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Treatment of Multifocal Renal Cell Carcinoma in a Solitary Kidney With Nivolumab

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Keywords

Immunotherapy; Partial nephrectomy; Targeted therapy

Introduction

Renal cell carcinoma (RCC) remains one of the most commonly diagnosed cancers in the United States, with 62,700 new cases and 14,240 deaths expected in 2016.¹ For patients with organ-confined disease, excellent oncologic outcomes have consistently been achieved with surgical resection; active surveillance and thermal ablation are also reasonable treatment options in carefully selected cases.² However, for patients with metastatic disease, the survival rates are poor.³

Since 2006, 9 targeted therapies directed against vascular endothelial growth factor, its receptor, or the mammalian target of rapamycin, have been approved by the Food and Drug Administration^{4–13} (Table 1). Although these agents offer improved survival, durable complete responses remain exceptionally rare.^{14–16} Recently, immunotherapeutic checkpoint inhibitors have begun to reshape the treatment landscape for metastatic cancer. We report the case of a patient with metachronous multifocal organ-confined RCC in his solitary kidney after previous radical nephrectomy who experienced remarkable improvement after first-line systemic treatment with nivolumab.

Case Report

A 65-year-old man had originally presented in 2007 with gross hematuria and was found to have a right-sided kidney mass. He underwent right radical nephrectomy at that time, with removal of a 9-cm × 7-cm clear cell RCC, Fuhrman grade 2, tumor with negative margins. He subsequently developed multiple renal masses in his remaining left kidney in 2011. After these left renal lesions continued to grow, the decision was made to proceed with left partial nephrectomy in 2012. Two tumors were removed during this surgery; both were clear cell RCC, Fuhrman grade 2, with the largest measuring 1.5 cm. At that point, no evidence was found of residual active disease, except for multiple kidney masses < 3 cm seen on

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computed tomography. Shortly thereafter, he presented to the emergency room with progressive dizziness and a syncopal episode. Magnetic resonance imaging of the head showed a mass in the left parietal lobe consistent with metastatic disease. He underwent craniotomy, and pathologic examination of the mass confirmed metastatic RCC. He received adjuvant gamma knife radiation with complete resolution on follow-up imaging. A genetic analysis was completed and revealed he was von Hippel-Lindau negative. A full metastatic workup revealed no active disease in any other organs. He then underwent serial imaging with the expectation that he would eventually require systemic therapy for metastatic disease.

The patient's disease was stable until November 2014. At that time, the largest renal lesion was 2.4 cm on cross-sectional imaging. By July 2015, multiple enhancing complex tumors were found, the largest of which was 3.7 cm and had grown to 3.9 cm in November 2015 (Figure 1A). Further treatment was encouraged, given the growth kinetics of his current tumors and the absence of new distant disease. He considered nephrectomy but opted against an aggressive surgical approach owing to the resulting need for dialysis and the dramatic change he believed it would cause in his quality of life. Additionally, he was deemed a poor candidate for renal transplantation because of his age and the need for a 5-year cancer-free window before being eligible for transplantation. Finally, surgical enucleation of his multifocal renal tumors was offered.^{17, 18} However, his creatinine level was 1.7 mg/dL, with an estimated glomerular filtration rate of 41 mL/min/1.73 m². Also, the patient was concerned that even nephron-sparing surgery would compromise his renal function, given that he had experienced significant acute kidney injury after his previous partial nephrectomy.

We decided to pursue off-label nivolumab. This therapy was started in November 2015 at the standard dose of 3 mg/kg intravenously every 2 weeks. Repeat scans after approximately 3 months of therapy revealed significant improvement, with all previously complex enhancing lesions in the left kidney no longer enhancing and the cystic components appearing more homogeneous. Several of the lesions appeared smaller in size, and no new lesions were seen (Figure 1B). He tolerated nivolumab extremely well, although he did report symptoms of mouth dryness after the seventh treatment. The antibody testing (SS-A/Ro and SS-A/La) results to evaluate for Sjögren's disease were negative. At the last follow-up visit, the patient was continuing with nivolumab therapy without a drug holiday or dose reduction.

Discussion

Nivolumab is a programmed cell death 1 (PD-1) immune checkpoint inhibitor antibody that blocks the interaction of PD-1 expressed on activated T cells and PD-1 ligand 1 (PD-L1), which is normally expressed on immune cells. The binding of PD-1 to its ligand has an inhibitory effect on activated T cells and is part of the innate mechanisms to restrict autoimmunity. Tumor cells have also been shown to express PD-L1 as a method to evade the cellular immune response.¹⁹ Blockade of this interaction by nivolumab promotes T-cell function and increases antitumor immunity. PDL1 is not expressed on normal kidney tissue but is significantly expressed on primary and metastatic RCC specimens.^{20, 21} Tumor PD-L1 expression has been correlated with advanced tumor stages and was shown to be an

independent risk factor for cancer-specific death and overall mortality, in addition to metastatic progression, in patients with localized RCC.²²

Several studies have established nivolumab's efficacy in treating metastatic RCC.^{23–25} Most recently, a phase III trial comparing nivolumab to everolimus, a mammalian target of rapamycin inhibitor, in patients previously treated with anti-vascular growth factor therapy, demonstrated a greater median overall survival for patients in the nivolumab arm (25.0 months; 95% confidence interval [CI], 21.8 to not estimable) versus the everolimus arm (19.6 months, 95% CI, 17.6–23.1 months).²⁵ Additionally, the hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57–0.93; $P = .002$), which met their prespecified criteria for superiority.²⁵ The objective response rate also favored nivolumab over everolimus (25% vs. 5%; odds ratio, 5.98; 95% CI, 3.68–9.72; $P < .001$).²⁵ Finally, nivolumab had an improved safety profile, because only 19% of patients who received it developed grade 3 or 4 treatment-related adverse events compared with 37% of patients who received everolimus.²⁵ Given these results, the U.S. Food and Drug Administration approved the use of nivolumab for the treatment of metastatic RCC in the second-line setting in November 2015.

Our case highlights a unique situation in which the patient had previously undergone right radical nephrectomy and left partial nephrectomy, leaving him with stage 3b chronic kidney disease. Therefore, further surgical intervention for the lesions in his left kidney could have resulted in temporary or permanent hemodialysis. Although the patient in our case had had a solitary metastatic lesion in his brain treated 3 years previously, no evidence of metastatic disease was present when nivolumab treatment was initiated. As such, we believe this is the first report of a patient undergoing successful nivolumab therapy in systemic treatment-naïve, organ-confined disease. This could suggest a role for nivolumab as a therapeutic agent in the neoadjuvant setting or in situations in which surgery is not feasible.^{26–28}

Conclusion

We report the case of a patient with organ-confined multifocal RCC who was treated with nivolumab in lieu of surgery. As immunotherapeutic treatments such as this become more commonplace, further prospective studies are needed to elucidate the full spectrum of this novel therapy's clinical utility in RCC.

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Clinical Practice Points

- The PD-1 inhibitor nivolumab is currently approved by the Food and Drug Administration as a second-line systemic therapy for metastatic clear cell RCC.
- Minimal evidence is available regarding nivolumab's efficacy as a first-line agent or in organ-confined disease.
- We report the case of a man with organ-confined multifocal clear cell RCC in a solitary kidney who experienced a dramatic response to systemic therapy with nivolumab in the absence of previous systemic therapy.

Figure 1.
(A) Magnetic Resonance Imaging Scan of the Abdomen Showing a Solitary Left Kidney With Multifocal Renal Cell Carcinoma. Largest Lesion Measured 3.9 cm. (B) Reimaging Study 3 Months After Initiation of Nivolumab Therapy Showing That All Lesions Were Smaller and Without Enhancement. The Index Lesion Had Shrunk to 1.2 cm From 3.9 cm.

Table 1**FDA-Approved Targeted Therapies for Clear Cell Renal Cell Carcinoma**

Therapy	Target	Treatment Line	Comparison Arm	Primary Endpoint
Axitinib ⁴	VEGFR	Second	Sorafenib	PFS
Bevacizumab plus IFN- α (AVOREN) ⁵	VEGF	First	Placebo plus IFN- α	OS
Bevacizumab plus IFN- α (CALGB) ⁶	VEGF	First	IFN- α	OS
Cabozantinib ⁷	VEGFR, MET, AXL	Second	Everolimus	PFS
Lenvatinib plus everolimus ⁸	VEGFR, mTOR	Second	Everolimus	PFS
Everolimus ⁹	mTOR	VEGFR failure	Placebo	PFS
Pazopanib ¹⁰	VEGFR	First-line or cytokine failure	Placebo	PFS
Sorafenib ¹¹	VEGFR	Cytokine failure	Placebo	OS
Sunitinib ¹²	VEGFR	First	IFN- α	PFS
Temsirolimus ¹³	mTOR	First	IFN- α	OS

Abbreviations: AVOREN = Avastin and Roferon in Renal Cell Carcinoma; CALGB = Cancer and Leukemia Group B; FDA = Food and Drug Administration; IFN = interferon; mTOR = mammalian target of rapamycin; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Modified with permission from Singer et al.¹⁴