Letter to the Editor

Pembrolizumab in hemodialysis patients. Is it safe?☆

Pembrolizumab en pacientes en hemodiálisis ¿es seguro?

ARTICLE INFO

Dear Editor,

Patients with chronic kidney disease on dialysis, and particularly those with kidney transplant, have a higher incidence of cancer than the general population.[1] Chemotherapy for these patients poses special challenges, primarily in relation to adjusting the dose according to renal function, drug interactions and increased side effects.[2] In recent years, great advances have been achieved in the treatment of various cancers based on immunotherapy. Specifically, *check-point* inhibitor drugs have been developed which, by negatively inhibiting co-stimulation signals from T lymphocytes, enable them to remain reactive against cancer cells.[3] These drugs inhibit the CTLA-4, PD-1 or PD-L1 protein, and many of their side effects are related to the persistent activation of T lymphocytes, thereby leading to a higher incidence of acute tubulointerstitial nephropathy, acute tubular necrosis and minimal change disease.[1] Pembrolizumab is a monoclonal antibody which selectively binds to PD-1, blocking the negative impact of this receptor on T lymphocyte function. It is indicated in the treatment of a number of different types of cancer, including melanoma, renal carcinoma and lung cancer.

There is very little experience of such treatment in patients on renal replacement therapy with dialysis or kidney transplantation. We report the case of a patient on haemodialysis with lung cancer who received treatment with pembrolizumab and probably developed immune intolerance of the non-functioning graft.

This was a 58-year-old male, former smoker, having smoked for 24 years (24 pack years), diagnosed with IgA mesangial glomerulonephritis, who began haemodialysis for the first time in 1996. He received a cadaveric kidney transplant a few months later. He developed chronic graft nephropathy and returned to haemodialysis in 2000 with subsequent transplantectomy. He received a second cadaveric kidney transplant in 2006. In 2015, he started on a peritoneal dialysis programme as a result of deteriorating kidney function due to global glomerulosclerosis and interstitial fibrosis with tubular atrophy of probable pyelonephritic origin, subsequently being switched to haemodialysis in March 2019 after peritoneal leakage into the right hemithorax with pleural effusion. At that point the patient was anuric. In May 2019, he developed pain in the right superior costal margins, with chest X-ray showing a lytic lesion in the posterior region of the 2nd right costal cartilage. He was diagnosed with stage IV-A undifferentiated clear cell carcinoma of probable pulmonary origin (cT1a N2 M1b), the molecular study for EGFR/ALK/ROS1 mutations was negative, with PDL-1 expression in 90% of the cells. He was started on treatment with pembrolizumab in July 2019. After 4 weeks of treatment, the patient experienced low-grade fever, graft discomfort and macroscopic haematuria.

Blood tests showed constant elevation of CRP, without leucocytosis, neutrophilia or eosinophilia; from the outset, all cultures, including urine, pleural fluid and blood were negative. Findings of the Doppler ultrasound of the graft were nonspecific, with increased echogenicity of the sinus, thinning of the cortex and pyramid hypertrophy, and persistent intrarenal flow. With suspected immune intolerance of the graft, it was decided to start treatment with low doses of corticosteroids, with some improvement, although the scant haematuria continued. Treatment was continued with 200 mg of pembrolizumab every 3 weeks (after the last weekly session) and low doses of prednisone.

There is very little experience in treating haemodialysis patients with immunotherapy. Reported predisposing factors to developing toxicity include the previous use of

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corticosteroids, being female, previous history of autoimmune disease, and abnormal kidney function.[4] Although they are well-tolerated drugs, their side effects are related to the activation of T lymphocytes and are relatively common, most notably skin, gastrointestinal, thyroid, pulmonary and renal disorders.[5] From the renal point of view, the main complications are acute tubular necrosis, acute tubulointerstitial nephropathy, and some forms of glomerulonephritis.[6] Nevertheless, these drugs have been used safely in haemodialysis patients.[7,8]

There is also limited experience with these treatments in kidney transplant patients. In fact, there have been reports of some cases in which immunotherapy, by preserving the activation of T lymphocytes, has led to graft rejection and its use is therefore not safe in patients with a functioning transplant.[9]

In our patient, the association of treatment with pembrolizumab and the development of fever, local symptoms and haematuria posed a significant challenge in terms of diagnosis. Furthermore, it was possible that he had developed acute tubulointerstitial nephropathy, and although the blood test showed absence of eosinophilia, we could not exclude this diagnosis. However, we believe it more likely that the patient had developed an immunological intolerance on the non-functioning graft, which until then had been well tolerated. Unfortunately, we were unable to perform a graft biopsy given the patient's situation and the fact that the lesion would presumably have had severe chronic damage.

The differential diagnosis between the two processes was very important, since in the case of patients with a functioning kidney graft, withdrawal of treatment would be indicated, as well as performing the biopsy for an accurate diagnosis and the taking of decisions accordingly.[10] In the case of immunological intolerance to the non-functioning graft, which was the most likely case in our patient, treatment with low doses of corticosteroids is recommended, in order not to inhibit the therapeutic effect of pembrolizumab; in fact, the symptoms in our patient improved, and for the moment it has been possible to continue treatment.

Finally, to the best of our knowledge, we have described the first haemodialysis patient treated with pembrolizumab to have likely suffered from treatment-related non-functioning graft immune intolerance.

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