Clinical and histological response to combination nivolumab and ipilimumab in metastatic renal cell carcinoma

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ABSTRACT

Patients with renal cell carcinoma (RCC) often remain asymptomatic until the disease is advanced, with about 25% presenting at an advanced stage. We present a case of metastatic RCC treated with combination ipilimumab and nivolumab with complete radiological and pathological response. Currently, combination nivolumab and ipilimumab is a preferred option for intermediate- and poor-risk patients with clear cell stage IV RCC.

KEYWORDS Complete response; immunotherapy; nivolumab and ipilimumab; renal cell carcinoma

Renal cell carcinoma (RCC) comprises approximately 4.2% of all new cancer diagnoses and 2.4% of all cancer deaths.¹ Most patients with RCC remain asymptomatic, and about 25% present at an advanced stage. The treatment approach for metastatic RCC (mRCC) depends on prognostic risk factors, with the Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Data Consortium (IMDC) the most commonly used prognostic models.² Currently, immunotherapy with checkpoint inhibitors and targeted therapy with vascular endothelial growth factor (VEGF) inhibitors are the primary systemic modalities for the management of advanced RCC.^{3–6} We present a case of mRCC with poor-risk features and heavy disease burden treated with combination checkpoint therapy (ipilimumab and nivolumab) with a complete clinical, radiological, and pathological response.

CASE DESCRIPTION

A 56-year-old-man presented with frank hematuria, left flank pain, and weight loss. His past medical history included localized low-risk prostate cancer, for which he was under active surveillance. Initial laboratory workup showed a hemoglobin of 10.7 g/dL, creatinine of 1.2 mg/dL, platelet

count of $3.5 \times 10^9/L$, absolute neutrophil count of $8.7 \times 10^9/L$, blood urea nitrogen of 33 mg/dL, lactate dehydrogenase of 674 U/L, and corrected calcium of 11.5 mg/dL (9–10.5 mg/dL). A computed tomography (CT) scan revealed a large enhancing mass in the left kidney measuring $10.2 \times 11.8 \times 11$ cm with extension into the left renal vein, renal pelvis, left ureter, bladder, multiple liver nodules, left adrenal nodule, and multiple subcentimeter lung nodules (*Figure 1a, 1b*). Ultrasound-guided needle biopsy of the liver confirmed clear cell RCC (*Figure 2a*). The patient was categorized as stage IV RCC and as high risk by the IMDC prognostic model based on the presence of anemia, elevated lactate dehydrogenase, hypercalcemia, thrombocytosis, and neutrophilia. His Eastern Cooperative Oncology Group performance status was 2.

After four cycles of combination nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks followed by nivolumab at 3 mg/kg every 4 weeks, a restaging CT scan showed a 25% reduction in the left renal mass with complete resolution of liver metastasis, lung nodules, the left adrenal mass, and left renal vein involvement and a decrease in para-aortic lymphadenopathy. The left-sided lung nodules had resolved, with an interval decrease in locoregional lymphadenopathy. Subsequently, he was treated with maintenance nivolumab

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Figure 1. CT scans. (a) Transverse section revealing the left renal mass. (b) Coronal section showing the renal mass and extension of tumor to the renal pelvis down to the left ureter. (c) Repeat scan after 10 cycles of combination nivolumab and ipilimumab showing near complete resolution of the left renal mass.

Figure 2. (a) Histologic sections of the ultrasound-guided liver biopsy showing neoplastic cells with prominent nucleoli in a nested pattern admixed with uninvolved liver parenchyma (hematoxylin and eosin, 20 $\times$). (b) Histologic sections of the radical nephrectomy demonstrating complete tumoral necrosis without viable tumor cells (left). The adjacent uninvolved renal parenchyma showed marked chronic inflammation and glomerulosclerosis.

therapy every 4 weeks. After six cycles of nivolumab monotherapy, a repeat CT scan revealed further improvement in the left renal mass with no signs of local extension or metastasis (*Figure 1c*). The patient had significant improvement in performance status and subsequently underwent left radical nephrectomy. Pathology revealed complete tumor necrosis, diffuse chronic inflammation, and cystic degeneration without evidence of viable RCC (*Figure 2b*). He continues to be on maintenance nivolumab every 4 weeks without evidence of recurrence, 18 months after diagnosis, and is tolerating the nivolumab with no evidence of toxicity.

DISCUSSION

The treatment for mRCC depends on the presence of prognostic risk factors. MSKCC and IMDC are the most commonly used prognostic models in the treatment of mRCC.² The MSKCC model was developed in patients treated with cytokine therapy, whereas the IMDC model was developed in patients treated with targeted therapy with VEGF inhibitors. The IMDC model uses six parameters (time of diagnosis to systemic therapy, performance status, hemoglobin, calcium level, neutrophil, and platelet count) to stratify patients to favorable, intermediate, and poor risk groups.^{7,8} Our patient was categorized as poor risk.

As an immunogenic cancer, RCC is very responsive to immunotherapy.⁹ Currently, checkpoint inhibitors and

targeted therapy with VEGF inhibitors are the primary systemic modalities for the management of advanced RCC. A number of targeted treatments have been approved by the Food and Drug Administration for the treatment of advanced RCC as first-line or subsequent lines of therapy.¹⁰ Tyrosine kinase inhibitors like sunitinib and pazopanib are preferred first-line treatments for favorable-risk mRCC.^{3,4} The CheckMate 214 trial compared the combination of nivolumab plus ipilimumab with sunitinib for previously untreated clear cell advanced RCC. This study showed that overall survival and objective response rates were significantly higher in combination therapy than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced RCC.⁵ This trial led to the approval of nivolumab in combination with ipilimumab as a preferred treatment option for first-line treatment of intermediate- and poor-risk patients with mRCC. The checkpoint inhibitor pembrolizumab combined with the tyrosine kinase inhibitor axitinib is approved as a first-line treatment in all risk group patients with mRCC.⁶

Very few cases of mRCC with complete response to checkpoint inhibitors have been reported to date. Treveno et al reported a complete response of mRCC with the combination of nivolumab and ipilimumab.¹¹ Shirotake et al reported a complete radiological and histological response with nivolumab in a patient with mRCC who initially did not respond to other molecular therapy.¹² Updated

results of the CheckMate 214 trial showed a complete response rate of 11% in the nivolumab plus ipilimumab group vs 6% in the sunitinib group.⁵ It is unclear why some patients have a dramatic response while others have only a partial response to immunotherapy. Some authors have highlighted the importance of an immune-resistant tumor microenvironment that helps to evade the immune system. The tumor microenvironment factors help to maintain intratumoral hypoxia, acidosis, and interstitial pressure, generating a barrier to immune cell infiltration.¹³ Unlike other tumors, in RCC high PD-L1 expression did not correlate with response to immunotherapy.¹⁴ Another hypothesis is that mRCC with poor-risk features may have a high mutational burden and hence respond to immunotherapy. Obtaining a tumor mutational burden in patients who achieved complete response could be helpful to better understand the reasons why these patients have a complete response.¹⁵

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