Published in final edited form as:

Clin Genitourin Cancer. 2018 December ; 16(6): 485–488. doi:10.1016/j.clgc.2018.07.015.

Renal Cell Carcinoma Pseudoprogression with Clinical Deterioration: To Hospice and Back

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Keywords

Checkpoint inhibitors; Hyperprogression; Immune-related adverse events; Immunotherapy; Infection; SBRT

Introduction

Metastatic renal cell carcinoma (RCC) is a leading cause of cancer deaths in developed nations.¹ The past decade has seen the approval of numerous systemic therapies for RCC, most recently immune checkpoint inhibitors (ICI). Nivolumab, an anti-programmed cell death 1 antibody, was superior to everolimus in a large phase 3 trial in clear-cell RCC (ccRCC), and is now approved by the US Food and Drug Administration for metastatic RCC after progression on prior anti-angiogenic therapy.² The overall response rate is 25%, and there is a subset of patients who demonstrate pseudoprogression where initial tumor growth is followed by decreased tumor burden.³ Differentiating between progression and pseudoprogression has been challenging.

Herein we report the case of a patient with metastatic ccRCC with clinical deterioration and progression after 3 doses of nivolumab who went to hospice, only to come back 6 months later with less disease.

Case Report

The patient was a 70-year-old white man with a medical history of type 2 diabetes, hypertension, a cerebrovascular accident, and stage III chronic kidney disease. He was diagnosed with metastatic ccRCC in March 2015. At diagnosis, the patient had a 7.3 cm

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Disclosure

J.B. is a consultant/advisory board member for Bethyl Laboratories. The other authors have stated that they have no conflict of interest.

right renal mass with an associated level IV tumor thrombus extending to the right atrium. There was aortocaval nodal involvement and numerous pulmonary nodules measuring up to 2 cm. Biopsy was performed of a pulmonary lesion; the findings demonstrated ccRCC. Fuhrman nuclear grade was read as 3, and the tumor was PAX8 positive (Figure 1A, B).

Because of his morbid obesity and comorbidities, and despite the tumor thrombus, cytoreductive nephrectomy was not pursued and he initiated systemic therapy. He was first treated with pazopanib (requiring a dose reduction resulting from fatigue, diarrhea, and palmoplantar erythrodysesthesia), but he experienced a durable response, with shrinking of the tumor thrombus to level III, for 1 year. Subsequently he experienced progression in the liver and underwent stereotactic body radiotherapy (SBRT) to 2 liver lesions. Thereafter, he initiated therapy with an investigational agent (PT2385), a first-in-class *HIF-2* inhibitor.⁴ PT2385 was well tolerated, but there was progression after 1 month of treatment. Axitinib was chosen as third-line therapy, and it controlled his disease for 5 months. At progression, there was an increase in lung and liver metastases as well as a new soft tissue metastasis in the left deltoid muscle.

The patient then began therapy with nivolumab. He received simultaneous SBRT (40 Gy over 5 fractions) to a painful 5 cm deltoid metastasis as well as a large (7.7 cm) left lower lobe lung metastasis that was thought to be responsible for a bothersome cough. The patient received 3 nivolumab infusions (3 mg/kg) over a period of 6 weeks. After the third cycle of nivolumab, the patient appeared weak with a decline in his Eastern Cooperative Oncology Group performance status from 1 to 3. He lost 12.2 kg over the 6-week treatment period, and endured significant nausea and vomiting. Imaging studies revealed marked progression with interval increase in size of nearly all previously identified lung and liver lesions, development of innumerable pulmonary nodules, and new pancreatic and hepatic metastases (Figure 2). He also developed a large left-sided pleural effusion. The decision was made to pursue hospice care.

Six months after entering hospice, the patient's wife contacted the clinic to report that the patient was alive and feeling well. He gradually improved after the rupture of a cutaneous abscess on his pannus shortly after entering hospice. At evaluation, the patient appeared well and had gained 18.1 kg since last seen in clinic. Eastern Cooperative Oncology Group performance status was 1. Imaging revealed that his radiated deltoid and left lower lobe metastases had decreased (from 5.1 cm to 2.9 cm and from 8 cm to 3 cm, respectively) (Figure 2). A similar decrease was observed in the dominant liver mass (from 4.0 cm to 1.9 cm), which had not received radiation, as well as other liver metastases. Many lung nodules had completely resolved.

The decision was made to resume nivolumab (3 mg/kg every 2 weeks). Three months later, however, the patient developed acute renal failure, with serum creatinine peaking at 9.3 mg/dL. Results of a kidney biopsy confirmed acute interstitial nephritis (AIN), likely the result of nivolumab therapy (Figure 1D). Nivolumab therapy was stopped, and the patient was treated with prednisone (0.5 mg/kg daily), which resulted in full recovery of kidney function 3 weeks later.

The patient subsequently received everolimus monotherapy because of its favorable side effect profile; however, lenvatinib was added 3 months later after progression of a soft tissue metastasis in the left calf, which was subsequently irradiated. Treatment was complicated by a nonhealing ulcer, resulting in interruptions in therapy to allow healing. Three and a half years after diagnosis with stage IV ccRCC, and 2 years after enrolling in hospice, the patient died of complications of pneumonia.

Discussion

Here we present a case of pseudoprogression with clinical deterioration followed by a dramatic and sustained clinical response to nivolumab. Atypical response patterns to ICI were first described in clinical studies evaluating ipilimumab in melanoma and have since been observed in most clinical trials evaluating ICI regardless of tumor type.^{5,6} Pseudoprogression, defined as an initial increase in tumor burden followed by a response to therapy, has been observed in 7% to 8% RCC patients treated with nivolumab.^{6,7} Hyperprogression, defined as a > 2-fold increase in tumor growth rate after the initiation of ICI therapy, has been recently described as a pattern of progression.^{8,9} In a single-center retrospective analysis of multiple tumor types treated with ICI, hyperprogression was observed in 12 (9%) of 131 patients.⁸ The root cause of hyperprogression is unclear, and it may reflect various factors such as a brisk inflammatory response (pseudoprogression) as well as withdrawal from the effects from prior therapy, which despite overall tumor progression might have still inhibited tumor growth to some extent.

Differentiating between pseudoprogression and true progression is important. Continuing ICI in the setting of true progression exposes patients to adverse side effects and delays potentially effective treatment, and terminating an effective therapy prematurely may reduce its benefit. Exemplifying this is a recent subgroup analysis of a phase 3 trial, CA209–025, which compared nivolumab to everolimus in metastatic RCC. Among 155 patients in the nivolumab arm who continued to receive treatment despite progression by radiologic criteria, 74 (48%) had a reduction in tumor burden and 20 (13%) qualified as having a partial response on subsequent imaging.^{2,3} However, the decision to treat past progression was based on patient tolerance of the treatment and determination by the investigator of benefit, which was based largely on functional status. The case presented shows, however, that there may be patients who derive long-term benefit from ICI despite what appears to be initial hyperprogression and a decrease in functional status, highlighting the need for biomarkers and imaging techniques that can help differentiate between pseudoprogression and true progression in a clinically relevant time frame.

Of note, based on programmed death ligand 1 (PD-L1) expression in the tumor and pretherapy neutrophil-to-lymphocyte ratio (NLR),¹⁰ our patient's disease might have been expected not to respond to nivolumab. PD-L1 expression was < 1% in a baseline biopsy sample (Figure 1C). In RCC, tumor PD-L1 expression showed mixed results as a predictive biomarker and does not currently drive clinical decision making.¹¹ Increasing infiltration of tumor lymphocytes appears to be predictive in melanoma treated with ipilimumab.¹² However, this relies on serial biopsies and is often impractical. Peripheral blood-based markers such as pretherapy NLR < 3 correlates with improved progression-free (and overall)

survival with nivolumab in RCC in a single-center retrospective study.¹³ In our patient, the pretreatment NLR was 12. However, NLR has not been investigated as a dynamic biomarker to predict response in RCC.

One variable that could contribute to the extreme presentation described is the coadministration of SBRT with nivolumab. Radiation has been hypothesized to have immunomodulating effects since the observation of the abscopal effect. This may result from inflammation and the exposure of tumor antigens to antigen-presenting cells after radiation.¹⁴ Combined immunotherapy with radiotherapy is an actively studied modality, and several trials are underway, such as NCT03065179, which combines ipilimumab–nivolumab with SBRT.

Another interesting feature of this case is the development of AIN as an immune-related adverse event. In 2 recent retrospective analyses of multiple tumor types treated with ICI, the development of immune-related adverse events correlated with improved overall response rates and longer progression-free survival.^{15,16} Further investigation is warranted to determine whether there may be an association between AIN in particular and response in RCC, as there may be a degree of antigenic crossover between ccRCC and healthy renal epithelial cells.

To our knowledge, this is the second report in the literature of hyperprogression followed by a response to nivolumab and SBRT in RCC.¹⁷ Identifying novel approaches to identify disease response to therapy and to monitor disease progression warrants further study.

Acknowledgments

J.B., P.K., and I.P. are supported by the National Institute of Health (grant P50CA196516).

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Clinical Practice Points

- Increasing adoption of immune checkpoint inhibitors in the management of renal cell carcinoma is resulting in a higher rate of atypical responses. They include pseudoprogression, where initial tumor growth is followed by response, and hyperprogression, where there is accelerated growth rate after discontinuation of the previous therapy.
- In clinical trials evaluating nivolumab monotherapy in renal cell carcinoma, the rate of pseudoprogression was as high as 8%; however, atypical responses may be even more frequent when radiotherapy is added.
- Presently, there is no definitive way to differentiate pseudoprogression from true progression at the time it occurs. In clinical trials, when faced with radiologic progression, investigators often rely on changes in functional status to determine whether to treat beyond progression.
- Changes in functional status may not, however, reliably differentiate pseudoprogression and true progression, and there is a need for novel biomarkers or imaging techniques that could guide timely clinical decision making.

Figure 1. Histological Analyses. (A) CT-guided core biopsy sample from a lung nodule showing metastatic ccRCC, Fuhrman grade 3. Immunohistochemistry is positive for PAX8 (B) but negative for PD-L1 (C). (D) Post-treatment renal biopsy sample showing acute interstitial nephritis and interstitial fibrosis with tubular atrophy (arrow).

Abbreviations: ccRCC = clear-cell renal cell carcinoma; CT = computed tomography; PAX-8 = paired-box 8; PD-L1 = programmed death ligand 1.

Figure 2. Pseudoprogression After Nivolumab in ccRCC. Coronal reconstruction (A-C) and axial (D-F) CT images of chest 1 week before initiation of nivolumab, immediately after treatment (2 months), and 8 months later. Arrow indicates dominant metastatic lesion in left lower lobe; arrowheads, pulmonary nodules; and asterisk consolidation of left hemithorax. Axial contrast-enhanced MRI (G-I). Arrow indicates liver metastasis; arrowhead, inferior vena cava thrombus. DWI MRI (J-L). Arrow indicates tiny pancreatic metastasis; arrowhead, liver metastasis. Abbreviations: ccRCC = clear-cell renal cell carcinoma; CT = computed tomography; DWI MRI = diffusion weighted magnetic resonance imaging.