Report of ipilimumab in a heart transplant patient with metastatic melanoma on tacrolimus

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Practice points

- Ipilimumab is a newly approved immunotherapy for metastatic melanoma with the potential for durable response.
- There is only one report describing the use of ipilimumab in a patient with solid organ transplant and no defined guidelines for its use in the immunosuppressed population.
- In the reported case, a patient with metastatic melanoma and orthotopic heart maintained on tacrolimus was treated with ipilimumab. He experienced disease progression, but no other significant adverse events related to drug treatment.
- There is a possibility of organ rejection or ineffective treatment when using ipilimumab or other immune checkpoint inhibitors in patients who are chronically immunosuppressed.

Ipilimumab is the first immunotherapy shown to increase overall survival in patients with metastatic melanoma. Currently, there are no accepted guidelines for use of ipilimumab in organ transplant patients. There is only one report in the literature on successful administration of ipilimumab in two kidney transplant recipients. In this report, a heart transplant patient with metastatic melanoma was successfully treated with ipilimumab. He experienced no adverse drug reactions. However, after standard treatment with regimen of four doses at 3 mg/kg, he experienced disease progression. Here, we address concerns of organ rejection or ineffective treatment when using ipilimumab or other immune checkpoint inhibitors in patients who are chronically immunosuppressed.

Melanoma is the sixth most common form of cancer in the USA [1,2]. Skin cancer is also the most common form of malignancy in chronically immunosuppressed organ transplant patients [3]. Melanoma tumorigenesis is known to be immune-mediated and limited data exist regarding the management of transplant recipients with advanced disease at this time [4].

Historically, for patients diagnosed with stage IV disease prognosis was poor, with median overall survival (OS) with treatment ranging from 8 to 12 months [5]. In 2011, the US FDA approved ipilimumab, a first-in-class monoclonal antibody against CTLA-4 for the treatment of metastatic melanoma [6]. Ipilimumab was shown to increase overall survival, and demonstrated potential for durable response in a subset of patients, data that have now been validated with longer-term follow-up [7,8]. The most common toxicities appear to be immune mediated, and include dermatitis, enterocolitis, endocrinopathy and hepatotoxicity [9]. With the exception of endocrinopathies, most are treatable and reversible, though serious and life-threatening events can occur.

Since 2011, a number of other agents, including PD-1 antibodies, have also been identified to have the potential to improve clinical outcomes. Despite these landmark advances, however, treatment options remain limited for a number of patients with metastatic melanoma and little or

KEYWORDS

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no data exist regarding the safety and efficacy of immune checkpoint blockade in solid organ transplant patients. Currently, there are only two documented cases of successful administration of ipilimumab in solid organ transplant patients, and both were renal transplants [10]. In the first case, the patient had partial response 2 years after treatment and had no immune-related adverse events. In the second case, the patient experienced grade 2 colitis and disease progression after treatment.

Here, we present the case of a 75-year-old solid organ recipient with metastatic melanoma who tolerated ipilimumab therapy.

Case report

In 2002, the patient, a 62-year-old Caucasian male underwent orthotopic heart transplant for ischemic cardiomyopathy. His past medical history was significant for diffuse large B-cell lymphoma successfully treated with CHOP/rituximab in 2011, cholelithiasis, diverticulosis, atherosclerosis, hepatic steatosis and gastroesophageal reflux disease.

In 2009, he was diagnosed with melanoma on the left upper back (Breslow 1 mm, Clark level IV, nonulcerated, *BRAF* wild-type) and underwent wide local excision and sentinel lymph node biopsy with one out of two nodes positive. Left axillary dissection was then performed with 0/13 nodes positive. The melanoma recurred locally in November 2012, and a wide local excision was performed with negative margins. In August 2013, there was another local recurrence with PET/computed tomography (CT) showing increased fluorodeoxyglucose (FDG) activity, which was excised with negative margins. In January 2014, PET/CT showed no evidence of disease. A follow-up PET/CT scan in July 2014 and subsequent biopsy showed recurrence with two new FDG avid lymph nodes in the left axilla. Brain MRI at this time showed no evidence of metastasis.

The axillary metastases were determined to be technically resectable. However, because he had multiple recurrences in a short interval, along with the development of small lung nodules concerning for metastases, immunotherapy rather than surgical intervention was chosen. Ipilimumab was initiated in July 2014 at 3 mg/kg. Cycle two was delayed for 1 week due to one to two episodes of watery nonbloody diarrhea. At this time, he also experienced an episode of mild abdominal pain and nausea,

which was relieved with prochlorperazine. It was subsequently felt that the symptoms were related to diet, as the patient had experienced similar episodes in the past, prior to the initiation of ipilimumab. Once therapy resumed, the patient was able to complete all four cycles by October 2014 with no other delays or toxicities.

In November 2014, 4 months after starting treatment with ipilimumab, PET/CT imaging showed a slight increase in the size of his disease. There were two new pulmonary nodules 0.6 and 0.5 cm in size in the lingula and the left lower lobe, respectively. Additionally, the left subpectoral lymph node increased in size from 0.7 × 0.6 cm to 1.2 × 1.1 cm. At this time, the patient was still asymptomatic. The pulmonary nodules, while potentially concerning for metastasis, were still small in size. Additionally, only one of three lymph nodes increased significantly in size. Thus, to rule out pseudoprogression, PET/CT was obtained again in 2 months. In January 2015, PET/CT confirmed disease progression with enlarging pulmonary nodules and enlarging subpectoral lymph nodes. The patient was then started on treatment with pembrolizumab at 2 mg/kg. At the time of this writing, the patient has completed five cycles of pembrolizumab and has tolerated treatment with no adverse reaction and continues to have an excellent performance status. PET/CT after three cycles of treatment showed slight enlargement of his subpectoral lymph node as well as persistent multiple pulmonary nodules. A new 1.1 × 1.1 cm subpectoral lymph node was also identified on this imaging. A short interval scan will be performed to determine if the changes noted above are evidence of true versus pseudoprogression in the setting of treatment with immunotherapy.

His immunosuppression regimen had been maintained with tacrolimus 3 mg twice daily at 0.046 mg/kg. He had no issues with cardiac health during treatment with ipilimumab. After completion of four cycles of ipilimumab, a transthoracic echocardiography and stress echocardiography report showed no significant findings with ejection fraction and diastolic function within normal limits, no evidence of ischemia and target heart rate. This was unchanged from his echocardiogram before treatment began in 2012.

Discussion

In this case, a patient with a history of a heart transplant in 2002 with metastatic melanoma was treated with ipilimumab. After a standard

treatment regimen of four doses at 3 mg/kg, he experienced disease progression.

Immunotherapies, including ipilimumab and PD-1 blocking antibodies such as nivolumab and pembrolizumab are now a mainstay of treatment for patients with metastatic melanoma. Tacrolimus functions via a separate mechanism as a calcineurin inhibitor and inhibits T-cell signal transduction and IL-2 transcription. Of note, the CTLA4–CD80/86 pathway is also targeted as a less toxic alternative to calcineurin inhibitors. Belatacept, approved for the use of kidney transplant rejection prophylaxis, is a CTLA4–IgG1 fusion protein, which blocks CD80/86 and thus blocks T-cell costimulation [11].

Most importantly, in the case described above, the patient did not experience any clinical or functional evidence of chronic allograft rejection. His echocardiogram from before and after treatment with ipilimumab showed the same level of cardiac function. Additionally, he was maintained on tacrolimus 3 mg twice daily throughout therapy without issue. This is significant as it is known in murine models, that monotherapy with CTLA-4 Ig resulted in delayed organ rejection [12]; and blockade of CTLA-4 in murine models resulted in organ rejection, as well as decreased expression of PD-1 and IDO [13].

We speculate that his normal cardiac function was in part due to his low level of immunosuppression required as well as the length of time that had passed since successful transplantation. It is known that the frequency of organ rejection decreases with years after surgery, and in asymptomatic patients, subclinical chronic rejection with histological changes was found in 10% of patients at 7 years after cardiac transplantation [14,15]. While functionally there is no evidence of rejection in this patient, endomyocardial biopsy was not conducted to assess subclinical cardiac allograft vasculopathy. Although ipilimumab did not result in adverse immune-related effects in this patient, more studies are needed to characterize the side-effect profile of the drug on patients who are also organ transplant recipients.

Finally, it is of interest that this patient was treated with rituximab, an anti-CD20 antibody, for B-cell lymphoma prior to his diagnosis of melanoma. There are reports in the literature describing melanoma recurrence and metastasis following treatment with rituximab [16,17]. CD20⁺ B cells are known to be present in the

melanoma microenvironment, although no mechanism or causality between treatment with rituximab and melanoma has been clearly established. Conversely, treatment targeting a subpopulation of melanoma cells expressing CD20 has been as an adjuvant treatment for melanoma. One small study found six of nine patients at high risk of melanoma recurrence to be disease free after a median observation of 42 months [18]. In this case, we believe the patient's immune-compromised status, rather than rituximab exposure, to be the larger risk factor for the development of metastatic melanoma [4].

Conclusion

It is well documented that there is an increased risk of skin cancer in the population of solid organ transplant recipients. There is a 2.4-times increase in incidence of melanoma after transplantation [19]. Transplant patients with melanoma are also found to have significantly worse outcomes than non-transplant patients [20].

Currently, there is insufficient data on the use of ipilimumab in patients with a history of organ transplantation. A 2012 study by Waldron-Lynch *et al.* found that in mice, ipilimumab accelerated graft rejection while teplizumab (anti-CD3 mAb) delayed graft rejection [21]. With the exception of the previously mentioned case report, there have been no studies or other reports to date in humans [10].

When administering immunotherapy in an effort to treat metastatic melanoma, it is reasonable to think carefully about the implications in an immunosuppressed patient such as a transplant recipient. The interaction between CTLA-4 blockade with both melanoma tumorigenesis as well as cell-mediated organ rejection needs to be studied further.

Future perspective

The use of immunotherapies, including ipilimumab, nivolumab, and pembrolizumab, has demonstrated the ability to prolong survival in patients with unresectable stage III or IV melanoma. However, currently, it is poorly understood which cohorts of melanoma patients may derive the most benefit from immunotherapies and which groups may be most susceptible to potentially serious adverse drug reactions.

While future prospective studies or larger cohort analyses are warranted, this case demonstrates that ipilimumab or other checkpoint inhibitors may be a therapeutic option in

patients with a history of solid organ transplantation. This is of particular relevance given the increasing use of immune checkpoint inhibitors in oncology beyond melanoma.

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Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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• of interest; •• of considerable interest

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