Combined dabrafenib and trametinib therapy in metastatic melanoma and organ transplantation: Case report and review of the literature

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INTRODUCTION

Improved surgical techniques and superior post-transplant care have increased graft survival after solid organ transplantation, and complications of lifelong immunosuppression are increasingly prevalent in clinical practice. The excess relative risk of melanoma attributable to transplantation is between 2 and 12 times that of the general population,[1] and given the high tumor burden, this has important implications for the surveillance and management of organ transplant recipients (OTRs). Several risk factors for melanoma are known, including immunosuppression, the presence of atypical nevi, light skin phototype, ultraviolet light exposure, and a family or personal history of skin cancer.[1,2] Here we report a case of cutaneous melanoma arising posttransplant, highlighting the substantial morbidity and mortality of this disease in OTR. In view of the increased risk of melanoma and high potential for metastasis, dermatologists should monitor OTRs closely and institute multidisciplinary care without delay.

Abbreviations used:

AJCC:	American Joint Committee on Cancer
CT:	computed tomography
OTRs:	organ transplant recipients
PET:	positron emission tomography

CASE

A 66-year-old white woman with Fitzpatrick skin type II received a heart transplant in 2001 for familial hypertrophic cardiomyopathy and was maintained on cyclosporine. She presented to the dermatology department in 2005 for the evaluation of a rapidly growing pigmented lesion on the umbilicus. A biopsied found this lesion was a primary malignant melanoma of 17.5 mm Breslow thickness. Wide local excision was performed, and sentinel lymph node biopsy found 1 of 1 positive node in the left side of the groin and 0 of 1 positive nodes in the right side of the groin. In 2008, surveillance positron emission tomography (PET)/computed tomography (CT) detected left groin node recurrence, and a subsequent radical left inguinal dissection found nodal positivity in 18 of 21 nodes. At that time, the patient underwent definitive adjuvant radiation treatment to the left groin.

In 2011, a surveillance PET/CT found multifocal retroperitoneal lymphadenopathy, and a diagnosis of metastatic melanoma was confirmed by CT-guided biopsy. A BRAF V600E mutation was detected, and the patient was enrolled in a phase 3 clinical trial evaluating combined dabrafenib and trametinib therapy (selective BRAF and mitogen-activated protein kinases inhibitors, respectively). She tolerated the regimen well, showing no evidence of disease recurrence for 15 months. Unfortunately, a single metastasis was found in the right side of the skull in 2013, which was managed with stereotactic radiotherapy (15000 Gy). Because of tumor progression, the patient was withdrawn from the study and unfortunately died from complications of metastatic disease later in the year.

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DISCUSSION

Three distinct clinical entities are of interest in relation to melanoma in the OTR: donor-derived melanoma, melanoma preceding organ transplantation, and de novo melanoma arising after transplant. In this report, we focus on de novo posttransplant melanoma, the scenario most frequently encountered in clinical practice. Melanoma is an immune responsive tumor, and the regression of benign and malignant melanocytic lesions in response to immune mechanisms is well documented.[1,2] Iatrogenic immunosuppression, therefore, is expected to worsen melanoma outcomes after transplantation, although to date no population-based study with adequate power has addressed this issue in OTRs. Small, retrospective studies have found that Breslow thickness is inversely correlated with melanoma survival in this population.[1,3-5] In a case series of 100 transplant patients, Matin et al[6] found that OTRs with melanomas of greater than 2 mm thickness (American Joint Committee on Cancer [AJCC] TNM stage T3 or T4) had a significantly worse prognosis than did immunocompetent patients with similar tumors, whereas the prognosis did not differ in tumors of ≤ 2 mm thickness (TNM stage T1 and T2). These data indicate that iatrogenic immunosuppression may be associated with worse prognosis in patients with thicker tumors and highlight the need for close surveillance and early diagnosis in the OTR.

The initial approach to posttransplant primary melanoma follows the same principles as the nontransplanted general population. Surgical excision with wide margins is the first step after diagnostic biopsy and can cure tumors that have not spread. The size of the surgical margin is guided by the Breslow thickness of the primary lesion. Tumors of more than 4.0 mm require 2-cm margins, and, because of the high risk of nodal and distant metastasis, in this clinical setting more extensive surgical resection is unlikely to yield better outcomes. The AJCC published an international melanoma staging system that guides melanoma prognosis and treatment in immunocompetent patients.[7] The AJCC predicted that 5-year survival for patients with early, regional nodal, and metastatic melanoma disease is 85%, 24% to 69.5%, and 6%, respectively, where the 24% to 69.5% range varies according to the number of positive lymph nodes at diagnosis.[7] Sentinel lymph node biopsy is indicated for tumors greater than 1-mm Breslow thickness or in the presence of increased mitotic activity and ulceration on histology. Sentinel lymph node positivity is found to be the strongest predictor of mortality in melanoma,[4,8] and in nodal disease, PET/CT or direct CT yield information about tumor staging and disease progression. Surgical control was deemed unlikely in our patient, as she presented with a primary lesion of 17.5-mm Breslow thickness and positive lymph node status. Completion lymphadenectomy was not performed at diagnosis, as this procedure is not found to increase survival in early nodal disease.[9]

There is no cure for metastatic melanoma, which has a median survival time of 7.5 months from diagnosis.[10] Conventional treatment strategies, such as surgery, chemotherapy, and radiotherapy are not effective in limiting the progression of tumor metastasis and are often associated with adverse effects and poor quality of life. Reassuringly, immunotherapy and molecular targeted therapy have achieved partial success in a subset of patients with unresectable metastatic melanoma. High-dose interleukin-2[11] and, more recently, anti−CTLA-4 (ipilimumab)[12] and anti−PD-1 (nivolumab)[13] used as single agents or in combination therapy, have achieved a long-term survival of 5 years or longer. Dabrafenib and trametinib, targeted BRAF and MEK1 inhibitors, respectively, have achieved a progression-free survival of up to 3 years when used as monotherapy,[14,15] although as with most treatments based on oncogene-targeted small molecules, tumor resistance has limited the therapeutic response to these agents. Preclinical and early development studies of combination dabrafenib/trametinib have shown promising results, with fewer side effects and less tumor resistance that either agent used alone.[16] Our patient had BRAF V600 mutant metastatic melanoma and was therefore deemed a good candidate for enrollment in a phase 3 clinical trial testing combined BRAF and MEK inhibitor treatment. She had an excellent initial response to therapy, with progression-free survival of 15 months or 5.5 months higher than the median (9.4 months vs 6 to 7 months for monotherapy).[16,17] Although these numbers are promising, at this stage we cannot generalize her response to the transplanted population as a whole. Further research on melanoma outcomes in OTRs is likely to inform effective treatment strategies in relation to both immune therapy and reduction of immunosuppression.

Melanoma is a potentially fatal complication of transplantation, and severe disease can dramatically reduce both the quality of life and the chance of survival in OTRs. The optimal setting for treating OTRs who have melanoma is a multidisciplinary clinic led by the primary transplant team. In the presence of life-threatening tumors, a reduction or modification of immunosuppression should be considered, after carefully balancing the risk of allograft rejection against the risk of melanoma mortality. Dermatologists play a key role in this

assessment, as they may be the only team members able to quantify the tumor burden. A decision was made against a reduction of immunosuppression in our patient, as her cyclosporine regime was deemed necessary to preserve allograft function.

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