Long term anti-vascular endothelial growth factor receptor treatment impairs renal function in renal cell carcinoma

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Research Article

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Abstract

Background: The overall survival has been dramatically improving in metastatic renal cell carcinoma (mRCC) patients. Although anti-vascular endothelial growth factor receptor (VEGFR) treatment is one of essential therapeutic strategies for mRCC, the impact on renal function during their lifetime remains unclear. This study aimed to assess the comparison between the duration of anti-VEGFR treatment and chronic kidney disease (CKD) progression.

Methods: A total of 147 mRCC patients who started systemic therapy in Yamagata University Hospital from November 2005 to December 2018 were included in the study. We analyzed the probability of progression to CKD grades 4 and 5 using the Kaplan–Meier method and the log-rank test. To identify the factors independently associated with progression to CKD grade 4, multivariate analysis using logistic regression was performed with baseline eGFR, follow-up duration, duration with anti-VEGFR treatment, proteinuria, hypertension, and diabetes mellitus as the exposure variables.

Results: No patients with normal baseline renal function progressed to CKD grade 4 or 5. Two out of 85 patients with baseline CKD grade 3 progressed to grade 5 8 years after the start of the treatment. Three of five patients with baseline CKD grade 4 progressed to grade 5 within 2 years of starting the treatment. The estimated probability of the patients progressing to grade 4 was increased with worsening baseline CKD grade as determined by univariate analysis (P < 0.001). Multivariate analysis showed that baseline eGFR (P = 0.002), the duration of anti-VEGFR treatment (P = 0.014) and DM (P = 0.040) were independently correlated with progression to CKD grade 4.

Conclusions: Long-term anti-VEGFR treatment could impair renal function in mRCC patients with baseline CKD grade 3 or worse.

Background

Since several targeted drugs, including anti-vascular endothelial growth factor (VEGF) receptor (VEGFR) agents, became clinically available, the overall survival (OS) of patients with metastatic renal cell carcinoma (mRCC) improved [1–4]. The international mRCC database consortium (IMDC) group reported the clinical outcomes of real-world patients with clear cell mRCC on first-line sunitinib, anti-VEGFR agent, whose median OS was 28.6 months and the median OS in the IMDC favorable risk group was as long as 52.1 months [2]. We previously reported the outcomes of Japanese patients with mRCC in the targeted therapy era and showed that the 5-year OS was 36.5% overall and 68.1% in the IMDC favorable risk group [4]. The OS is further extended with the recent advent of immune checkpoint inhibitor (ICI) combination therapies. The CheckMate 214 study, a randomized phase 3 trial comparing the ICI combination of nivolumab and ipilimumab with sunitinib, showed that the 42-month OS was 52% [5]. Moreover, long-term survivors were seen even in the intermediate and poor-risk groups in this trial [6]. The other four ICI and VEGFR inhibitor combination regimens (avelumab + axitinib, pembrolizumab + axitinib, nivolumab + cabozantinib, and pembrolizumab + lenvatinib) also showed good early effects with short observation
periods and are expected to increase the number of long-term survivors [7–10]. As the survival of mRCC patients improves, the prevention of chronic adverse events becomes more important.

While VEGF blockade can rationally impair glomerular epithelial cells [11], several reports mentioned that renal function in mRCC patients is not markedly impaired by anti-VEGFR agents during the use of the drug [12–16]. However, the OS of mRCC patients has been dramatically prolonged and anti-VEGFR agents remain an important part of the mRCC treatment strategy as ICI combination or sequential therapy. Nevertheless, the impact on renal function during their lifetime remains unclear. Hence, we retrospectively assessed the correlation between the progression of chronic kidney disease (CKD) grade and the duration of treatment with anti-VEGFR agents in patients with mRCC.

Material And Methods

The medical records of 171 patients who started systemic therapy for mRCC in the Yamagata University Hospital from November 2005 to December 2018 were reviewed. Patients with an observation period of less than 3 months were excluded. Hence 24 out of 171 patients were excluded from this study and 147 were analyzed to investigate the rate of CKD at the initiation of systemic therapy. The last follow-up data were collected in March 2021.

Next, to analyze the probability of progression to CKD grade 5, 8 patients with baseline CKD grade 5 were eliminated, and 139 were analyzed as “Cohort 1.” We evaluated the probability of progressing to CKD grade 5 for each baseline CKD grade in this Cohort 1 (Fig. 1).

We had hoped to investigate the predictive factors associated with progression to CKD grade 5, we could not because of the small number of the events and the large number of deaths. Hence, to analyze the progression to CKD grade 4, we additionally eliminated five patients with baseline CKD grade 4, and 134 patients were analyzed as “Cohort 2” (Figure. 1). We evaluated the probability of progression to CKD grade 4 for baseline CKD grade, and then investigated the predictive factors independently associated with progression to CKD grade 4 in Cohort 2.

The date of progression to CKD grades 4 and 5 was defined as the first date of less than 30 ml/minute/1.73 m$^2$ and 15 ml/minute/1.73 m$^2$ estimated glomerular filtration rate (eGFR) lasting for over 3 months, respectively. The baseline date was defined as the initial date of the first systemic therapy.

Normal eGFR was defined as 60 ml/minute/1.73 m$^2$ or higher. eGFR was calculated with the following formula: eGFR (ml/minute/1.73 m$^2$) = 194 × (serum creatinine)$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [17]. Proteinuria was defined as a spot urine protein to creatinine ratio of 0.5 or higher. The probability of progressing to CKD grades 4 and 5 was estimated using the Kaplan–Meier method, and 7 values (CKD grade, proteinuria, hypertension [HT], diabetes mellitus [DM], Nephrectomy, anti-VEGFR agent use, and mammalian target of rapamycin [mTOR] inhibitor use) were compared using the log-rank test. The multivariate analysis using logistic regression was performed to identify factors independently associated with progression to CKD grade 4. Six variables (baseline eGFR, follow-up duration, duration of
treatment with anti-VEGFR treatment, proteinuria, HT, and DM) were included in the multivariate analysis. The correlation between baseline eGFR and nephrectomy/proteinuria/anti-VEGFR agent use was analyzed using the Mann–Whitney U test. The OS was estimated using the Kaplan–Meier method, and the correlation between OS and eGFR was assessed using the Cox proportional model. P-values of < 0.05 were considered statistically significant. Statistical analyses were performed using the statistical software package R version 3.6.1 (https://cran.r-project.org).

Results

Patient characteristics

Among 147 patients with evaluable baseline eGFR, only 49 (33.3%) had normal eGFR values. CKD grade 3a was the most common (39.5%), and end-stage kidney disease (ESKD; kidney disease requiring hemodialysis [HD]) was also present (5.4%) (Fig. 1). The median baseline eGFR (interquartile range [IQR]) was 53.0 (43.6–69.4) ml/minute/1.73 m². The baseline eGFR was statistically correlated with nephrectomy (66.3 ml/minute/1.73 m² in patients with nephrectomy vs. 50.6 ml/minute/1.73 m² in patients without nephrectomy, P < 0.001, Fig. 2A), proteinuria (45.6 ml/minute/1.73 m² in patients with proteinuria vs. 54.4 ml/minute/1.73 m² in those without proteinuria, P = 0.015, Fig. 2B), and HT (48.2 ml/minute/1.73 m² in patients with HT vs. 55.9 ml/minute/1.73 m² in those without HT, P < 0.001, Fig. 2C). The median baseline eGFR in patients with DM was relatively lower than that in those without DM, although it did not show statistical difference (46.8 vs. 53.4 ml/minute/1.73 m², P = 0.053, Fig. 2D). The median OS (95% confidence interval [CI]) was 35.4 (26.2–42.8) months. There was no statistically significant correlation between OS and baseline eGFR (hazard ratio; 1.005, 95% CI; 0.9978–1.013, P = 0.169).

The characteristics of Cohort 1 (patients with ≥ 15 ml/minute/1.73 m² eGFR, n = 139) and Cohort 2 (patients with ≥ 30 ml/minute/1.73 m² eGFR, n = 134) are shown in Table 1. The median follow-up time (IQR) was 2.81 (1.24–5.20) and 2.89 (1.23–5.40) years in cohorts 1 and 2, respectively. More than half of patients were censored due to RCC death. Approximately 70% of the patients underwent nephrectomy in both cohorts. Most of the patients (86.3% in Cohort 1 and 85.8% in Cohort 2) received anti-VEGFR therapy (Table 2).

Probability Of Progress To Ckd Grades 4 And 5 For Each Baseline Ckd Grade

No patients with normal baseline eGFR progressed to CKD grade 4 or grade 5 (Fig. 3A and 3B). Among 85 patients with baseline CKD grade 3, 2 progressed to grade 5 after 8 years. Among five patients with baseline CKD grade 4, three progressed to grade 5 within 2 years (Fig. 3A). The estimated probabilities of progress to CKD grade 4 in the patients with baseline CKD grade 3a in 1, 2, and 5 years after the start of systemic therapy were 1.8%, 3.9%, and 15.6%, respectively. The patients with baseline CKD grade 3b had
a higher rate of progress to CKD grade 4, and the estimated probabilities in 1, 2, and 5 years were 7.4%, 24.8%, and 55.9%, respectively (P < 0.001, Fig. 3B).

Clinical Course Of Two Cases Introduced To Hemodialysis Despite Baseline Ckd Grade 3a

In two cases, baseline CKD grade 3a progressed to ESKD. Figure 4 shows the progression to hemodialysis.

The first case was that of a man who had undergone radical nephrectomy. Two years later, he developed multiple lung metastases at the age of 71. He had HT and his baseline eGFR was 48.3 ml/minute/1.73 m². He was initially treated using interferon-α + interleukin-2 + tegafur/uracil. Twenty months later, the disease progressed, and the treatment was switched to sunitinib. Although sunitinib treatment showed partial response, proteinuria appeared immediately after the introduction. CKD progressed to grade 4 3 years after the start of sunitinib and then to grade 5 7 years later, and hemodialysis was introduced 9 years later (Fig. 4A).

The second case was that of a 55-year-old woman who underwent radical nephrectomy. Three months later, she developed multiple lung and muscle metastases. She had no comorbidity other than CKD grade 3a with eGFR 47.8 ml/minute/1.73 m². She was treated with sorafenib. She had hypertension grade 3 and proteinuria shortly after the introduction of sorafenib, while she showed complete response. Two years later, although a complete response was maintained, CKD progressed to grade 4, and sorafenib treatment was discontinued. Ten years later, although a complete response was still maintained, CKD progressed to grade 5, and hemodialysis was introduced (Fig. 4B).

Factors Affecting Progression To Ckd Grade 4

The patients with proteinuria at baseline had a high probability of early progression to CKD grade 4 (P = 0.0195, Fig. 5A). Nephrectomy had no statistical correlation with the probability of CKD progression (P = 0.898, Fig. 5B). The patients without anti-VEGFR agents did not progress to CKD grade 4 (P = 0.032, Fig. 5C). The use of mammalian targets of rapamycin inhibitors had no statistically significant correlation with the probability of CKD progression (P = 0.194, Fig. 5D).

Finally, we conducted multivariate analysis using six variables (baseline eGFR, follow-up duration, duration of treatment with anti-VEGF agents, proteinuria, HT, and DM). Multivariate analysis showed that the duration of anti-VEGFR treatment (P = 0.014), baseline eGFR (P = 0.002), and DM (P = 0.040) were independently correlated with progression to CKD grade 4 (Table 3).

Discussion
Since nephrectomy is an essential part of RCC treatment, CKD is prevalent in patients with RCC. Huang et al. demonstrated that the 3-year probability of progression to CKD grade 3a and 3b in patients that underwent radical nephrectomy was 65% and 36%, respectively [18]. At the initiation of systemic therapy for metastatic disease in the present study, two-thirds of patients showed CKD grade 3 or higher in the present study (Fig. 1).

Several previous studies demonstrated that anti-VEGFR agents had a mild impact on renal dysfunction during the use of the drug. Khan et al. mentioned that patients on sorafenib or sunitinib did not develop ESKD while taking the drugs and the median time to maximum renal insufficiency was 6.6 months (range 0.4–19.6 months) [19]. Oya et al. also reported that eGFR did not change after the 12 months of sorafenib use [13]. Meanwhile, Ishihara et al. reported that sunitinib had more impact on renal dysfunction than sorafenib. They revealed that eGFR decreased by more than 10% in half of the patients taking sunitinib [15]. Takayama et al. demonstrated that eGFR decreased during the long-term use of sorafenib and/or sunitinib, which is consistent with the results of our study. However, no patients progressed to ESKD during their follow-up period [16]. Miyake et al. reported that reversible proteinuria might not impair renal function [20]. Our study is the first one to explore renal function during the lifetime of mRCC patients treated with anti-VEGFR agents. In this study, none of the patients who did not use anti-VEGFR agents progressed to CKD grade 4 or 5 (Figure. 5C). Besides, the duration of therapy with anti-VEGFR agents was an independent risk factor for progression to CKD grade 4 (Table 3). The patients who progressed to CKD grade 5 within 2 years were limited to those with baseline CKD grade 4 (Fig. 3A). However, with longer follow-up, two patients with a baseline CKD grade 3a were found to progress to ESKD (Figures. 3A and 4). In these patients, proteinuria occurred soon after the commencement of treatment with anti-VEGFR agents (Fig. 4). In the second case we reported, proteinuria was not resolved even after the withdrawal of sorafenib. CKD had progressed and HD was introduced 10 years after the start of sorafenib (Figure. 4B). Now that the prognosis of patients with mRCC is improving, tighter control of proteinuria and renal function is required, especially for patients with long-term survival. Furthermore, active surveillance should be challenged for patients with low tumor burden or slowly progressive disease [21, 22].

This study has several limitations. First, this was a retrospective study with a small sample size in a single institute. Since all patients were Japanese, the results may not be generalized. Second, the treatment strategies in this study were outdated because we set the eligible criteria for patients who started systemic therapy before December 2018, in order to observe patients using anti-VEGFR agents for a long enough time. Actually, 40% of patients were treated with cytokine, which is limited to use in the modern era (Table 2). However, owing to treatments other than anti-VEGFR agent, we were able to compare CKD progression and anti-VEGFR agent use in this study. Few patients used recently available anti-VEGFR agents (lenvatinib and cabozantinib), which have high affinity for tyrosine kinase receptors other than VEGFR. The inhibitory functions on fibroblast growth factor receptors in lenvatinib and Met/Axl in cabozantinib could theoretically worsen kidney function [23–25]. Third, the shorter survival in this study than that in the modern era caused small number of patients with CKD progression. The primary endpoint had to be set to grade 4, since only five patients progressed to CKD grade 5.
Nevertheless, this study could still provide valuable information because not only CKD grade 5 but also CKD grade 4 is a surrogate marker for ESKD [26]. Fourth, the treatment strategies in this study were heterogeneous and no mention was made of the differences between anti-VEGFR agent types. Fifth, we did not have detailed information about comorbidities at the start of the treatment, such as obesity. Finally, we did not follow the course of proteinuria or HT during treatment with anti-VEGFR agents. These complications should affect renal function. As mentioned above, this study includes several limitations. Nevertheless, now that overall survival is prolonging and anti-VEGFR agents are still commonly used, our study could provide important information; long-time use of anti-VEGFR agents could impair renal function.

Conclusions

The long-term use of anti-VEGFR agents could impair renal function. Patients with CKD grade 4 could progress to grade 5 within 2 years, and even patients with grade 3a could progress to ESKD when under long-term anti-VEGFR treatment.

Abbreviations

VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; OS, overall survival; mRCC, metastatic renal cell carcinoma; IMDC, international mRCC database consortium; ICI, immune checkpoint inhibitor, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rate, HT; hypertension, DM; diabetes mellitus, mTOR; mammalian target of rapamycin, ESKD; end stage kidney disease, HD; hemodialysis, IQR; interquartile range, CI; confidential interval,

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of Yamagata University Faculty of Medicine (approval no. 2016-403). The methods were carried out in accordance with the approved guidelines. The requirement for participants’ informed consent was waived by the same institutional review board due to retrospective design of this study, which is in accordance with Ethical Guidelines for Medical and Health Research Human Subjects published by Japanese ministry of Economy, Trade and Industry.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: Sei Naito received honoraria from Bristol Meier’s squibb Japan Inc., Ono Pharma. Pfizer Japan Inc., Merk biopharma Japan Inc., Takeda Pharma., MSD and Eisai as their sponsored speaker. Tomoyuki Kato received honoraria from Pfizer Japan Inc. as their sponsored speaker. Norihiko Tsuchiya received honoraria from Pfizer Japan Inc. Janssen, Novartis, Ono, Bayer, Sanofi, Takeda Pharm,
Bristol-Myers Squibb Japan, and Astelas Pharma., and research funds from Pfizer Japan Inc. and Eisai outside the submitted work. The other authors have declared that no conflict of interest exists.

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**Author Contributions:** KO, SN, TN, and NT participated in the design of the present study. KO drafted the manuscript and figures. SN performed statistical analyses. KO, TN, HF, YT, MU, MY, and HN collected data. SN, TK, HF, HN, and NT participated in the coordination and helped with the drafting of the manuscript. All authors have read and approved the final manuscript.

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**References**


Tables

Table 1-3 is available in the Supplemental Files section.

Figures
Flowchart of the patient cohort. Abbreviations: mRCC, metastatic renal cell carcinoma; eGFR, estimated glomerular filtration rate; HD, hemodialysis; CKD, chronic kidney disease
Figure 2

The correlation between eGFR and nephrectomy (A), proteinuria (B), HT (C), or DM (D). Abbreviation: eGFR, estimated glomerular filtration rate; HT, hypertension; DM, diabetes mellitus.
Figure 3

Kaplan–Meier curves to estimate the rate of progression to CKD grade 5 (A) and grade 4 (B).

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

A. 71 y. male
Prior radical nephrectomy
pT1bNx
multiple lung and pleural metastases
IMDC favorable risk.
Co-morbidity: HT
Baseline eGFR: 48.3 ml/minute/1.73m²

B. 55 y. female
Prior radical nephrectomy
pT4Nx
multiple lung and muscle metastases
IMDC intermediate risk.
Co-morbidity: No
Baseline eGFR: 47.8 ml/minute/1.73m²

Figure 4

The process of two cases whose baseline CKD grade 3a and whose CKD progressed to grade 5.

Abbreviations: IMDC, international metastatic renal cell carcinoma data consortium; HT, hypertension; eGFR, estimated glomerular filtration rate; UPt, urinary protein; HD, hemodialysis; Nv, nivolumab
Figure 5

Kaplan–Meier curves to estimate the rate of progression to CKD grade 4 on proteinuria (A), HT (B), DM (C), nephrectomy (D), anti-VEGFR agent use (E), and mTOR inhibitor use (F). Abbreviations: CKD, chronic kidney disease; HT, hypertension; DM, diabetes mellitus; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx