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Original Research

Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient

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Abstract ***Background:*** Immune-checkpoint inhibitors have been approved for the treatment of metastatic melanoma based on several phase III trials. Patients after organ transplantation and patients with impaired renal function were excluded from these studies. Recently, allograft rejections were reported in organ transplant recipients receiving PD-1 blocking antibodies.

Patients and findings: Four patients with metastatic melanoma and impaired kidney function (baseline serum creatinine 1.79–2.59 mg/dl) were treated with immune-checkpoint blockers, of which one was a kidney-transplant recipient receiving immunosuppressive therapy with tacrolimus and prednisolone. The patient was initially treated with the anti-CTLA-4 antibody ipilimumab after detailed explanation of the potential risk of allograft rejection. Upon disease progression, therapy was switched to the anti-PD-1 antibody nivolumab. The other three patients were treated with nivolumab or pembrolizumab, two of them after previous therapy with ipilimumab.

Results: The patients received a median of six doses (range 3–21) of anti-PD-1 antibodies and 3–4 doses of ipilimumab. Kidney function tests remained stable throughout the course of checkpoint blockade. In the kidney transplant recipient, neither ipilimumab nor nivolumab led to an allograft rejection. Responses to anti-PD-1 treatment were divergent with two patients showing disease progression, one achieving a mixed response and one experiencing a complete response.

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Conclusion: These cases show that checkpoint inhibitors can be a safe therapeutic option in patients with impaired kidney function. Furthermore, we report the first organ transplant patient with malignant melanoma who received ipilimumab followed by nivolumab without experiencing a kidney allograft rejection.

1. Introduction

Malignant melanoma is one of the most aggressive skin cancers of the western world with increasing incidence in the last years [1]. Major advancements have been made in the last 5 years in the systemic therapy of metastasised melanoma. Overall survival can now be improved by employing new therapeutics such as targeted therapies and immunotherapies [1]. Immunotherapy with so-called immune-checkpoint inhibitors showed clinical activity in randomised clinical trials in metastatic melanoma first, but is now approved for the treatment of various human malignancies [2–8]. For treatment of advanced melanoma, the anti-CTLA-4 antibody ipilimumab and the anti-PD-1 inhibitors nivolumab and pembrolizumab have been approved based on randomised phase III trials showing remarkable improvement of progression-free and/or overall survival [2–5].

Renal failure with increased serum creatinine is a frequent finding among adults [9], and end-stage renal failure is associated with an increased risk to develop melanoma [10]. Organ transplant recipients (OTRs) also have an increased risk for skin cancer including melanoma due to the immunosuppression required to prevent organ rejection [11]. However, OTRs as well as patients with a serum creatinine above 1.5× of upper limit (ULN) are generally excluded from enrolment in clinical trials employing immune-checkpoint blockade on malignant melanoma and other solid tumours including renal cell cancer [2–5,12,13]. Usage of ipilimumab has been reported to be safe in patients who received an allogeneic liver or kidney transplantation [14–16], but recent reports indicate that PD-1 blockade can lead to renal allograft rejection [17–19]. While renal adverse events related to immune-checkpoint blockade are rare and have been studied [20], no data have been reported on the safety in patients with chronic renal failure.

Here, we report a series of patients suffering from chronic renal failure and one patient with allogeneic kidney transplant receiving PD-1 inhibitors (either nivolumab or pembrolizumab) to treat metastatic melanoma.

2. Patients

2.1. Case 1

A 46-year-old male patient was diagnosed with a 2.1-mm ulcerated nodular malignant melanoma on his left foot in January 2013. After wide excision and inguinal sentinel lymph node biopsy on the left side, which showed a conglomerate of lymph node metastases, a complete inguinal lymph node dissection was performed and showed no further metastases. Subsequently, the patient received adjuvant high-dose interferon alpha, which had to be terminated due to insomnia and neurasthenia after 11 months.

In his medical history, a monoclonal gammopathy of undetermined significance was diagnosed in May 2014 with chronic renal failure due to a light chain cast nephropathy. After deterioration of kidney parameters, the patient received an induction polychemotherapy with bortezomib, cyclophosphamid and dexamethasone (VCD protocol) in October 2014 and high-dose polychemotherapy with melphalan with subsequent autologous stem cell transplantation in February 2015.

In September 2015, the patient developed multiple intransit metastases on the left lower leg and thigh. CT scans showed no evidence of distant metastases or locoregionary lymph node involvement. On molecular pathological analysis, a mutated BRAF V600E was detected. After interdisciplinary discussion in the tumour board, systemic therapy with an anti-PD-1 antibody was recommended due to the rapidly evolving metastases expanding on the complete left limb. The patient received a total of six doses of pembrolizumab 2 mg/kg body weight (BW) q3wk from December 2015 until February 2016. Treatment was tolerated well without any immune-related adverse events. Serum creatinine, urea and glomerular filtration rate remained stable during PD-1 inhibition (Fig. 1). A CT scan in February 2016 still showed no distant metastases. However, due to regional progression on the left leg, therapy with pembrolizumab was discontinued and dual MAPK inhibition has been started.

2.2. Case 2

A desmoplastic malignant melanoma with a Breslow index of at least 4 mm of the left cheek was diagnosed in an 85-year-old male patient in May 2012. A sentinel lymph node biopsy was refused by the patient. A chronic renal insufficiency due to hypertensive nephropathy was present at time of melanoma diagnosis (serum creatinine 2.04 mg/dl, GFR 33 ml/min/1.73 qm).

In November 2012, a local recurrence on the cheek, 3 cm in diameter, was detected. Surgical resection was