldwide¹ and about 30% of patients have metastatic disease at the time of diagnosis.² Many target therapies have been approved to treat advanced or metastatic RCC (mRCC) including vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target rapamycin (mTOR) inhibitors. VEGF pathway and mTOR inhibitors have been the main treatment agents for mRCC in the last decade. However,

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limitations of these drugs are in adverse events (AEs) and durable response.³ Immuno-oncology drugs such as anti-programmed death 1 (PD1) and anti-CTLA4 have received attention for mRCC due to their long durable response and relatively fewer AEs.

Nivolumab is a fully human IgG4 antibody. It is a PD-1 immune checkpoint inhibitor that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and programmed cell death receptor ligand 1 (PD-L1) or 2 (PD-L2), which are expressed on immune cells and tumor cells.⁴⁻⁶ This is the first approved agent for use in treatment-refractory clear cell RCC.⁷ Motzer et al.⁷ reported that nivolumab is effective and safe as a second-line treatment for advanced RCC. In a phase III trial, overall survival (OS) was longer and fewer grade 3 or 4 AEs occurred for nivolumab versus everolimus.

In Japanese patients, the efficacy and safety of nivolumab for mRCC was different from a previous global study.⁸ Therefore, the efficacy and safety of immune checkpoint inhibitors for mRCC is expected to also be different in Korean populations compared to global populations. However, the experience for nivolumab in Korean patients with mRCC is still poorly reported. We report initial experiences on the efficacy and safety of nivolumab in Korean patients with mRCC previously treated with targeted therapy.

MATERIALS AND METHODS

1. Patients and Study Design

We retrospectively reviewed clinical data for 25 patients with mRCC who had failed targeted therapy from March 2017 through September 2018. All included patients were treated with nivolumab as second-line treatment for mRCC. Nivolumab was administered at 2 mg per kg body weight as a 60-minute intravenous infusion every 2 weeks. This study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2019-04-160). Informed consent was exempted by the board.

Assessed baseline characteristics were age, sex, body mass index, Heng risk factor, Eastern Cooperative Oncology Group (ECOG) performance status, metastasis status, and treatment history. The primary endpoint was objective response rate (ORR) defined as the number of patients with a complete response (CR), partial response (PR), stable disease (SD), or progression of disease (PD). The best objective response was as-

sessed by a urologist and uro-radiologist. Secondary endpoints included OS, progression-free survival (PFS), and safety profiles. The efficacy of nivolumab according to PD-L1 expression level was also assessed.

Disease assessments were performed using computed tomography or magnetic resonance imaging at baseline and every 6 to 8 weeks until disease progression or treatment discontinuation. Imaging data were evaluated for tumor response according to Response evaluation criteria in solid tumors version 1.1.⁹ OS was defined as the time from first dose to date of death. PFS was defined as time from nivolumab treatment to first documented RECIST-defined tumor progression or death from any cause.

Immunohistochemistry of tumor cells was performed using Dako PD-L1 immunostaining kits (Agilent, Santa Clara, CA, USA). Expression levels were classified according to presence or absence of quantifiable PD-L1 and were classified as more than 1% and less than 1%, as determined by a pathologist.

Patients were allowed to continue nivolumab after initial disease progression if clinical benefit was assessed and nivolumab had an acceptable side-effect profile. Safety assessments were conducted at each clinic visit. After treatment discontinuation, patient's last outpatient visit was confirmed for assessment of survival. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

2. Statistical Analysis

PFS and OS were estimated using Kaplan-Meier methodology. Statistical analysis was conducted using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) with a p-value <0.05 considered statistically significant.

RESULTS

1. Patient Characteristics

Baseline characteristics of the 25 patients are in Table 1. Median age was 60 years and most were male (64%). Of the patients, 4 (16%) were classified by Heng criteria as having favorable risk, 16 (64%) as having intermediate risk and 5 (20%) as having poor risk. Most patients had 0 (20%, n=5) or 1 (76%, n=19) ECOG performance status. Metastatic types were synchronous in 16 patients (64%) and metachronous in 9 (36%) with 20 patients (80%) having ≥ 2 metastasis sites. Metastasis sites were lung (88%, n=22), lymph node (68%, n=17), bone

Table 1. Baseline clinical characteristics of 25 patients with failed targeted therapy who were treated with nivolumab for metastatic renal cell carcinoma

Characteristic	Value
Age (yr), median (IQR)	60 (54-66)
Sex	
Male	16 (64)
Female	9 (36)
Body mass index (kg/m ²), median (IQR)	22.97 (20.29-25.48)
Heng risk group	
Favorable	4 (16)
Intermediate	16 (64)
Poor	5 (20)
ECOG performance status	
0-1	24 (96)
2	1 (4)
Histopathology	
Clear cell RCC	22 (88)
Nonclear cell RCC	3 (12)
Type of metastasis	
Synchronous	16 (64)
Metachronous	9 (36)
No. of metastasis	
Single	5 (20)
Multiple (≥ 2)	20 (80)
Site of metastasis	
Lung	22 (88)
Lymph node	17 (68)
Bone	12 (48)
Liver	4 (16)
Adrenal	3 (12)
Other soft tissue	3 (12)
Prior nephrectomy	23 (92)
Prior metastasectomy	7 (28)
Prior radiotherapy	9 (36)
No. of prior systemic regimens	
1	7 (28)
2	9 (36)
≥ 3	9 (26)
Type of previous systemic regimens	
Sunitinib	11 (44)
Pazopanib	14 (56)
Sorafenib	7 (28)
Axitinib	5 (20)
Everolimus	15 (60)
Interleukin-2	2 (8)
Patients with quantifiable PD-L1 expression	5 (25)
PD-L1 expression level	
$\geq 1\%$	4 (80)
$< 1\%$	1 (20)

Table 1. Continued

Characteristic	Value
Patients without quantifiable PD-L1 expression	15 (75)

Values are presented as number (%) unless otherwise indicated.

IQR: interquartile range, ECOG: Eastern Cooperative Oncology Group, PD-L1: programmed death-ligand 1.

Table 2. Efficacy of nivolumab treatment in patients with metastatic renal cell carcinoma previously treated with targeted therapy

Outcomes	Value
Objective response rate*	8 (32)
Best objective response*	
Complete response	1 (4)
Partial response	7 (28)
Stable disease	8 (32)
Progressive disease	8 (32)
Progression-free survival (mo)	
Median (95% CI)	3.0 (1.4-4.6)
Overall survival	
Median (95% CI)	Not reached

Values are presented as number (%) unless otherwise indicated.

CI: confidence interval.

*One patient has not undergone response evaluation yet among a total of 25 patients.

(48%, n=12), liver (16%, n=4), adrenal (12%, n=3), and other soft tissue (12%, n=3). Of the patients, 23 (92%) had prior nephrectomy and 7 (28%) had metastasectomy with 18 (62%) receiving at least 2 prior systemic treatments for RCC.

2. Efficacy

Objective responses were observed in 32% of patients (8 of 25) (Table 2). One patient has not undergone response evaluation yet among a total of 25 patients. Median time to response was 2.4 months (interquartile range, 1.3-5.2) among the 8 patients with a response: 1 (4%) showed CR, 7 (28%) showed PR, and 8 (32%) showed stable SD. Among patients with a treatment response, only 1 (12.5%) had a durable response (18 months). Patients 1 and 5 had a response at the time of analysis, and subsequent follow-up was not reflected in the results (Fig. 1). Median PFS was 3 months (95% confidence interval, 1.38-4.61). Median OS was not reached (Fig. 2).

3. PD-L1 Expression

Among 25 patients, 20 tissues were available to be analyzed. Quantifiable PD-L1 expression was observed in 5 patients

Fig. 1. Duration of response in patients who showed objective response (CR plus PR). CR: complete response, PR: partial response.

(25%): 1 of 5 (20%) had less than 1% PD-L1 expression and 4 (80%) had more than 1% PD-L1 expression. Quantifiable PD-L1 expression levels in 5 patients and corresponding ORR are in Table 3. Patients with less than 1% PD-L1 expression showed no objective response. Two patients with PD-L1 expression $\geq 1\%$ showed objective response. Representative im-

Table 3. Antitumor activity by PD-L1 expression level

Variable	PD-L1 <1%	PD-L1 $\geq 1\%$
No. of patients	1	4
Objective response rate	0	2
Best objective response		
Complete response	0	0
Partial response	0	2
Stable disease	0	1
Progressive disease	1	1

Quantifiable PD-L1 expression was observed in 5 patients (25%).

PD-L1: programmed death-ligand 1.

Fig. 2. Kaplan-Meier curves for progression-free survival (A) and overall survival (B). CI: confidence interval.

Fig. 3. Representative PD-L1 immunohistochemistry staining in renal cell carcinoma at $\times 200$ magnification. (A) PD-L1 positive case. Most of the tumor cells showed complete or partial membranous staining. (B) PD-L1 negative case of renal cell carcinoma. PD-L1: programmed death-ligand 1.

Table 4. Treatment-related adverse events (AEs)

Adverse event	Any grade	Grade 3 or 4
Any treatment-related AE	19 (76)	6 (24)
Nausea	9 (36)	1 (4)
Decreased appetite	7 (28)	1 (4)
Fatigue	7 (28)	1 (4)
Pruritis	5 (20)	2 (8)
Cough	4 (16)	1 (4)
Pneumonitis	1 (4)	0 (0)
Hyperthyroidism	1 (4)	0 (0)
Others*	6 (24)	0 (0)

Values are presented as number (%).

*Other adverse events: only one case of mucositis, tinnitus, chest discomfort, sweating, melena, and insomnia were reported among 25 patients, respectively.

ages of positive and negative PD-L1 expression are in Fig. 3.

4. Safety

Treatment-related AEs for all patients are in Table 4. Treatment-related AEs of any grade occurred in 19 of 25 patients (76%). The most common treatment-related AEs were nausea (9 patients, 36%), decreased appetite (7 patients, 28%), fatigue (7 patients, 28%), and pruritis (5 patients, 20%). Grade 3 or 4 treatment-related AEs occurred in 6 of the 25 patients (24%). The most common grade 3 or 4 event was pruritis (2 patients, 8%). No patients discontinued treatment due to treatment-related AEs and no deaths from drug toxic effects were reported.

DISCUSSION

To our knowledge, this study is the first reported the effectiveness and safety of nivolumab for Korean patients with mRCC who had failed targeted therapy. We also found that the effect of an anti-PD1 inhibitor was dependent on PD-L1 expression level.

RCC is histologically known as an immune-related disease.¹⁰ Interferon- α (INF- α) and interleukin-2 (IL-2) have mainly been used to treat mRCC.¹¹ However, about 5% of patients showed a durable response to high-dose IL-2 but with significant AEs.^{12,13} The treatment of mRCC has seen major changes since 2005. Several tyrosine kinase inhibitors (TKIs) targeting the VEGF pathway and mTOR inhibitors have been approved for managing mRCC. Pazopanib, sunitinib, temsirolimus, and bev-

acizumab (in combination with INF- α) are approved as first-line treatment and everolimus, sorafenib, axitinib, and cabozantinib as second-line treatment.¹⁴⁻¹⁸ Despite significant progress in treatment outcomes with these agents, the median OS for patients with mRCC is only 22-29 months.^{18,19} Remaining target therapies do not show significant OS benefits other than temsirolimus treatment.²⁰ Therefore, new treatments for mRCC are needed.

Immunotherapy for solid tumors is a possible less-toxic form of immune checkpoint inhibitors. These treatments inhibit innate immune inhibition by blocking PD-1 among T-cell receptors, as well as targeting PD-L1 and PD-L2 expressed in cancer cells. Expression of PD-1, PD-L1 and PD-L2 in cancer cells induces tumor resistance to the immune response and tumor growth. PD-1, PD-L1, and PD-L2 inhibitors that block this resistance mechanism can improve the host immune response to tumors.^{21,22}

In a large-scale, long-term, phase III trial, the immune checkpoint inhibitor nivolumab showed superior OS and higher ORR than everolimus for mRCC patients who had previous treatment such as TKIs.⁷ In that trial, ORR was about 25% in the nivolumab group.⁷ Our study had an ORR that was comparable to the previous study.

PFS in our study was shorter than in previous studies.^{7,8} Unlike previous studies that evaluated the efficacy of nivolumab as a second-line treatment after failure of first-line treatment, a majority of patients in our study received more than third-line nivolumab treatment. This difference may be the cause of differing results from previous studies.

In earlier studies, any grade AEs occurred in 79% of patients and grades 3-4 AEs in 19%.⁷ A similar incidence rate of AEs was obtained in a Japanese subgroup⁸ and in our study. This similarity suggests that the incidence of AEs of nivolumab is consistent regardless of race.

When efficacy according to PD-L1 expression was confirmed by immunohistochemical staining, OS was 21.8 in group with more than 1% expression and 27.4 months in a group with less than 1% expression in a previous study.⁷ This result, although not evaluated for statistical significance, was contrary to expectations. In addition, no comparative analysis of ORR according PD-L1 expression level was performed. In contrast, in our study, ORR was higher in patients in the group with more than 1% expression. Although there was no statistical significance, this result suggested that the expression levels of

PD-L1 and nivolumab efficacy may be related. However, the number of patients who underwent immunohistochemical staining was small, so validation of PD-L1 expression is required in a larger number of patients.

Our study had several limitations. It was retrospective and therefore had unavoidable bias such as bias in selection. A lack of clinical data and possible misclassification of registered patients may have influenced our results. Our study included a small number of patients and we used only a single tertiary center database. The median follow-up of our study was short, at 5 months. Because of this length, OS was not reached. The heterogeneity of previous systemic therapies may have produced more inferior results than expected.

CONCLUSIONS

In conclusion, we reported the initial experiences with anti-PD1 (nivolumab) treatment in Korean patients with mRCC who had failed targeted therapy. Our efficacy and safety data were comparable to data from recent clinical trials on nivolumab in mRCC. Our data provide valuable information on immuno-oncology drugs for treating mRCC that will be useful for real-world clinical practice.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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