CASE REPORT

One dose of immunotherapy leading to an exceptional and durable response in a patient with metastatic renal cell carcinoma

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Abstract

A 72-year-old man with metastatic clear cell renal carcinoma, who had progressed after previous treatment with Sunitinib and Axitinib, was given one dose of immunotherapy. He was initially unwell after treatment with fever, shortness of breath, chest pain and raised inflammatory markers. Following this he elected not to have any further immunotherapy. Before the treatment he had multiple pulmonary metastases and hilar and mediastinal lymph nodes on chest X-ray and suffered with a persistent cough. Chest X-ray 10 months after treatment showed normal appearances and his cough had largely resolved. The patient initially declined repeat computed tomography imaging but agreed to it 2 years after the immunotherapy, the results showed a maintained response. Some patients with renal cell carcinoma show a durable response to immunotherapy but we are not aware of other published cases where a patient has shown such a dramatic and sustained response to one dose.

INTRODUCTION

Immunotherapy with Nivolumab is a second line treatment option for metastatic clear cell renal cell carcinoma [1]. Nivolumab is a fully human IgG4 monoclonal antibody that blocks the programmed cell death protein 1 (PD-1) receptor expressed on activated T cells [2]. When the ligands PD-L1 and PD-L2 bind to the PD-1 receptor, it leads to inhibition of the cellular immune response [2]. Tumour cells can exploit this pathway by upregulating PD-L1 to escape immune surveillance [3]. Studies have shown that increased PD-L1 expression is associated with a poor prognosis in renal-cell carcinoma (RCC) [2].

Standard practice is to treat with Nivolumab until progression or unacceptable toxicity; however, some studies have elected to stop treatment after 2 years [4]. It is not known exactly how long we should be treating patients for if they are responding and there is no agreed definition of a durable response [5]. We present a case study of a patient with metastatic RCC who received only one dose of Nivolumab and has demonstrated a significant and enduring response 2 years later.

CASE REPORT

A 72-year-old man, well apart from a history of eczema, underwent a left radical nephrectomy in 2006. Histology confirmed a T3b Fuhrman grade 3 clear cell renal carcinoma. Five years later he developed multiple lung nodules, biopsy of which confirmed metastatic clear cell carcinoma. He was treated for 2 years with Sunitinib, switching on progression to Axitinib, which he took until further progression in February 2015.

He became troubled by symptoms 2 years later with a persistent cough and lumbar back pain. A new baseline computed tomography (CT) scan of his chest, abdomen and pelvis showed a significant increase in size and number of the pulmonary...
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Figure 1: Chest X-ray taken prior to Nivolumab in May 2017 (A) showing multiple pulmonary nodules and hilar lymphadenopathy. Repeat chest x-ray from February 2018 (B) now shows normal appearances.

He consented to Nivolumab and Cycle 1 was given at a dose of 3 mg/kg. Nine days after this, he presented to the Emergency Department with fever, chest pain and shortness of breath. A cardiovascular event was excluded on the basis of a normal ECG and troponin level. Blood tests were notable for a high CRP of 442 mg/L. He was treated with antibiotics and given 2 mg/kg of methylprednisolone. A high resolution CT chest excluded pneumonia. He improved to the point of discharge 6 days later. No source of infection was isolated, it was postulated that his symptoms could represent a response related inflammatory process.

In the outpatient clinic one week later he reported symptoms of cough, weight loss and a poor appetite. Bloods showed liver and renal dysfunction with an ALT of 124 U/L and creatinine 160 umol/L. A random glucose level was raised at 21.6 mmol/L. Insulin therapy for diabetes was initiated, thought to be either as a complication of immunotherapy or more likely of steroid treatment. Both his liver and renal function had normalized by the time he was seen in clinic a month later. At this point his breathing was improved, his cough mostly resolved and he was weaning the prednisolone dose. After 1 cycle of Nivolumab he elected to stop therapy and discontinue oncology follow up.

Ten months later, in February 2018, he presented to his GP with acute symptoms of shortness of breath and cough. A chest X-ray showed resolution of the original lung metastases and mediastinal lymphadenopathy (Fig. 1).

He had previously declined repeat CT scans but agreed to have one 2 years after the immunotherapy. The images showed that original pulmonary metastases and mediastinal lymphadenopathy were no longer visible; there was a stable para-tracheal node and reduction in the presumed right renal metastases. A pathological fracture was seen affecting the bony metastasis at L1. There were no new sites of disease (Fig. 2).

DISCUSSION

Patients with metastatic RCC can exhibit a durable response to Nivolumab [6]. There is also evidence that a response can be maintained when a patient is off therapy, a phase I study had four patients who showed sustained responses for 19 weeks and >45, 51 and 59 weeks after stopping the treatment [4]. At present, we have no reliable way to predict which patients will have a meaningful and sustained response.

Theoretically higher PD-L1 expression might predict response to Nivolumab but the Checkmate 025 study showed a benefit in advanced RCC irrespective of PD-L1 expression levels [2]. The Checkmate 214 study compared dual immunotherapy with Nivolumab and Ipilimumab to Sunitinib as first line therapy. It showed a median progression free survival (PFS)
of 11.0 months in patients with <1% PD-L1 expression with dual immunotherapy, compared to 22.8 months in the ≥1% expressers [7]. PD-L1 expression cannot be used as a sole tool to select patients for immunotherapy treatment as 143 out of 212 patients in the study who had a complete or partial response had PD-L1 expression of <1% [8]. Characterization by International Metastatic Renal Cell Carcinoma Database Consortium risk groups in the study did help identify which patients would benefit from immunotherapy. On extended follow up, for a median of 32.4 months, patients with an intermediate or poor risk score did not reach a median OS compared to 26.6 months in the group with an intermediate or poor risk score did not reach a median OS compared to 26.6 months with Sunitinib (HR = 0.76 [95% CI: 0.59–0.99]) [10]. High T effector/IFN γ gene expression was associated with PD-L1 expression and this group had a longer PFS with Atezolizumab and Bevacizumab than Sunitinib (HR 0.76 [95% CI: 0.59–0.99]) [10].

This is a highly heterogeneous group of patients and the data on biomarker analyses and the prediction of response needs to be prospectively validated. In the future, molecular characterization may guide us. In malignant melanoma patients, treated with Ipilimumab, development of grade-3 toxicities has been shown to correlate with higher response rates and a longer median duration of response [3]. Our patient experienced significant toxicity with immunotherapy. Should we rechallenge our patient with Nivolumab in the future upon progression given the toxicity experienced? Data is limited on the safety of this and clearly would depend on the severity of the immune adverse event, patient wishes and availability of other treatments [5].

**CONFLICT OF INTEREST STATEMENT**
None declared.

**FUNDING**
No financial support was received for this study.

**ETHICAL APPROVAL**
No approval is required.

**CONSENT**
Written informed patient consent was obtained.

**GUARANTOR**
L.W. is the guarantor of this study.

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