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CASE REPORT

Durable complete response to combination nivolumab and ipilimumab in metastatic renal cell carcinoma

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ABSTRACT

Immune checkpoint inhibitors, which promote or suppress the anti-tumor immune response, are becoming the mainstay of cancer treatment. In 2018, CheckMate 214 study showed a higher response rate with ipilimumab and nivolumab combination therapy compared to conventional therapy for advanced renal cell carcinoma. We report a case of complete response and durable response for two years to ipilimumab and nivolumab combination therapy in a patient with postoperative renal cancer recurrence that caused immune-related adverse events such as interstitial pneumonia and hepatotoxicity.

Keywords: Immune Checkpoint Inhibitor; Ipilimumab; Nivolumab; Combination Therapy; Advanced Renal Cell Carcinoma; Durable Response; Immune-related Adverse Events

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1. Introduction

The advent of immune checkpoint inhibitors is an epoch-making moment in the treatment of cancer[1]. Those currently approved for human use include immunotherapies targeting programmed cell death 1 and cytotoxic T lymphocyte-associated protein 4[2]. In 2018, the CheckMate 214 study showed that the combination of the ipilimumab and nivolumab (IPI+NIVO) significantly improved overall survival compared with the conventional standard of care sunitinib (SUN) in untreated metastatic renal cell carcinoma[3].

Based on this result, in August 2018, the combination of ipilimumab and nivolumab was covered for high-risk patients in the International Metastatic Renal Cell Carcinoma Database Consrtium (IMDC) risk category with chemotherapy-naive unresectable or metastatic renal cell carcinoma. We report a case of complete response and durable response in two years with ipilimumab-nivolumab combination therapy for metastatic renal cell carcinoma at Takatsuki Red Cross Hospital.

2. Case report

An 84-year-old Japanese man was diagnosed with left renal mass on a computed tomography (CT) scan during follow-up for ulcerative colitis. The CT scan revealed an enhancing mass in the left kidney measuring 56.4 × 48.9 × 51.0 mm. The patient underwent a left radical nephrectomy with pathological evaluation identifying T3N0M0 renal

cell carcinoma (RCC) (clear cell carcinoma, grade 2, Fuhrman grade 2, INFb, ly0, v0) (**Figure1**). Three months after nephrectomy, a surveillance CT scan identified extensive presumed metastases in the iliopsoas at the height of the renal artery from the aortic bifurcation and single lung legions (16 × 11 mm) (**Figure 2**). Echo-guided percutaneous needle biopsy of a presumed metastatic lesion was consistent with metastatic RCC.

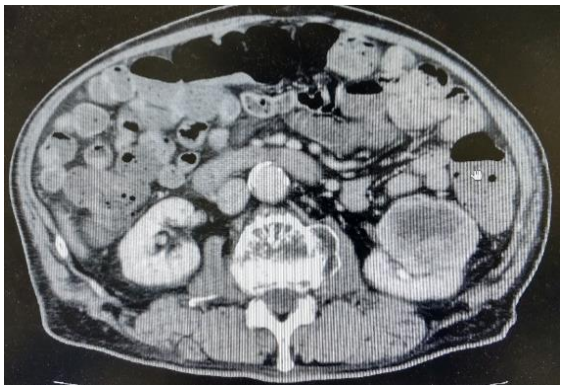

Figure 1. CT scan shows the left renal mass (56.4 × 48.9 × 51.0 mm) transverse section**.**

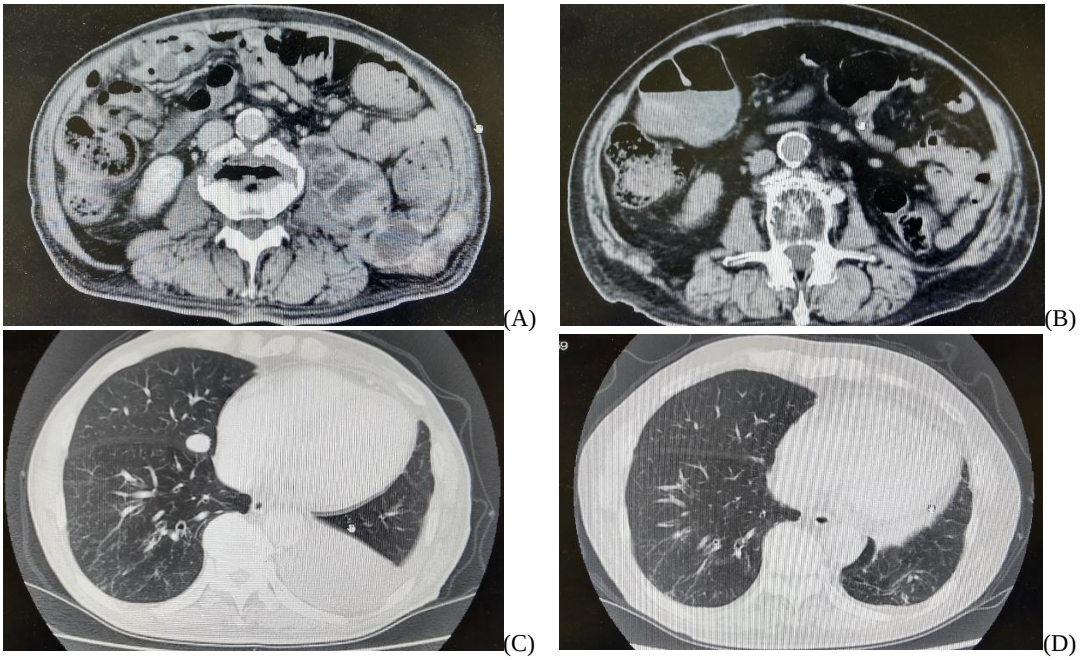

Figure 2. CT scans show a metastatic iliopsoas lesion (**A**) and a complete response after 4 cycles of immunotherapy (**B**). A 16 × 11 mm lung metastasis (**C**) and a complete response after 4 cycles of immunotherapy (**D**)**.**

Laboratory workup before starting treatment showed a hemoglobin of 6.4 g/dL, creatinine of 1.1 mg/dL, platelet count of 2.6 × 10^9/L, absolute neutrophil count of 7.3 × 10^9/L, blood urea nitrogen of 21.1 mg/dL, lactate dehydrogenase of 281 U/L, and C-reactive protein of 25.99 mg/dL.

IMDC risk classification was poor risk due to Karnofsky performance status 70%, low hemoglobin and recurrence within 1 year. IPI+NIVO combination therapy (ipilimumab 1 mg/kg, nivolumab 240 mg/body) was started as first-line therapy. After administration, the patient struggled to cope with tumor fever, anorexia, high CRP, and delirium, but by day 23, fever had resolved, food intake had increased, and CT scan on day 30 showed disappearance of lung lesions and more than 80% reduction in the iliopsoas muscle legion. Two months after the administration of IPI+NIVO, nivolumab as a single agent was administered 3 times in total, and complete response (CR) was maintained, but renal function worsened slightly to creatinine of 2.0 mg/dL, so the drug was temporarily withdrawn. After that, this case maintained CR for 2 years without relapse.

3. Immune-related adverse events (irAEs)

Four months after the last dose of nivolumab, the patient caused grade 4 interstitial pneumonia and required 2 months of hospitalization for steroid pulse therapy (methylprednisolone 1,000 mg/day) (**Figure 3**). Three months later, during steroid tapering (prednisone 15 mg/day), the patient developed steroidal diabetes mellitus (HbA1c 12.3%) and required hospitalization for one month for insu-

lin induction. One month after discharge, the patient had grade 4 hepatotoxicity (ALT 1099 IU/L, AST 67 IU/L) and required 2 months of hospitalization for half-steroid pulse therapy (methylprednisolone 500 mg/day). The following 10 months passed without any adverse events or hospitalization.

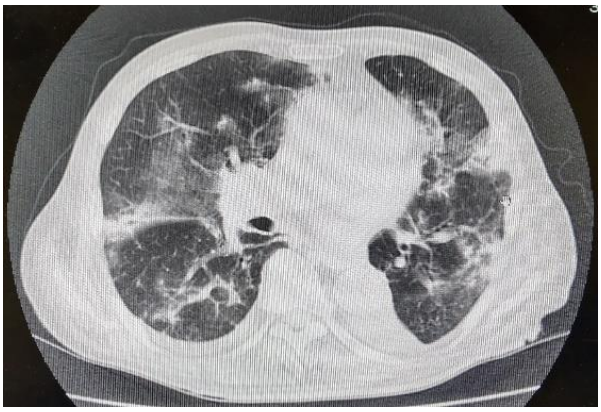

Figure 3. CT scan shows grade 4 interstitial pneumonia 4 months after the last dose of nivolumab.

4. Discussion

Metastatic RCC is refractory to anticancer agents and radiation therapy. Although immunotherapeutic agents such as IFN-α and IL-2 have been used, the therapeutic results have been inadequate, with a response rate of around 10% and a median overall survival of 1 year[5]. In 2006, molecular targeted agents targeting angiogenesis inhibition were introduced, and the treatment of metastatic RCC began to focus on molecular targeted agents. Although these drugs provide a certain therapeutic effect, there are few cases in which a CR can be achieved by the drugs alone, and the effect is not permanent, with tumor relapse eventually appearing[6]. In 2015, nivolumab, an immune checkpoint inhibitor, was introduced, and in an international randomized phase III trial (CheckMate 025) for metastatic RCC after second-line treatment, it was reported that overall survival (OS) and response rate in the nivolumab group were significantly higher than in the everolimus group, which was the previous second-line treatment[7]. Furthermore, the combination of ipilimumab and nivolumab in untreated metastatic renal cell carcinoma emerged from the CheckMate 214 trial mentioned. In this international phase III study (CheckMate 214), the 18-month OS rate was 75% in the IPI+NIVO group and 60% in the SUN group[3]. In the extended 4-year follow-up of this study, the OS rate at 48 months was 53.4% in the IPI+NIVO group and 43.3% in the SUN group. In the intermediate/poor risk group, the 48-month OS rate was 50.0% in the IPI+NIVO group and 35.8% in the SUN group[4].

The first characteristic of combined immune checkpoint therapy is a high CR rate. In the CheckMate 214 study in advanced RCC, the CR rate of was 10.7% with IPI+NIVO vs 2.6% with SUN in all patients, and 10.4% with IPI+NIVO vs 1.4% with SUN in the intermediate/poor risk patients. Durable response is also one of the notable features of immunotherapy. It was reported that high-dose interleukin-2 therapy, which is also an immunotherapy, had a sustained effect with almost no recurrence in about 7% of patients with advanced RCC[8]. In the CheckMate 214 trial, 27 of 59 patients (45.8%) in the IPI+NIVO had a complete response, 67 of 156 patients (42.9%) had a partial response in the IPI+NIVO, 3 of 13 patients (21.4%) in the SUN had a CR, and 39 of 163 patients (23.9%) had a partial response in the SUN and subsequent systemic therapy was not required after discontinuation[3].

On the other hand, irAEs are unavoidable, and their management is extremely important. The incidence of irAEs caused by immune checkpoint inhibitors has been reported to increase with combination therapy compared with nivolumab or ipilimumab alone[9]. In this case, the patient had grade 4 interstitial pneumonia, hepatotoxicity, and also steroidal diabetes associated with the treatment. Adverse drug reactions of 3–4 grades were 47.3% for IPI+NIVO, 64.1% for sunitinib, but adverse drug reactions leading to discontinuation were 22.1% for IPI+NIVO, 12.9% for sunitinib, and treatment-related deaths were 8/547 and 4/535. Pulmonary toxicity, which also appeared in this case, was 6.8% for all grades and 1.1% for grades 3–4, and hepatic toxicity was 10.2% for all grades and 8.6% for grades 3–4[3]. In addition, endocrine disorders such as pituitary dysfunction and type 1 diabetes mellitus are more frequently observed with combination therapy than with monotherapy[10]. Even so, the possibility of immune-related toxicity should be kept in mind both during and after ICI treatment. In

conclusion, this case embodied “good medicine tastes bad” with high CR rate, durable response, and strong irAEs.

Conflict of interest

The authors declare no potential conflicts of interest.

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References

1. Furukawa F. The Nobel Prize in Physiology or Medicine 2018 was awarded to cancer therapy by inhibition of negative immune regulation. Trends in Immunotherapy 2018; 2(1). doi: 10.24294/ti.v2.i3.1065
2. Seidel JA, OtsukaA, Kabashima K. Treating tumors with immune checkpoint inhibitors: Rationale and limitations. Trends in Immunotherapy 2017; 1(1): 2–9. doi: 10.24294/ti.v1.i1.20
3. Motzer RJ, Tannir NM, McDermott DF, *et al*. Nivolumab plus ipilimumab versus sunitinib in sdvanced renal-cell carcinoma. New England Journal of Medicine 2018; 378(14): 1277–1290. doi: 10.1056/NEJMoa1712126
4. Albiges L, Tannir NM, Burotto M, *et al*. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020; 5(6): e001079. doi: 10.1136/esmoopen-2020-001079
5. Motzer RJ, Mazumdar M, Bacik J, *et al*. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. Journal of Clinical Oncology 1999; 17(8): 2530–2540. doi: 10.1200/JCO.1999.17.8.2530
6. Iacovelli R, Alesini D, Palazzo A, *et al*. Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials. Cancer Treatment Reviews 2014; 40(2): 271–275. doi: 10.1016/j.ctrv.2013.09.003
7. Motzer RJ, Escudier B, McDermott DF, *et al*. Nivolumab versus everolimus in advanced renal-cell carcinoma. New England Journal of Medicine 2015; 373(19): 1803–1813. doi: 10.1056/NEJMoa1510665
8. Rosenberg SA. IL-2: The first effective immunotherapy for human cancer. The Journal of Immunology 2014; 192(12): 5451–5458. doi: 10.4049/jimmunol.1490019
9. Escudier B, Porta C, Schmidinger M, *et al*. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2019; 30(5): 706–720. doi: 10.1093/annonc/mdz056
10. Inaba H, Ariyasu H, Okuhira H, *et al*. Endocrine dysfunctions during treatment of immune-checkpoint inhibitors. Trends in Immunotherapy 2020; 4(1): 18–26. doi: 10.24294/ti.v4.i1.606