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Case Report

Combination Therapy of Pembrolizumab plus Axitinib for a Patient on Hemodialysis with Metastatic Renal Cell Carcinoma: A Case Report

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Keywords
Axitinib · Hemodialysis · Pembrolizumab · Renal cell carcinoma

Abstract
Here, we discuss the safety and management of adverse events associated with pembrolizumab plus axitinib combination therapy for metastatic renal cell carcinoma in patients on hemodialysis. A 76-year-old man was diagnosed with cT3aN0M0 renal cell carcinoma due to gross hematuria. Stereoscopic radiotherapy for metastatic lesions of the ipsilateral kidney was performed 9 years after right laparoscopic radical nephrectomy. Soon after, the patient started to receive hemodialysis due to end-stage renal disease. Further stereoscopic radiotherapy was needed for metastasis of the ipsilateral kidney and lung. Fifteen years after diagnosis, systemic therapy was necessary to control new metastases, such as in the right scapular bone. We selected pembrolizumab plus axitinib combination therapy as the first-line systemic therapy for any risk as defined by the International Metastatic RCC Database Consortium. Although we needed to pay attention to the adverse events unique to hemodialysis, he underwent this combination therapy without any difficulty for 6 months. Here, we report the practice of combination therapy in patients on hemodialysis in light of the literature.

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Introduction

Pembrolizumab plus axitinib combination therapy has been indicated as the first-line treatment for metastatic renal cell carcinoma (mRCC) and expanded as a treatment option for mRCC. Combination therapies of immune checkpoint inhibitor (ICI) plus tyrosine kinase inhibitor (TKI) have become mainstream in the treatment of mRCC [1, 2]. In the KEYNOTE-426 trial, there is a report that the combination therapy of pembrolizumab plus axitinib had more grade 3/4 liver enzyme elevations than the monotherapy [3]. However, there have been no reports to date of this combination therapy for mRCC in patients on hemodialysis (HD) due to end-stage renal disease (ESRD). There are some unclear points regarding the safety and efficacy of this combination therapy of ICI and TKI in metastatic renal cancer in patients on HD. A patient on HD who was considered to have an intermediate risk according to the International Metastatic RCC Database Consortium (IMDC) was treated with pembrolizumab plus axitinib combination therapy in our institute. Through the case, we discuss the safety and efficacy of this combination therapy, especially in patients on HD.

Case Presentation

A 76-year-old man was diagnosed with right RCC due to gross hematuria 15 years prior to the time of writing. CT revealed a blood flow-rich tumor with a diameter of 85 mm (Fig. 1) and infiltration into the surrounding adipose tissue without lymph nodes or any metastasis, resulting in cT3aN0M0 at that time. Laparoscopic right nephrectomy was performed using the transperitoneal approach to identify pathologically clear cell carcinomas, pT3, G2 > G3, INFb, and v+.

A small high absorption area in the lower pole of the left kidney was observed on CT 7 years after surgery, followed by imaging inspection for 2 years after surgery (Fig. 2). However, MRI revealed an increasing mass of 24 mm in diameter, which was presumed to be RCC requiring treatment intervention. His serum creatinine level gradually increased to approximately 2 mg/dL. Therefore, stereotactic irradiation with 70 Gy in 10 fractions was selected for the renal mass to minimize renal damage. Unfortunately, after irradiation, his serum creatinine gradually increased to 9 mg/dL, and HD was induced, although the left renal mass continued to shrink.

Soon after induction of HD, a 15-mm renal mass in the upper pole of the left kidney (Fig. 3) and a single mass in the right lung were revealed by CT (Fig. 4). Stereotactic irradiation with 70 Gy in 10 fractions was applied to the mass of the upper pole of the left kidney, and 60 Gy in 8 fractions was applied to the mass of the right lung. The irradiated lesions were stable, without growth.

A soft tissue mass with destruction was noted on the right scapula by CT scan 2 years after the last irradiation; this was diagnosed as a bone metastasis of RCC by positron emission tomography-CT (Fig. 5, 6). Systemic treatment was deemed necessary. The IMDC risk with only 1 factor of lower Hb (12.6 g/dL) represented an intermediate risk. We selected combination therapy with ICI + TKI recommended as the first-line systemic therapy for mRCC at any IMDC risk. An intravenous infusion of pembrolizumab 200 mg every 3 weeks and axitinib 10 mg/day were started. Although the patient needed to decrease axitinib 2 months after initiation due to increased blood pressure and occasionally due to fatigue during HD and unexplained increased C-reactive protein level, he was able to continue the combination therapy on schedule for 6 months while undergoing HD without any obvious immune-related adverse events (AEs) as described in Figure 7.

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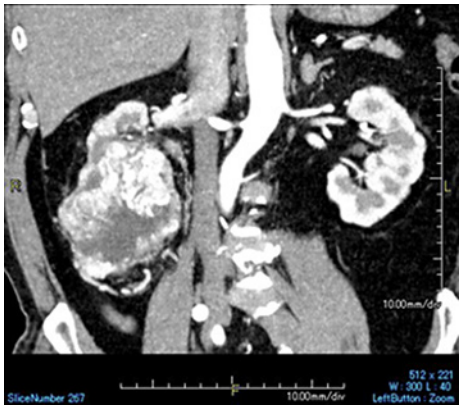

Fig. 1. Right kidney tumor on contrast CT at the first visit.

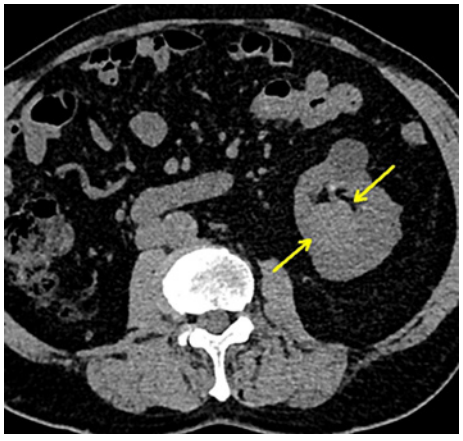

Fig. 2. Left kidney tumor on plain CT at the time of first recurrence.

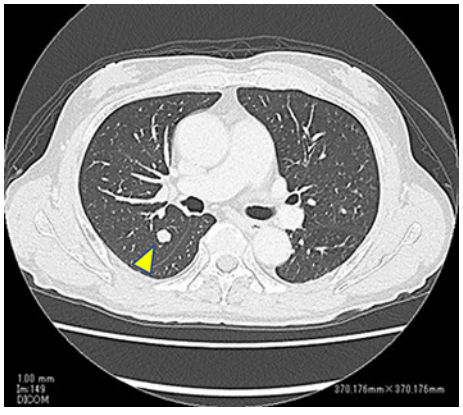

Fig. 3. Lung metastasis on plain CT at the time of second recurrence.

Discussion

In the KEYNOTE-426 trial, which demonstrated the efficacy of pembrolizumab plus axitinib combination therapy for metastatic renal cancer, patients with ESRD were excluded. Therefore, the safety and efficacy of this combination therapy are unclear for patients on HD. However, many patients with mRCC on HD need to be treated with this combination therapy. According to previous reports regarding the safety and efficacy of each single use

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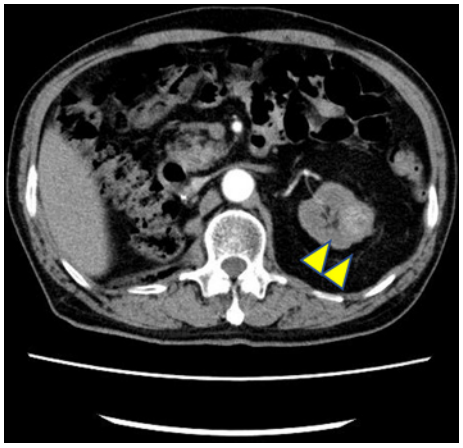

Fig. 4. Left kidney tumor on plain CT at the time of second recurrence.

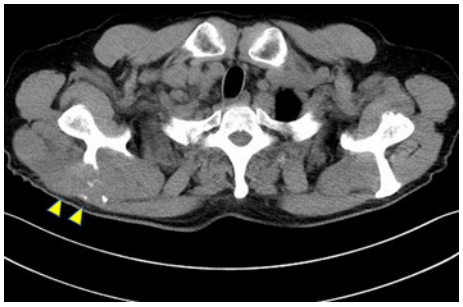

Fig. 5. Right scapula metastasis on plain CT.

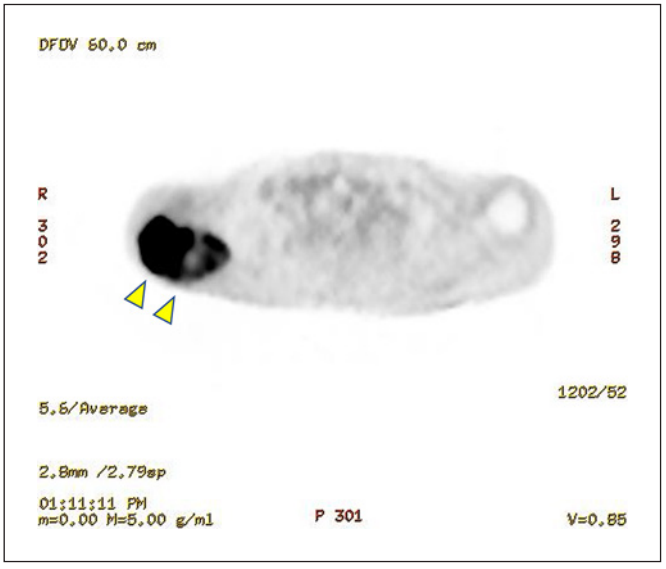

Fig. 6. Right scapula metastasis in bone scintigraphy.

of pembrolizumab or axitinib for patients on HD, each drug could be used for them at the same dosage as patients with normal renal function because the amount of each drug removed by the dialyzer was found to be small enough that the influence of HD could be ignored. Thiery et al. [4], Kopecky et al. [5], and Ishihara et al. [6] reported the efficacy and safety of normal use of axitinib in patients with ESRD. Although axitinib has a small molecular weight, it is not removed by dialysis because it binds to proteins such as albumin.

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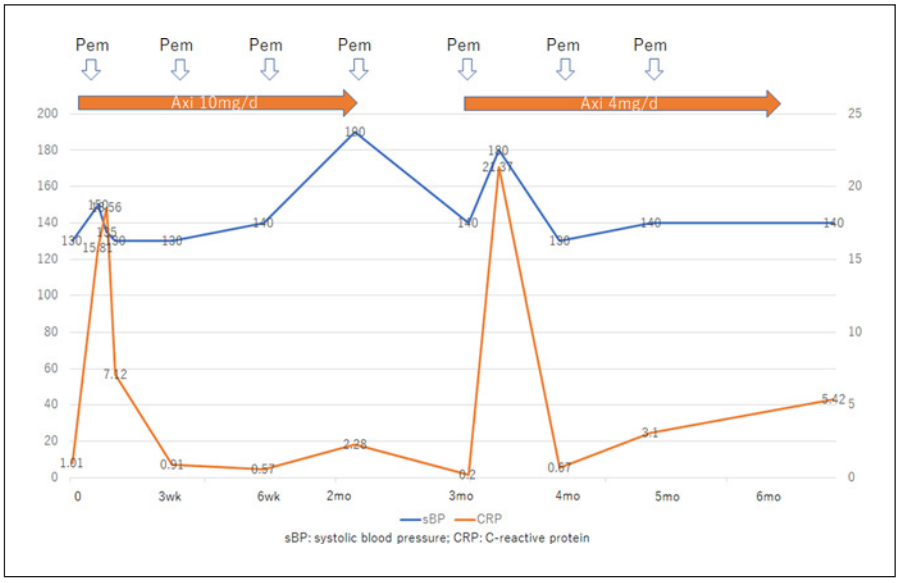

Fig. 7. A timeline concerning pembrolizumab administration, axitinib dose adjustment, and adverse events (sBP transition and serum CRP level transition). sBP, systolic blood pressure; CRP, C-reactive protein.

Therefore, a rebound phenomenon concerning HD, which represents the temporary rise in serum concentration due to water removal, is known. Because of this, patients on HD have a risk of temporary adverse symptoms, such as nausea and poor physical condition during and after HD. Sorafenib has been reported to become more toxic due to repeated increased exposure during HD [7]. Axitinib has been reported to be more likely to cause increased blood pressure as an adverse effect, especially in patients on HD who experience cardiac stress with every single HD session. Conversely, long-term administration of sorafenib and sunitinib for >2 years in patients on HD could be safe and effective without major problems [8]. Since our TKI clearance findings strongly depended on the individuals from our study, therapeutic drug monitoring for TKIs could be reported to contribute to minimizing AEs [9, 10].

With regard to immunotherapy concerning patients on HD, Ishizuka et al. [11] reported that the safety and efficacy of pembrolizumab for patients on HD in non-small cell lung cancer was similar to those with normal renal function. A humanized immunoglobulin G4 monoclonal antibody against human PD-1 cannot pass through the glomerular membrane of the kidney and is unlikely to be removed by dialysis because of its high molecular weight [12]. Thus, the antitumor effect of pembrolizumab-bound lymphocytes was not diminished in patients on HD. Likewise, Chang et al. [12] have also reported the safety and efficacy of pembrolizumab in patients on HD with melanoma. Moreover, Kobayashi et al. [13] reported the safety and efficacy of combination therapy with nivolumab and ipilimumab (anti-CTLA-4 antibody) in patients on HD. However, a case of hypercarbic respiratory failure was reported 2 weeks after nivolumab administration, although the authors stated that it was not related to nivolumab administration because it was shown to be different from anti-PD-1-related pneumonia on CT images, and it was improved only by antibiotic administration without administration of steroids [14]. Table 1 shows the safety and efficacy of each drug in patients on HD. In this patient on HD, we selected a combination therapy of pembrolizumab plus axitinib to prevent a high prevalence of immune-related AEs that can be caused by the combination therapy of nivolumab plus ipilimumab.

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Table 1. The safety and efficacy of each drug in patients on HD

Author	Therapy	Type of cancer	AE	Therapeutic effect
Ishizuka et al. [11]	Pem	Non-small cell lung cancer	G1 rash	PR
Chang et al. [12]	Pem	Melanoma	None	PR
Morinaga et al. [15]	Niv	Renal cell carcinoma	None	SD
Ito et al. [16]	Niv	Renal cell carcinoma	None	CR
Carlo et al. [14]	Niv	Renal cell carcinoma	G2 hypercarbic respiratory failure	PR
Kobayashi et al. [13]	Ipi and Niv	Renal cell carcinoma	None	SD
Thiery-Vuillemin et al. [4]	Axi	Renal cell carcinoma	G3 hypertension G1 diarrhea G1 anemia	PR
Kopecky et al. [5]	Axi	Renal cell carcinoma	G1 fatigue, G1 anemia	PD
Nishida et al. [17]	Axi	Renal cell carcinoma	G1 hypertension	SD

AE, adverse event; Axi, axitinib; Niv, nivolumab; Pem, pembrolizumab.

According to previous reports, we found that the combination therapy of pembrolizumab plus axitinib could be used in patients on HD in the same manner as in non-HD patients. However, patients on HD have some problems peculiar to HD, such as cardiovascular fragility, susceptibility to infection, malnutrition, atherosclerosis syndrome, and unexpected symptoms requiring emergency care. The combination of ICI plus TKI for patients on HD requires close follow-up, drug withdrawal as needed, and fine dose adjustment of TKIs. In the era of combination therapy, it will become increasingly important to comprehensively understand patients on HD with metastatic carcinoma between oncologists and nephrologists to use new combination therapy.

Conclusion

Even with a short follow-up period of 6 months, a typical dosage of pembrolizumab plus axitinib combination therapy could be acceptable in view of the safety of patients on HD with mRCC.

Acknowledgments

Study processes, including data collection and management, were performed by Natsue Abe, a scientific officer at the Department of Urology, Tohoku University Graduate School of Medicine, Sendai. We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

This study for a case report was approved by the Ethics Committee of Tohoku University Hospital (Approval No. 23355). We have obtained written informed consent for publication from the patient's family.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yuki Katsumata and Yoshihide Kawasaki contributed to conception or design of the work. Kayu Tanaka, Daisuke Nakayama, Hiromichi Katayama, Yohei Satake, Takuma Sato, Naoki Kawamorita, Shinichi Yamashita, Tetsuya Sato, Kosuke Shoji, Koji Mitsuzuka, and Akihiro Ito contributed to interpretation of data for the work. Yuki Katsumata and Yoshihide Kawasaki drafted the manuscript. Yuki Katsumata and Yoshihide Kawasaki critically revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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