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Efficacy and Safety of Axitinib Therapy After Nivolumab for Patients With Metastatic Renal Cell Cancer

SHOTARO YASUOKA[1,2], TAKESHI YUASA[1], RYO FUJIWARA[1], YOSHINOBU KOMAI[1], NOBORU NUMAO[1], SHINYA YAMAMOTO[1], YUKIHIRO KONDO[2] and JUNJI YONESE[1]

[1]*Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan;*
[2]*Department of Urology, Nippon Medical School Hospital, Tokyo, Japan*

Abstract. *Background/Aim: Tyrosine kinase inhibitors (TKI) and immune-checkpoint inhibitors (ICI) are treatment options for metastatic renal cell cancer (mRCC). However, the treatment options after nivolumab are unclear. Patients and Methods: The medical records of 57 consecutive Japanese mRCC patients who underwent treatment with axitinib were reviewed. Among those, 17 patients received axitinib treatment after nivolumab and 40 patients received axitinib treatment after other chemotherapy regimens except nivolumab. Results: Of the 57 patients with mRCC, only 17 underwent axitinib therapy after nivolumab. Among these 17 patients, the objective response rate (ORR) and median tumor shrinkage rate were 56.3% and −30%, respectively. They were significantly better in patients who underwent axitinib therapy after nivolumab than after other therapies (p=0.026 and p=0.012, respectively). However, all 17 patients experienced some adverse events and nine patients (52.9%) required a dose reduction or axitinib treatment interruption. Conclusion: Axitinib therapy after the immune checkpoint inhibitor nivolumab showed good efficacy with a moderate risk of adverse events. Careful management by skilled professionals may be required.*

Nivolumab is an immune checkpoint inhibitor that is a fully human IgG4 programmed death 1 (PD-1) antibody. It has been available in Japan for the treatment of metastatic renal cell cancer (mRCC) since 2016 (1). Because of its promising anti-tumor efficacy and manageable safety profile, it has been rapidly introduced into mRCC treatment regimens, and this treatment strategy has dramatically changed clinical practice (2). We have previously reported the efficacy and safety profile of nivolumab therapy for Japanese patients with mRCC (3). However, to date, there has only been limited information regarding medical treatment after nivolumab therapy in clinical practice or in clinical trials (4-6). Axitinib, a tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor (VEGF) receptor, is most frequently used after nivolumab at our Institution. In this study, we retrospectively analyzed the efficacy and safety of axitinib after nivolumab monotherapy, as a second-line or later medical treatment for mRCC patients.

Correspondence to: Shotaro Yasuoka, MD, Department of Urology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. Tel: +81 335200111, Fax: +81 335200141, e-mail: syasuoka0317@gmail.com

Key Words: Nivolumab, metastatic renal cell carcinoma, axitinib, immune checkpoint inhibitor.

Patients and Methods

The medical records from patients with mRCC who received axitinib (Inlyte, Pfizer, Tokyo) as a second-line or later treatment at our Institution between January 2011 and July 2019 were retrospectively reviewed. In this study, patients who underwent cytokine therapy were excluded. We also included patients who did not undergo nivolumab (Opdivo, Ono/Bristol-Myers Squibb, Osaka, Japan) therapy, but were treated with TKIs as a first-line therapy. This study was approved by the Institutional review board at the Cancer Institute Hospital, Japanese Foundation for Cancer Research (2012-1008). Before axitinib administration, all patients provided written informed consent.

Treatment and follow-up examination. Initially, axitinib (5 mg) was administered twice a day (10 mg/day) and the dose was increased to more than 20 mg/day, as described previously (2, 7). Due to adverse events, the attending physicians decided to decrease the dose. We recorded the patients' medical history, including physical examination findings, Karnofsky performance status (KPS), laboratory findings, and chest radiography data before initiating treatment and during axitinib therapy. All data were assessed based on the attending physician. The response to therapy was objectively evaluated by computed tomography every 2 or 3 months using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 (8). Toxicity was assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (9).

Statistical analysis. Progression-free survival (PFS) and overall survival (OS) periods, which were defined as the periods from initial administration of axitinib until diagnosis of progressive disease or death from any cause, respectively, were assessed in all patients. Survival curves were estimated using the Kaplan–Meier method and

Table I. *Patient characteristics (n=17).*

Age (years)	71 (range=50-90)
Male/Female	13 (76.5%)/4 (23.5%)
Pathological type: ccRCC or non-ccRCC	16 (94.1%)/1 (5.9%)
Radical Nephrectomy	13/17 (76.5%)
KPS: ≥80/<80	12 (70.6%)/5 (29.4%)
Number of prior regimens: 2/3	12 (70.6%)/5 (29.4%)
Metastatic sites	
Lung	14 (82.4%)
Bone	6 (35.3%)
Liver	2 (11.8%)
Pancreas	2 (11.8%)
Lymph node	4 (23.5%)
Hemoglobin (mg/dl): ≥10/<10	10 (58.8%)/7 (41.2%)
Calcium (mg/dl): <10/≥10	13 (76.5%)/4 (23.5%)
Platelet count: <ULN/≥ULN	15 (88.2%)/2 (11.8%)
Neutrophils: <ULN/≥ULN	16 (94.1%)/1 (5.9%)
Time from diagnosis (year): ≥1/<1	10 (58.8%)/7 (41.2%)
IMDC risks: good/intermediate/poor	3 (17.6%)/12 (70.6%)/2 (11.8%)

ccRCC: Clear cell renal cell carcinoma; KPS: Karnofsky-performance status; ULN: upper limit of normal range; IMDC: International Metastatic Renal Cell Cancer Database Consortium.

compared using the log-rank test. All statistical analyses were performed using JMP software version 14.0 (SAS Institute Inc., Cary, NC, USA) and *p*-values <0.05 were considered to be significant.

Results

Patient characteristics. Fifty-seven consecutive patients were treated with axitinib for mRCC at our hospital between January 2011 and July 2019. Among these, 17 patients had received nivolumab therapy before axitinib. The characteristics of these 17 patients are described in Table I. Thirteen (76.5%) patients were male and the median age of patients who received axitinib therapy after nivolumab therapy was 71.5 years (range=50-90 years). Among these patients, 12 (70.6%) and five (29.4%) patients received axitinib as third and fourth-line treatments, respectively. As first line treatment (n=17), 9 and 8 patients were treated with pazopanib and sunitinib, respectively. Twelve patients who received axitinib as third line treatment were treated with nivolumab as second line therapy followed by axitinib. Five patients who received axitinib as fourth line treatment were treated in order of axitinib as second line therapy and nivolumab as third line treatment. According to the International Metastatic renal cell cancer Database Consortium (IMDC) classification, 3 (17.6%), 12 (70.6%), and 3 (11.8%) patients were classified into the favorable, intermediate, and poor risk groups, respectively (Table I). Among remaining 40 patients who had no history of nivolumab or any immune therapy before axitinib treatment, eleven (30.6%), 13 (36.1%), and 12 (33.3%) patients were classified into favorable, intermediate, and poor risk categories, respectively, based on the IMDC classification (four patients could not be classified because of incomplete laboratory data). In addition, 32 (80%), five (12.5%), and three (7.5%) patients were treated with second, third, and fourth-line therapy, respectively. As first line treatments (n=40), 28, 7, 4 and 1 patients were treated with sunitinib, pazopanib, sorafenib and everolimus, respectively. As for second line treatments (n=8), 4, 2 and 2 patients treated by everolimus, sorafenib and sunitinib, respectively. As third line treatment (n=3), 2 and 1 patients treated by everolimus and dovitinib, respectively.

Table II. *Treatment-related adverse events of axitinib after nivolumab (n=17).*

	Grade 1-2 (Grade 3-4)	Reduction or interruption
Total number of adverse events	17 (10)	8 (47.1%)
Types of adverse events		
Hypertension	14 (10)	2 (5.9%)
Diarrhea	7 (0)	1 (5.9%)
Appetite loss	4 (0)	2 (5.9%)
Hepatic dysfunction	1 (0)	1 (5.9%)
Hand and foot syndrome	1 (0)	1 (5.9%)
Arthritis related to nivolumab	1 (0)	1 (5.9%)

Efficacy of axitinib. The median follow-up period from axitinib initiation was 14.6 months (range=6.0-23.4 months) in 17 patients who were previously treated with nivolumab. Among these patients, one patient had no evaluable target lesion (bone metastases). Drug efficacy was evaluated in the remaining 16 patients and the objective response rate (ORR) and median tumor shrinkage rate were 56.3% (9/16) and −30%, respectively (Figure 1A). Median PFS and 6 month- and 12 month-PFS rates after the initiation of axitinib therapy were 7.9 months, 64.7%, and 21.2%, respectively (Figure 1B). Median OS and 6 month- and 12 month-OS rates after initiation of axitinib therapy were 22.2 months, 100%, and 79.0%, respectively (Figure 1C). In addition, the 3-year and 5-year OS rates from the initiation of treatment of these patients with mRCC were 76.4%, and 65.5%, respectively (Figure 1D).

Adverse events. Among the 17 patients who were previously treated with nivolumab, all patients experienced adverse events and ten patients (58.8%) had severe (Grade 3/4) adverse events. Fourteen (82.4%) and seven (41.2%) patients experienced hypertension and diarrhea, respectively. Dose reduction or interruption of axitinib treatment occurred in eight patients (47.1%). The reasons were hypertension (n=2), appetite loss (n=2), hepatic disfunction (n=1), hand and foot syndrome (n=1), diarrhea (n=1), and arthritis possibly because of the previous nivolumab treatment (n=1) (Table

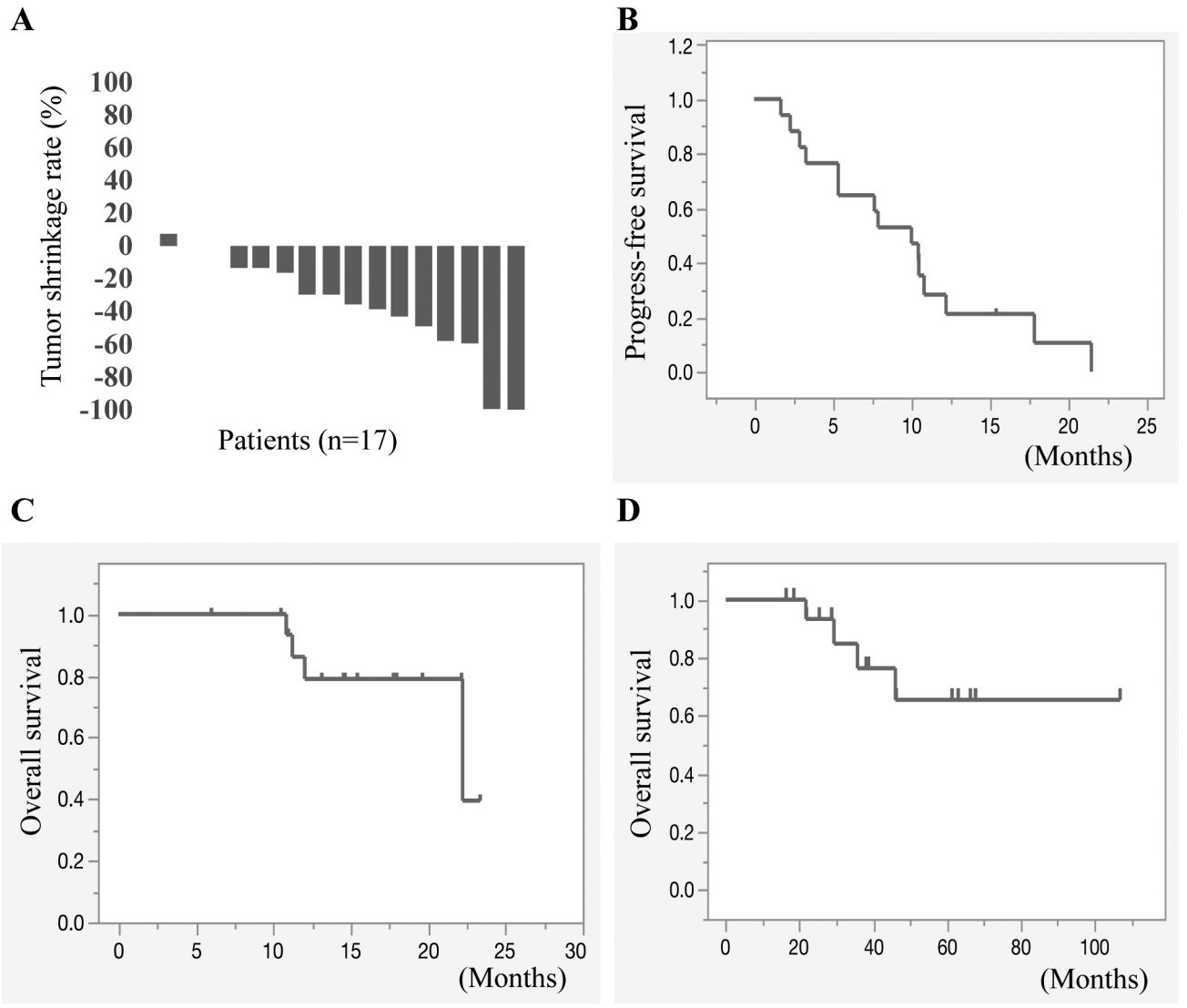

Figure 1. *Efficacy of nivolumab as a second-line or later treatment for Japanese patients with nivolumab-resistant metastatic renal cell cancer. Waterfall plots of the response to axitinib (A: n=16). Progression-free survival and overall survival curves from axitinib therapy after nivolumab (B, C: n=17). Overall survival from the initial treatment for the patients with metastatic renal cell cancer (D: n=17).*

II). Five patients (29.4%) stopped axitinib therapy because of the adverse events without disease progression.

Comparison of the efficacy between patients treated axitinib after nivolumab and patients treated axitinib who had no history of nivolumab therapy. To investigate the characteristics of axitinib after nivolumab therapy, we compared the outcomes of patients treated axitinib after nivolumab with those of patients treated axitinib but had no history of nivolumab therapy. Forty patients did not have a history of nivolumab or any immune therapy before axitinib treatment. Among these 40 patients, antitumor efficacy could be evaluated in 37 patients. The ORR and median tumor shrinkage rate were 24.3% and −3%, respectively. Median PFS was 10.4 months. The median OS period and 6- and 12-month OS rates were 33.8 months, 92.0%, and 75.5%, respectively. The PFS and OS after initiation of axitinib therapy showed no significant difference between the patients treated with axitinib with or without a history nivolumab treatment. However, the ORR and tumor shrinkage rate were significantly better in patients who were previously treated with nivolumab (p=0.026, p=0.012).

Discussion

Currently, there are two treatment options when using nivolumab. For patients who are classified into the IMDC

intermediate or poor risk category, the first-line combination of ipilimumab and nivolumab is standard care based on the phase III randomized clinical trial CheckMate 214, in which the combination of nivolumab and ipilimumab demonstrated superior efficacy over sunitinib in previously untreated mRCC patients (10). Currently, there are two reports that investigated the efficacy and safety profile of TKIs after using first-line immune checkpoint inhibitors (4, 5). Auvray *et al*. reported the outcomes of 33 patients who received subsequent TKIs after the combination of nivolumab and ipilimumab (4). The best response was assessed in 30 patients, as follows: 12 patients showed partial response (36%), 13 patients stable disease (39%), and five patients progressive disease (15%) (4). Median PFS from the initiation of TKI was 8 months and the 12-month OS rate was 54% (4). Shah *et al*. demonstrated similar results, showing that one patient (1.5%) achieved complete response, 27 patients (39.7%) had a partial response, and 36 patients (52.9%) had stable disease, and the median PFS was 13.2 months (5). These results seemed to be relatively better than those of previously reports (7, 11-13). They reported another important result, which was that 45% of subjects required a dose reduction and 27% of patients discontinued treatment because of toxicity (5). Thus, the efficacy of TKI after immune checkpoint inhibitors seemed to be better, but with a higher rate of toxicity compared with previous studies including the AXIS trial, which reported that the median PFS of axitinib in patients who were previously treated with the sunitinib regimen was 4.8 months and the ORR was 19% (7).

Another treatment option is using nivolumab for mRCC patients as second-line monotherapy after using first-line TKIs (1-3). Nivolumab monotherapy is the current standard second-line therapy after TKI first-line therapy. In a single center retrospective study (n=45), we reported that although the median PFS period was 14.9 months, the 1-year and 2-year OS rates from initiation of nivolumab were 91.1%, and 86.2%, respectively (3). These results suggested that subsequent therapy after nivolumab showed good efficacy. To date, information about medical therapy followed by nivolumab monotherapy is lacking except for a small pilot study (n=6) and a case report (14, 15). Here, we demonstrated that the ORR was 56.3% (Figure 1A) and the median PFS and OS periods and 6- and 12-month OS rates after initiating axitinib therapy were 7.9 months, 22.2 months, 100%, and 79.0%, respectively (Figure 1B, C). In addition, the ORR and tumor shrinkage rate were significantly better in patients who were previously treated with nivolumab (p=0.026, p=0.012). However, all patients experienced some adverse events and nine patients (52.9%) needed dose reduction or axitinib treatment interruption (Table II). Additionally, five patients (29.4%) stopped axitinib therapy because of adverse events without disease progression. Thus, TKI therapy after immune checkpoint inhibitor therapy seems to have good efficacy with moderate to high risk for adverse events. Careful management by skilled professionals is required. In addition, the OS period of these mRCC patients seemed to be increased in this immune checkpoint inhibitor era (Figure 1D).

The precise mechanism of the substantially good efficacy with increased toxicity of axitinib after nivolumab remains unknown. Currently, there are two combinations of immune checkpoint inhibitors and TKIs, which include pembrolizumab/axitinib and avelumab/axitinib, and these have just started to be used in mRCC clinical practice because of their superior results compared to sunitinib monotherapy (16, 17). Both trials have also demonstrated increased toxicities, dose reduction, and treatment-related discontinuation compared to axitinib monotherapy (7). In both the combination therapy and sequential therapy, the tumor microenvironment and/or immune system was altered by the immune checkpoint inhibitor therapy, which seems to have influenced the efficacy as well as the toxicity. Further investigations will clarify these important clinical aspects.

Major limitations of our study are its retrospective design and the small cohort size. However, no large, multi-institutional, and prospective or retrospective studies of TKIs for patients with a history of previous nivolumab therapy have previously been published. Our findings describe the outcomes of axitinib therapy for metastatic RCC patients, and they may be informative for current clinical practice.

In conclusion, for the first time, we demonstrated the efficacy and safety profile of axitinib therapy for patients with metastatic RCC in real-world clinical practice. Patients treated with axitinib after nivolumab therapy showed relatively better efficacy compared with patients who did not have a history of nivolumab or any immune therapy before axitinib treatment. However, patients who were previously treated with nivolumab, experienced adverse events that were more frequently associated with axitinib. Although adverse events should be monitored, axitinib may be a good option for mRCC patients as a third-line or later treatment after nivolumab therapy.

Conflicts of Interest

T. Yuasa received remuneration for lectures from Pfizer Japan (Tokyo, Japan), Novartis Pharma Japan (Tokyo, Japan), Ono Pharma (Osaka, Japan), and Bristol-Myers Squibb Japan (Tokyo, Japan). The other Authors have no conflicts of interest to declare.

Authors' Contributions

Shotaro Yasuoka: study design, data collections, writing, data analysis. Takeshi Yuasa: Study design, writing, editing, data analysis. Ryo Fujiwara: supervision. Yoshinobu Komai: super vision. Noboru Numao: supervision. Shinya Yamamoto: supervision. Yukihiro Kondo: supervision. Junji Yonese: supervision, validation.

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