CASE REPORT

Safety and efficacy of pembrolizumab in a patient with advanced melanoma on haemodialysis

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SUMMARY

Patients with end-stage renal disease present with a distinct challenge in oncology. Many anticancer drugs and their metabolites are excreted by the kidney, but data to guide dose and schedule adjustments in renal dialysis are scant. Pembrolizumab is an anti-programmed cell death protein 1 monoclonal antibody proven to be effective in patients with metastatic melanoma. It has demonstrated promising results and was granted US Food and Drug Administration (FDA) approval in September, 2014 for metastatic melanoma. It was additionally approved for patients with metastatic non-small cell lung cancer by the FDA in October, 2015. We present the first case, to the best of our knowledge, of a patient with metastatic melanoma successfully treated with pembrolizumab while on haemodialysis.

BACKGROUND

Prior to use of immunotherapy, patients with BRAF wild-type metastatic melanoma have poor prognosis with 1-year survival rates ranging from 33% in TNM M1c (visceral metastases) to 62% in M1a (metastases limited to skin and lymph nodes).[1] Dacarbazine is associated with an objective response rate between 5% and 14%.[2] Similarly, combination chemotherapy regimens have failed to show survival benefit when compared to dacarbazine.[3] With the advent of immunotherapy, significant survival benefits were observed, first with the anti-CTLA-4 antibody ipilimumab and most recently with anti-programmed cell death protein 1 (PD-1) antibodies.[4–7] Pembrolizumab is an IgG4-κ human anti-PD-1 monoclonal antibody which has demonstrated overall survival (OS) benefit. Recent updates from melanoma patients enrolled in KEYNOTE-001 showed 1-year OS rate of 67% and 2-year OS of 50%. The overall response rate was 34%[8] At a median follow-up duration of 14.8 months, median duration of response had not been reached.[8] Safety and efficacy of ipilimumab in two patients with melanoma undergoing dialysis has been reported.[9] However, there have been no reports of pembrolizumab in such patients. With prevalence of end-stage renal disease (ESRD) due to the rising prevalence of type II diabetes, data from National Institute of Diabetes and Digestive and Kidney disease suggested that there were 398 861 patients with ESRD being treated with some form of dialysis in the USA as of 2009.[10] Although melanoma is not one of the most common malignancies, anti-PD-1 antibodies are increasingly being used in other malignancies in clinical trials. A recent clinical trial in patients with advanced non-small-cell lung cancer showed that the objective response rate was 19.4% in patients treated with pembrolizumab. The efficacy was even higher for patients with PD-L1 expression in at least 50% of tumour cells.[11] This study led to accelerated approval of pembrolizumab by the FDA in patients with metastatic non-small cell lung cancer in October 2015. The incidence of new cases of lung cancer was expected to exceed 221 000 in 2015.[12] Taken together, the above data suggest the need for clinical data to inform the use of anti-PD-1 antibodies in patients undergoing haemodialysis. We present a case describing the use of pembrolizumab in a patient with ESRD on haemodialysis.

CASE PRESENTATION

A 63-year-old man with history of insulin-dependent type II diabetes, hypertension and ESRD on haemodialysis first presented with a thick melanoma arising from his left ear in October 2013. Original staging after wide local excision and neck dissection was stage IIIB (T4a, 7 mm depth, Clark level V, N2b (2.5 cm palpable lymph node with extracapsular extension)). A repeat positron emission tomography CT (PET/CT) scan in March, 2015 showed enlarging left neck nodes. The patient underwent left-modified radical neck dissection with parotidectomy in June 2015, revealing 10 of 42 involved lymph nodes without extracapsular extension. Mutation analysis revealed that the tumour harboured for BRAF V600K mutation on exon 15. No adjuvant treatment was given at the time because of his comorbidities. He developed abdominal pain and decreased appetite; restaging PET/CT scan in October 2015 showed multiple hypermetabolic lesions including increasing lung nodules and abdominal lymph nodes. CT-guided biopsy of a left para-aortic lymph node confirmed metastatic melanoma.

TREATMENT

After a long discussion of therapeutic options and the limited data on anti-PD-1 antibodies or BRAF inhibitors in haemodialysis, the patient made an informed decision to proceed with pembrolizumab. Pembrolizumab was administered at the standard dose of 2 mg/kg/dose, to be repeated every 3 weeks.

OUTCOME AND FOLLOW-UP

After one dose, his abdominal pain and appetite improved. His serum lactate dehydrogenase (LDH) decreased from 1182 to 354 units/L (reference

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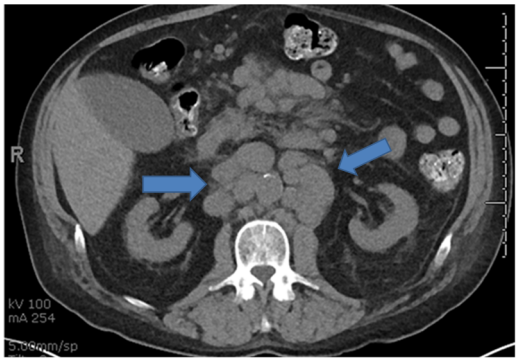

Figure 1 Abdominal CT scan showed extensive lymphadenopathy prior to initiation of pembrolizumab.

range 110–220 units/L). He continued to undergo haemodialysis three times a week with stable serum creatinine level. He noted mild fatigue but no other pembrolizumab-specific side effects. After three cycles, the CT scan showed resolution of pulmonary nodules and significant reduction of retroperitoneal lymphadenopathy (figures 1–4). LDH continued to decrease to 148 units/L. No other significant laboratory changes including thyroid function tests were observed. His urine output remained stable throughout the course of therapy. He has completed 10 cycles of pembrolizumab and is currently in complete remission.

DISCUSSION

Patients with ESRD on haemodialysis present with a unique challenge to oncologists. There are several considerations in treating this subset of patients with anticancer therapy. One important consideration is drug safety in patients with ESRD. Patients with ESRD are at risk of drug accumulation and results in drug toxicity. The CANcer and DialYsis (CANDY) study on patients requiring routine dialysis receiving anticancer drugs showed that 72% of dialysis patients received at least one drug that required a dosage adjustment.[13] The study also found a significant number of chemotherapy drugs for which there were no available recommendations in dialysis patients. The prescribing information for pembrolizumab reports that clearance of the drug is independent of renal function even in severe renal insufficiency (estimated glomerular filtration rate of 15–29 mL/min/1.73 m^2 body surface area), but gives no guidance on dose or timing for patients on dialysis.

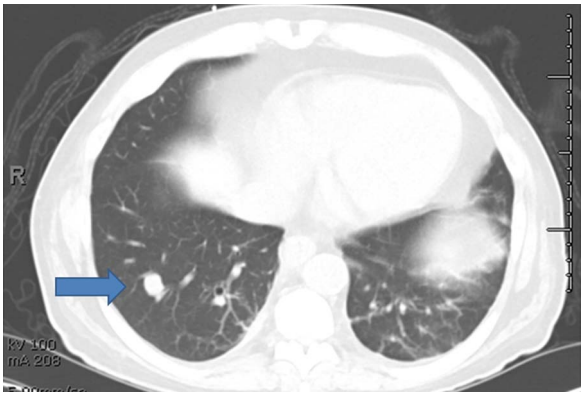

Figure 3 CT scan of chest showed two right lower lobe pulmonary nodules before initiation of pembrolizumab.

A major consideration for dialysis patients is the potential decrease in drug exposure due to ultrafiltration. The CANDY study found that of the patients receiving anticancer drugs, 82% required drug administration after the dialysis sessions.[13] Studies with other antibodies of similar sizes found that they are not dialysable due to large molecular weight.[14] Thus it appears likely that pembrolizumab can be given without regard to the timing of dialysis.

In addition, patients with ESRD are generally considered immunocompromised.[15] PD-1 antibodies such as pembrolizumab rely on the activation of the immune system for efficacy. The interaction between the PD-1 receptor and its ligands PD-L1 (B7-H1) results in T-cell inhibition and creates an immune-suppressive tumour microenvironment. PD-1 antibodies disrupt this interaction to allow the antitumour activities from T cells.[2] Our case report demonstrates that PD-1 antibodies can still be effective in dialysis-dependent ESRD. Further detailed study of the induced immune response in such patients is warranted.

As the underlying efficacy of PD-1 antibodies is relying on the enhancement of the immune system to target melanoma, immunotherapy with pembrolizumab can be associated with immune-related adverse events. In clinical trials, immune-mediated nephritis occurred in 0.4% of patients treated with pembrolizumab.[16] Though this may not be as crucial for patients with ESRD already on haemodialysis, one should be aware that patients with normal renal function or chronic kidney disease may develop this adverse effect. Immune-mediated nephritis has

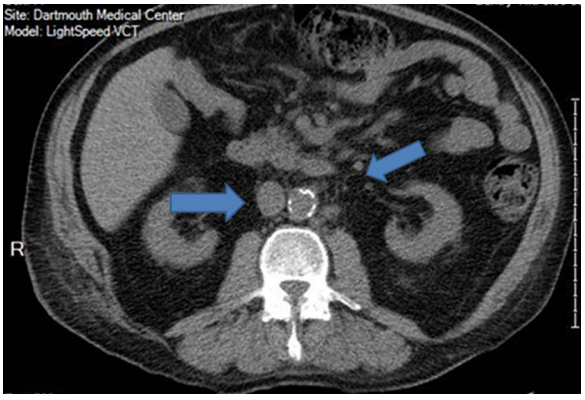

Figure 2 Abdominal CT scan showed resolution of retroperitoneal lymphadenopathy after three cycles of pembrolizumab.

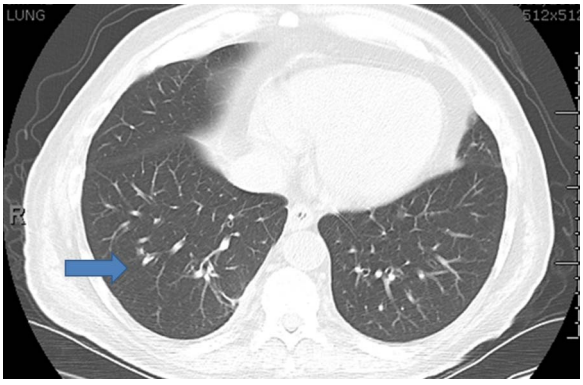

Figure 4 Interval resolution of the right lower lobe pulmonary nodules after three cycles of pembrolizumab.

also been reported to be <1% of patients in clinical trials when nivolumab and ipilimumab are used separately and 2.1% when used in combination.[17 18] Our patient did not experience any significant immune-related adverse events.

Learning points

- Pembrolizumab has been shown to be effective in patients with metastatic melanoma and non-small cell lung cancer including several other malignancies in recent trials.
- The usage of pembrolizumab is expected to rise with recent Food and Drug Administration approval in the management of non-small cell lung cancer. Furthermore, with increasing prevalence of type II diabetes, the number of patients undergoing routine dialysis continues to rise. Oncologists will be called on increasingly to prescribe immunotherapy to dialysis patients, and data to guide the use of these drugs are desired. To the best of our knowledge, this is the first report of the use of pembrolizumab in a patient requiring routine haemodialysis.
- Our case suggests that pembrolizumab can be safe and effective in the setting of haemodialysis.
- The limitation of this study is that this is a single case, and we have no pharmacokinetic data to report. Therefore, further study on a larger population cohort is warranted.

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Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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