Abstract. Background/Aim: There are few reports about the administration of nivolumab plus ipilimumab to hemodialysis patients and their efficacy and safety have not been established yet. Case Report: A 74-year-old male, who was receiving hemodialysis, was presented with metastatic renal cell carcinoma (mRCC). Two years later, more metastases were found, hence, immunotherapy involving nivolumab plus ipilimumab was initiated. After two doses of immunotherapy, interstitial pneumonia was observed. Thus, steroid pulse therapy was administered immediately. Subsequently, computed tomography (CT) findings and symptoms improved markedly. One month later, a CT scan showed a nodular shadow and an air cavity. A fungal infection was strongly suspected, so an antifungal drug was administered. Conclusion: Combination immunotherapy with nivolumab plus ipilimumab was demonstrated to be effective in a hemodialysis patient with mRCC.

The incidence of interstitial pneumonia has been reported to be 3.5% among patients treated with immune-checkpoint inhibitors (1). Furthermore, the incidence of interstitial lung disease (ILD) caused by combinations of immune-checkpoint inhibitors including cytotoxic T-lymphocyte antigen-4 inhibitors has been shown to be 10.2% (2). ILD is a severe immune-related adverse event (irAE) of such treatment. It has been reported that compared with ipilimumab monotherapy, nivolumab plus ipilimumab combination treatment has an odds ratio for all-grade pneumonia of 3.68 (3).

To our knowledge, this is the first reported case in which first-line nivolumab plus ipilimumab for metastatic renal cell carcinoma (mRCC) produced a response in a hemodialysis (HD) patient. In this case, the dose of immunotherapy of nivolumab plus ipilimumab was the same as that administered in patients with normal renal function.

The prevalence of fungal pneumonia in HD patients has been reported to be 0~2.1% (4). Based on the occurrence of lung disease in these cases, clinicians should be aware of the possibility of fungal infections when administering nivolumab plus ipilimumab to HD patients, who are susceptible to infection. Furthermore, dose reduction might be necessary when treating HD patients with nivolumab plus ipilimumab.

We report a case of severe fungal pneumonia after nivolumab plus ipilimumab for mRCC in a hemodialysis patient.

Case Report

A 74-year-old male, who was receiving HD, was referred to the Department of Urology, Teikyo Chiba Medical Center, Ichihara, Chiba, Japan, because of a left-sided renal tumor, hypoalbuminemia, high C-reactive protein levels, and iron deficiency anemia in April 2017. Based on a dynamic computed tomography (CT) scan and various other examinations, he was diagnosed with mRCC. His clinical stage was T3aN0M1 according to the TNM classification, and laparoscopic radical nephrectomy was carried out in May 2017. A pathological examination revealed clear cell carcinoma (pT3a, INFα, V1, Fuhrman nuclear grade 3). The anemia progressed from February 2019 onwards, and blood transfusions were performed during each HD session. After two months, CT revealed lung metastasis (Figure 1A), right adrenal gland metastasis (Figure 1B), right renal tumor (Figure 1C) and right psoas major muscle metastasis (Figure 1D). The patient was categorized as intermediate risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification. Interventional radiotherapy was performed to stop bleeding from the duodenal tumor twice (Figure 2A).
One month later, immunotherapy involving nivolumab plus ipilimumab (Nivo/Ipi: 240 mg nivolumab plus 1 mg/kg ipilimumab, administered intravenously every three weeks) was initiated. After two doses of immunotherapy, the patient suffered respiratory failure. A CT scan of the chest showed interstitial pneumonia (Figure 3A). So, we diagnosed the patient with drug-induced interstitial pneumonia, and steroid pulse therapy was administered immediately. Subsequently, the patient’s respiratory failure and CT findings improved markedly (Figure 3B), and the steroid dose was gradually reduced, before being maintained at 20 mg/day.

About three months after the initiation of the immunotherapy, a CT scan revealed partial responses in various metastatic organs. The lung metastasis, right adrenal gland metastasis, and right renal tumor had reduced to 52%, 62% and 33% of their original sizes, respectively (Figure 1E-G), and the right psoas major muscle metastasis had disappeared (Figure 1H). After nivolumab plus ipilimumab treatment and intravenous radiotherapy, the duodenal tumor was disappeared (Figure 2B). One month later, respiratory discomfort occurred again, and the steroid dose was increased. A CT scan showed a nodular shadow and an air cavity in the right lung field (Figure 3C). A fungal infection was strongly suspected based on the high levels of β-D-glucan, a positive result in an Aspergillus antigen test, and the findings of bronchofiberscopy. Therefore, an antifungal drug was administered. Although the steroid dose was increased to 30 mg/day, the patient developed hypotension during HD. Afterwards, it was difficult to continue with the HD, and the patient died within two weeks.

Figure 1. Computed tomography images. The lung metastasis, right adrenal gland metastasis, right renal tumor and psoas major muscle metastasis before nivolumab plus ipilimumab treatment (A, B, C, D) and after 2 doses of treatment (E, F, G, H). Reduction in size after two doses of nivolumab plus ipilimumab was observed. The red and yellow arrowheads indicate lesions caused by the disease.
Discussion

To our knowledge, there have not been any reports about the administration of nivolumab plus ipilimumab to HD patients with mRCC. Therefore, this report is considered to be very valuable. Although it was not possible to administer all four of the prescribed doses due to ILD occurring as an irAE, the patient’s CT findings suggested that the treatment was effective.

The CheckMate 214 trial reported that two of the three coprimary endpoints were met; i.e., among intermediate- and poor-risk patients the risk of death was 37% lower in the patients treated with nivolumab plus ipilimumab than in those treated with sunitinib, and the objective response rate was higher in the nivolumab plus ipilimumab group (42% vs. 27%, respectively) (5). Although treatment decisions regarding unresectable RCC differ depending on the risk classification, immune-checkpoint inhibitors

Figure 2. Gastroscopy images. A) Before nivolumab plus ipilimumab treatment, gastroscopy (GS) showed an irregular hemorrhagic elevated lesion of 15 mm in size at the bulb of duodenum. B) After nivolumab plus ipilimumab treatment and intravenous radiotherapy, the duodenal tumor was disappeared.

Figure 3. Computed tomography of the chest. A) Bilateral diffuse interstitial pneumonitis seen after two doses of nivolumab plus ipilimumab treatment. B) Amelioration of interstitial pneumonia induced by steroid therapy. C) Fungal pneumonitis and an air cavity. The red arrowheads indicate disease lesions caused by the disease.
have recently been used as first-line treatments in most cases.

Several case studies have reported on the use of either nivolumab or ipilimumab in patients with end-stage renal disease (ESRD). It is not necessary to adjust the dose of ipilimumab in patients with renal dysfunction (6). Cavalcante et al. have reported that ipilimumab was safe and effective in two patients with metastatic melanoma and ESRD (7). In addition, it has been suggested that HD patients can be prescribed the same dose of nivolumab as other patients (8). Carlo et al. have reported the case of a 77-year-old male HD patient with mRCC and ESRD, who received 4th-line treatment with nivolumab (9). Treatment with nivolumab produced a partial radiological response along with an improvement in pain control and performance status. Tabei et al. have described the case of a HD patient, who was successfully treated with nivolumab as a 7th-line therapy for mRCC (10). Ansari et al. have reported that the case of a 72-year-old male with mRCC and ESRD on dialysis who received second-line nivolumab therapy and achieved an excellent symptomatic and radiological response, remaining progression-free for over 22 months. They have recommended that patients with mRCC with ESRD and dialysis should be treated with standard protocols applicable to those with normal renal function (11). Osman-Garcia et al. have suggested that patients on hemodialysis could be treated with nivolumab in the same way as populations without impaired kidney function (12).

In the present case, the patient was categorized as intermediate risk according to the IMDC classification; therefore, we selected immunotherapy involving nivolumab plus ipilimumab. There are few reports about the administration of nivolumab plus ipilimumab to HD patients, and hence, we needed to determine appropriate doses of these drugs for our patient. As it had been reported that there is no need to reduce the dose of either drug in HD patients when they are used as single agents, we did not reduce the doses of nivolumab or ipilimumab in this case. Specifically, we prescribed the same doses as those administered to patients with normal renal function, while monitoring the patient for severe irAEs. After two doses of immunotherapy had been administered, we found that various metastases and the right renal tumor exhibited partial responses, which confirmed that the immunotherapy was effective. However, the patient developed drug-induced interstitial pneumonia after receiving two doses of immunotherapy. He subsequently developed a fungal infection and eventually died. In HD patients, who tend to develop to infections easily, we suggest that it is necessary to fully consider the risk of fungal infections.

Regarding the treatment of mRCC with nivolumab plus ipilimumab in HD patients, combination immunotherapy was demonstrated to be effective, but the concomitant irAEs that arose suggest that the prescribed doses should be reduced in such cases. However, it is difficult to decide how much the dose of each drug should be adjusted based on this case, and it will be necessary to accumulate more cases. Further evidence and research are needed to determine the treatment of HD patients with mRCC.

Conclusion

In the present case, the HD patient received the same doses of nivolumab plus ipilimumab for mRCC as patients with normal renal function. Although the effectiveness of treatment with nivolumab plus ipilimumab was recognized, the safety of the treatment was not verified. In dialysis patients, including those with end-stage renal failure, it has been suggested that there were cases that required dosage adjustment. Furthermore, it was important to identify patients who required dose reduction before administration. Therefore, further research should be performed to define appropriate treatments for HD patients with mRCC.

Conflicts of Interest

All Authors declare that have no conflicts of interest in regard to this study.

Authors’ Contributions

HM designed the study and acquired the data. HM prepared the manuscript and edited the manuscript. KM, KO, KH, TS, KA, SK and YN were involved in the care of the patient and reviewed the manuscript. All Authors read and approved the manuscript.

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