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Immune Checkpoint Inhibitors to Metastatic Melanoma and Renal Allograft Rejection: A Case Report

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ABSTRACT

A male patient who underwent a pre-emptive renal allograft and, nine years after the transplant, was diagnosed with nodular melanoma in the left shoulder, developing a few months later metastases. After two cycles of combined therapy with anti-PD-1 and anti- CTLA4, the patient was confirmed with acute rejection of the transplanted kidney allograft. A review and discussion about renal allograft rejection and the use of immune checkpoint inhibitors to metastatic melanoma is reported.

Keywords: Kidney; Renal allograft; Metastatic melanoma

INTRODUCTION

Metastatic melanoma is an aggressive disease that responds poorly to most standard chemotherapies, with less than 15% survival in 5 years. Immune Checkpoint Inhibitors (CPIs) and target therapy have revolutionized melanoma treatment with remarkable survival benefits.[1] Patients with Solid-Organ Transplantation (SOT) have an increased risk of developing cancer. Secondary malignancies have been reported as the second leading cause of death in this population, presumably because they receive chronic immunosuppressive therapy to maintain allograft tolerance and less aggressive cancer treatments.[2] As the indications for CPIs expand to many cancers, it is crucial to determine the risk-benefit ratio of CPI use in SOT recipients. However, safety and efficacy data lack CPIs in patients who have undergone Solid Organ Transplantation (SOT) because they have been excluded from clinical trials.

CASE REPORT

We report a case of a 68 years-old male, white, former smoker of 40 pack-years, intense sun exposure, type-2 diabetes mellitus, hypertension, and chronic renal failure that underwent a pre-emptive renal allograft. He had stable kidney function after the transplant. Nine years after the transplant, he underwent resection of nodular melanoma in the left shoulder, with 4.5 mm Breslow, Clark's level IV, with ulceration without the involvement of sentinel lymph nodes (pT4bN0M0 - 8ª ed AJCC) Nine months after resection, he was diagnosed with metastases in the liver, lymph nodes,and bones, the biopsy of which was confirmed to be wild BRAF melanoma metastasis.

The case was discussed at the multidisciplinary tumor board and proposed combined therapy with anti-PD-1 (Nivolumab 3mg/m²) and anti-CTLA4 (Ipilimumabe 1mg/m²) every 21 days for four cycles, followed by maintenance Nivolumab 3mg/m² until disease progression. There was a complete discussion involving graft loss risks with the patient, and he wished toproceed with the treatment.

Five days after the second cycle of the combined CPIs, he developed nausea, vomiting, fatigue, and abdominal pain. The transplanted kidney's ultrasound doppler showed acutekidney disease findings and poor perfusion related to transplant dysfunction and a graft nephrectomy was performed. Shortly after surgical recovery, the patient agreed to restartimmunotherapy.

After the fourth cycle of combined immunotherapy, the PET-CT showed a complete radiological response at all metastasis sites. Currently, the patient is asymptomatic, maintaining Nivolumab without limiting toxicities, undergoing a hemodialysis schedule,without evidence of melanoma.

DISCUSSION

Melanoma and nonmelanoma skin cancers after transplantation are common and are a cause of substantial mortality. Therefore, annual dermatological assessment is recommended for all renal transplant patients.[3] The studies suggest that the rejection rate may be higher with PD-1/L1 blockade because alloimmunity largely relies on an alloantigen-mediated response that resembles the mechanism of tumor immune rejection.[4] Besides, anti-PD-1/L1 has higher antitumor response rates than anti-CTLA-4 (CheckMate 067, Keynote 006),[5-8] and the differing allograft rejection rates may reflect this. Although anti-CTLA-4 demonstrated in retrospectivestudies show a lower risk of graft loss when compared to anti-PD-1, it also corresponds to a lower response rate.[9, 10] Prospective studies are needed to answer whether the risk of alloimmunity with anti-PD-1 differs from anti-CTLA-4.[11] In the institutional experience of MD Anderson Cancer Center, the median Overall Survival (OS) in melanoma patients with prior SOT was much lower (5 months 95% CI 1-9) than what has been recently reported in the interim analyses of the Keynote-006 trial and the 4-year updated safety analysis of the CheckMate-067 problem (12 months 95% CI 8-16). These data suggest that the occurrence of allograft rejection compromised OS in patients with prior SOT.[5,7] CPIs in SOT recipients have been previously reported in other reviews.[12, 13, 14] Theseprevious reviews identified some patients with allograft rejection and others who tolerated treatment with no adverse events. However, they did not synthesize the evidence on allograft rejection frequency by type of SOT, class of CPI, and anti-rejection immunosuppressant used at CPI initiation. The tumor response to CPI and OS to the occurrence of allograft rejection and the type of anti-rejection immunosuppression was not specified. Besides, they did not provide information on how rejections were managed and whether they necessitated permanent discontinuation of CPIs.[2] No prospective observational cohort studies have been published; therefore, we could notascertain allograft rejection incidence in patients with prior SOT. The lack of knowledge on the safety and efficacy of CPIs in patients with prior SOT poses asa major oncologic challenge. There are no clear recommendations on how to intervene for these patients. Hence the risk of allograft rejection and the reduction in survival compared with CPIs metastatic melanoma without treatment or chemotherapy should be explicitly conveyed to the patients. Studies are also needed to enhance our understanding of the complex interactions between the immune system, cancer neoantigens, and alloantigens to establish the ideal therapeutic plan to maintain allograft tolerance and maximize antitumor therapeutic benefits.

REFERENCES

1. http://seer.cancer.gov/statfacts/html/melan.html. (as of 3/15/2015).
2. Acuna SA,Fernandes KA,Daly C,Hicks LK,Sutradhar R,Kim SJ, et al. Cancer mortality among recipients of solid-organ transplantation in Ontario,Canada.JAMA Oncol. 2016;2(4):463-9.
3. Ascha M,Ascha MS,Tanenbaum J, Bordeaux JS. Risk Factors for Melanoma in Renal Transplant Recipients. JAMA Dermatol. 2017;153(11):1130-1136.
4. Dulos J,Carven GJ,van Boxtel SJ,Evers S,Driessen-Engels LJ,Hobo W,et al. PD-1blockade augments Th1 and Th17 and suppresses Th2 responses in peripheral blood from patients with prostate and advanced melanoma cancer. J Immunother. 2012;35(2):169-78.
5. Noha Abdel-Wahab, et al. Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic literature review. J Immunother Cancer. 2019;16;7(1):106
6. Ajithkumar TV,Parkinson CA,Butler A,Hatcher HM. Management of solid tumours in organ-transplant recipients. Lancet Oncol. 2007;8(10):921-32.
7. Hodi FS,Chiarion-Sileni V,Gonzalez R,Grob JJ,Rutkowski P,Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-1492.
8. Schachter J,Ribas A,Long GV,Arance A,Grob JJ,Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006).Lancet.2017;390(10105):1853–62.
9. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune-related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta- analysis. BMC Med. 2015;13:211.
10. Schadendorf D,Hodi FS,Robert C, et al. Pooled Analysis of Long-Term Survival DataFrom Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;10;33(17):1889-94.
11. Lipson EJ,Bagnasco SM,Moore J,Jang S,Patel MJ, Zachary AA, et al. Tumor regression and allograft rejection after administration of anti-PD-1.N Engl J Med. 2016;3;374(9):896-8.
12. Chae YK,Galvez C,Anker JF,Iams WT,Bhave M. Cancer immunotherapy in a neglected population: the current use and future of T-cell-mediated checkpoint inhibitors in organ transplant patients. Cancer Treat Rev. 2018;63:116-121.
13. Babey H, Quere G, Descourt R,Le Calloch R, Lanfranco L, Nousbaum JB, et al. Immune-checkpoint inhibitors to treat cancers in specific, Expert Rev Anticancer Ther.2018;18(10):981-989.
14. Maggiore U,Pascual J.The bad and the good news on cancer immunotherapy: implications for organ transplant recipients. Adv Chronic Kidney Dis. 2016;23(5):312-316.