VIA MEDICA

CASE REPORT

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Nivolumab in treatment of renal cell carcinoma during renal replacement therapy

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ABSTRACT

The prolongation of overall survival of advanced RCC patients requires the use of modern therapies including tyrosine kinase inhibitors and immune checkpoint inhibitors. Although these drugs have different pharmacokinetics, preclinical studies rarely indicate significant renal clearance. To date there has been a lack of prospective studies evaluating their efficacy and safety in end-stage renal disease patients undergoing dialysis.

This case study describes second-line treatment of RCC with nivolumab in a dialysed patient following bilateral nephrectomy.

Key words: kidney cancer, nivolumab, dialysis

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Introduction

Renal cell carcinoma (RCC) and commonly performed nephrectomy are associated with the risk of a decrease in glomerular filtration rate (GFR) [1], which may affect future oncological treatment. In patients with pre-existing chronic kidney disease or in rare cases when bilateral nephrectomy is necessary it could result in end-stage renal disease. Hence, it requires implementation of renal replacement therapy. Due to inclusion criteria that usually do not allow patients with severely impaired renal function to participate in clinical trials, this group of patients is deprived of access to modern therapies. This paper presents the case of a patient with disseminated clear cell RCC (CCRCC) after bilateral nephrectomy.

Case report

In 2016, a 57-year-old female patient with disseminated RCC was admitted to the Department of Oncology of the University Hospital in Krakow; the patient was receiving chronic dialysis due to bilateral nephrectomy and therefore was not eligible for the standard treatment.

In 1990, the patient was treated for cancer of the left kidney. A total left nephrectomy was then performed, and clear cell RCC was diagnosed. The patient remained under observation for 19 years. In 2009, she reported for control because of increasing, unproductive cough. In the computed tomography (CT) examination oncologically suspicious lesions were found in the right lung. After consultation of a thoracic surgeon, in March 2009 non-anatomical, wedge resection was performed. Histopathological examination confirmed the presence of clear cell RCC (CCRCC). The CT scan of the other anatomic regions performed at that time did not reveal other pathologies. After a further four years of follow-up, a CT scan detected two tumours in the right kidney (66 × 44 mm and 20 × 16 mm) and suspected regional lymph nodes. Considering the size of tumours and previous left-sided nephrectomy, in October 2013, partial right-side nephrectomy (nephron-sparing surgery — NSS) with lymphadenectomy was performed. The histopathological examination confirmed the presence of clear cell carcinoma reaching the cut line (R1).

A CT scan performed three months after the surgery showed the presence of metastatic, non-regional lymph nodes. During this period, the patient did not require dialysis. The patient was qualified for treatment with sunitinib in a standard dose of 50 mg/d on days 1–28, with a 14-day break (28 days on/14 days off). The patient started therapy in February 2014. The treatment was poorly tolerated, the patient complained about the symptoms of *palmar-plantar erythrodysesthesia* (PPE or hand-foot syndrome, HFS), clinically significant asthaenia, and increasing peripheral oedema. In subsequent studies, a decrease in platelet levels and deterioration of renal parameters was observed. There was also drug-induced hypothyroidism requiring levothyroxine supplementation. Taking into consideration the above circumstances, the dose of sunitinib was reduced to 37.5 mg/day, leading to resolution of the reported adverse effects and improvement of quality of life. The therapy was administered until September 2015, for a total of 19 months.

A follow-up CT examination performed after this period showed the presence of a nodular mass in the initial section of the right ureter (8 × 8 × 8 mm) and widening of the ureter up to 14 mm. The patient was referred for urological consultation. Due to the increasing widening of the ureter, a JJ catheter was implanted. There was also an unsuccessful attempt to collect material for histopathological examination from the lesion described in CT. The patient remained under observation until March 2016, at which point tomography described a tumour of the right renal hilus with dimensions 61 × 67 × 71 mm, with additional infiltration of the lower renal pole and shaping of the pyelocaliceal system. Numerous enlarged local lymph nodes were also described. In this situation the decision was made to perform a complete right-sided nephrectomy with removal of the tumour thrombus from the inferior vena cava (IVC). During the operation, which was carried out in March 2016, tumour infiltration into the liver parenchyma was observed. In the postoperative period there was serious bleeding into the abdominal cavity, which required reoperation. From that moment on, the patient was chronically dialysed. Renal cell carcinoma recurrence was confirmed in histopathological examination.

Until November 2016, the patient remained under observation, despite evident disease progression in imaging studies. Due to end-stage renal failure and dialysis, the patient was not eligible for second-line treatment under the drug program.

In November 2016, the patient was in good general condition (performance status, PS = 1). The patient was treated for hypothyroidism, probably associated with previous sunitinib treatment, and mild hypertension, presumably associated with chronic dialysis. Clinically the patient did not present symptoms associated with neoplastic disease, although the CT scan performed at that time revealed the presence of pathologic masses (57 × 36 × 72 mm) in communication with the IVC and aorta, as well as dissemination to the abdominal, mediastinal, liver, and lung lymph nodes.

Because nivolumab was available in the Oncology Clinic of the Jagiellonian University Medical College in Krakow as part of an extended access program (EAP), a sponsor was asked to agree to inclusion of the patient in the treatment, despite not meeting the formal recommendation for creatinine concentration. This request was supported by available literature data. The sponsor agreed, and from November 22, 2016 the patient started treatment with nivolumab in a standard dose of 3 mg/kg every two weeks.

The patient was treated for five months until April 2017. The therapy was well tolerated. There were observed fluctuations in TSH concentration requiring levothyroxine dose adjustment and a flat, slightly reddish, exfoliating rash of moderate intensity (G1). The CT follow-up performed in February 2017 showed the enlargement of metastatic lesions and the appearance of a new small lesion in the liver. However, due to the clear clinical benefit, they were considered a potential pseudoprogression, and a decision was made to continue treatment subject to an earlier CT scan after six weeks.

One month later, the patient reported an unplanned visit due to worsening general condition, severe dyspnoea at rest, and worsening of the rash to grade G2. X-ray examination did not show lesions in the lungs, saturation on admission was 79% in the atmospheric air. There were also mild peripheral oedemas of the upper and lower limbs and the face. The patient did not have a fever and denied any cough. Due to the clinical suspicion of interstitial autoimmune pneumonitis, the patient was referred for urgent hospitalisation and steroid therapy — prednisone was included at the dose of 1 mg/kg/day.

Due to ambiguities regarding the aetiology of oedema of the upper body, an angio-CT examination was also performed after the admission, which revealed a massive thrombosis of the entire superior vena cava (SVC) on the inserted dialysis catheter. This study showed no inflammatory or interstitial lesions in the lungs. Due to this, steroid therapy was terminated and unfractionated heparin was included in a continuous infusion, which after a few days was changed to treatment with low-molecular-weight heparin under the control of anti-Xa activity. After finishing the initial period of treatment of thrombosis, the patient was discharged home in good general condition.

A CT scan performed after the end of treatment showed further enlargement of metastatic lesions, which ultimately forced the discontinuation of nivolumab therapy. Due to the lack of other available therapeutic

options, the patient was treated symptomatically and died in early 2018.

Discussion

This report presents a patient who due to bilateral nephrectomy was deprived access to standard therapy. Tomography performed before inclusion in the treatment with nivolumab showed rapid progression of the disease and the risk of invasion of aorta and inferior vena cava. The use of immunotherapy allowed a 14-month survival, and the most serious complication — superior vena cava thrombosis — in the opinion of treating physicians, was not directly related to the therapy. It should also be noted that the occurrence of sudden dyspnoea with an uncharacteristic result of imaging examinations during treatment with PD-1 inhibitors may result from other reasons, such as heart failure, pulmonary embolism, or superior vena cava syndrome.

Currently there are no guidelines for the treatment of kidney cancer in patients with end-stage renal disease, because they are usually excluded from clinical trials. It should be noted that patients in this group are usually burdened with accompanying diseases, which may increase treatment-related risk. Except for the pazopanib program, all current drug programs of the National Health Fund require normal kidney function (defined as the value of estimated glomerular filtration rate [eGFR] > 30 mL/min or creatinine serum level < 1.5–2 × ULN [upper limit of normal]). These indications correlate with the inclusion criteria for relevant clinical trials, although they are not fully reflected in pharmacokinetic data.

Nivolumab, a human IgG4 monoclonal antibody directed against the receptor of programmed cell death 1 (PD-1), is registered in the second line of treatment for generalised renal cancer, based on the Checkmate 025 study. In this study, the drug was compared to everolimus in a group of 821 patients who had previously received anti-vascular endothelial growth factor receptor (VEGFR) treatment. It resulted in an increase in the median overall survival (25 months *vs.* 19.6 months; hazard ratio [HR] 0.73; 98.5% CI [confidence interval] 0.57–0.93; p = 0.002), as well as objective response rate (ORR) (25% *vs*. 5%, HR 5.98, 95% CI 3.68–9.72, p < 0.001). The differences in progression-free survival (PFS) between the study arms were not statistically significant, which is characteristic for immune checkpoint inhibitors, and the median PFS was 4.6 months [2]. The CheckMate 025 study did not address the clinical situation of patients during dialysis. The nivolumab Summary of Product Characteristics (SmPC) indicates that dose adjustment is not necessary in patients with mild to moderate renal impairment, and that there are no data available for the group of patients with severe renal impairment. Pharmacokinetic analysis in populations of patients previously receiving nivolumab in clinical trials showed no significant effect of eGFR on drug clearance in patients with mild (eGFR > 60 mL/min) and moderate (eGFR 60–30 mL/min) renal failure. The lack of this relationship is consistent with the physical properties of the drug, because its large molecule (144 kDa) is unlikely to be filtered in the glomerulus [3].

Available literature data do not include any prospective studies on the safety and efficacy of nivolumab in populations of patient during dialysis, and only a few case reports are available that do not allow safe recommendation of this treatment. However, due to the increasing number of patients in this clinical situation, it is necessary to take action to determine the optimal treatment regimen for patients with renal cell carcinoma with end-stage renal disease, both in the field of immunotherapy and the use of tyrosine kinase inhibitors. The lack of such data may result in the deprivation of treatment of patients who objectively require this form of therapy.

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