Treatment options for metastatic melanoma in solid organ transplant recipients

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INTRODUCTION

Solid organ transplant recipients (SOTRs) have a 2.4-fold increased risk for melanoma.[1] Renal transplant recipients have an incidence of melanoma up to 8 times greater than the comparison immunocompetent population.[2]

Posttransplant melanomas diagnosed at a later stage (Breslow depth 1.51-3.00 mm[3] and T3/T4 stage tumors[4]) have worse survival rates than non-SOTRs with melanoma. Immunosuppressive therapy for kidney transplantation or autoimmune disease at the time of melanoma diagnosis is associated with a greater risk of death from melanoma, suggesting that melanomas in the setting of immunosuppression are more likely to metastasize.[5]

The following case report documents the aggressive behavior of a melanoma in a kidney transplant patient. Because later stage melanomas in SOTRs have a high risk for metastasis, practitioners will benefit from understanding how immunosuppression influences the choice of treatment among the growing number of systemic medications approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma.

Abbreviations used:

CTLA:	cytotoxic T-lymphocyte–associated protein 4
FDA:	US Food and Drug Administration
IFN-α:	interferon alfa
MAPK:	mitogen-activated protein kinase
PD-1:	programmed death-1
SOTRs:	solid organ transplant recipients

CASE REPORT

A 43-year-old woman with a history of nonmelanoma skin cancers noted a changing skin lesion over her right deltoid. The lesion was initially unsuccessfully treated with cryotherapy. Her medical history was significant for kidney and pancreas transplantation from a deceased donor at the age of 36 secondary to childhood diabetes and pregnancy-associated renal complications. Immunosuppressive medications included tacrolimus, 2 mg twice daily, mycophenolate mofetil, 500 mg twice daily, and prednisone, 5 mg daily.

An excisional biopsy found a nonulcerated malignant melanoma, nodular type, with a Breslow thickness of 10 mm (Clark level V), and 37 mitoses per mm^2 (American Joint Committee on Cancer tumor stage T4a). Tumor-infiltrating lymphocytes, radial growth phase, microsatellitosis, lymphovascular invasion, and perineural invasion were absent.

She underwent wide local excision and sentinel lymph node biopsy. There was a microscopic focus (<0.1 cm) of residual melanoma in the subcutaneous fat adjacent to scar, less than 0.1 cm from the deep margin. Malignant melanoma was present in the right axillary sentinel lymph node. Positron emission tomography/computed tomography scan showed no evidence of metastatic disease. Right axillary lymph node dissection found malignant melanoma in 1 of 37 lymph nodes. The largest tumor deposit was 2.5 mm without extracapsular invasion. Her American Joint Committee on Cancer stage was stage IIIB (T4a, N2a, M0).

The medical oncology department recommended reduction of immunosuppression and active

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Table I. FDA-approved systemic treatments for melanoma

Therapeutic options	Year of approval	Mechanism	Indications
Cytotoxic chemotherapeutic agents			
Dacarbazine[7-9]	1975	Cell-cycle nonspecific DNA alkylation	Unresectable or metastatic melanoma
Immune therapy			
High-dose interleukin-2	1998	Enhance host immune function	Unresectable or metastatic melanoma
IFN-α[9-11]	1996 2011 (pegylated IFN)	Enhance host immune function, possible direct tumor effects	Adjuvant therapy after surgery for melanoma metastatic to lymph nodes
MAPK pathway Inhibitors			
Vemurafenib	2011	BRAF inhibitor	Unresectable or metastatic melanoma
Dabrafenib	2013	BRAF inhibitor	Unresectable or metastatic melanoma
Trametinib	2013	MEK inhibitor	Unresectable or metastatic melanoma
Immune checkpoint inhibitors			
Ipilimumab[12]	2011	CTLA-4 blockade	Unresectable or metastatic melanoma
Pembrolizumab	2014	PD-1 receptor blockade	Unresectable or metastatic melanoma, disease progression after ipilimumab and BRAF inhibitor (if $V600E^{+}$)

CTLA, Cytotoxic T-lymphocyte–associated protein 4; *PD-1*, programmed death-1.

observation without adjuvant therapy. Mycophenolate mofetil was discontinued, but tacrolimus and prednisone were continued.

Thirteen months after diagnosis, pneumonia developed, and a computed tomography scan of the chest showed multiple pulmonary and hepatic metastases. Imaging of the abdomen and pelvis did not show any additional metastatic foci.

Brain metastases subsequently developed, and she completed stereotactic radiosurgery to the left pons and right centrum semiovale (1600 cGy to each site). Weeks later, multiple new supratentorial metastases developed, and the patient underwent palliative whole brain radiation (3000 cGy total dose).

Fourteen months after the initial diagnosis, the patient presented with multiple palpable right axillary nodes. Fine-needle aspiration showed melanoma. BRAF testing had previously found wild-type status, and chemotherapy with temozolomide was initiated.

Interval imaging performed at 20 months after the initial diagnosis found innumerable pulmonary metastases and new liver and bone metastases. The patient died of metastatic melanoma 21 months after the initial diagnosis.

DISCUSSION

Evidence indicates that SOTRs have worse outcomes compared with immunocompetent patients for posttransplant melanomas diagnosed at Breslow depths $\geq$1.5 mm.[3,4] Even in the absence of transplant-associated immunosuppression, the tumor characteristics for our patient portended an unfavorable prognosis. Reduction of immunosuppression, which was done in our patient, is recommended in the setting of posttransplant melanoma.[6] However, it is unknown how this affects survival.[6]

Since 2011, the number of FDA-approved systemic therapies for melanoma has proliferated from 3 to 8 drugs (Table I).[13] None are specifically contraindicated in SOTRs according to the FDA-approved package inserts. All, with the exception of dacarbazine, carry a theoretic risk of graft rejection. Many additional medications are in clinical trials.[14]

Our patient potentially qualified for FDA-approved systemic therapy at 2 points: (1) for adjuvant therapy after wide local excision of the primary tumor and axillary lymph node dissection of metastatic disease and (2) 13 months after her initial treatment when distant organ metastases were detected.

Because SOTRs with intermediate and deep primary melanomas have increased risk for poor outcomes,[3,4] effective adjuvant treatment would be useful. Interferon alfa (IFN-α) is the only FDA-approved adjuvant systemic therapy. The landmark clinical trials for IFN-α[15,16] did not include immunosuppressed patients, and the use of IFN-α in this population causes concern for organ rejection. Indeed, the few cases reported in the literature treated metastatic melanoma in kidney transplant recipients with IFN-α either in conjunction with withdrawal of immunosuppression or removal of the transplanted kidney.[7,10,11] Because of a marginal survival benefit for IFN-α and the possibility to enroll patients in clinical trials with more effective medications, its use has declined. Immunosuppression

disqualified our patient for most, if not all, clinical trials, and we did not treat our patient with IFN-α.

SOTRs with metastatic melanoma have especially poor prognosis, as illustrated by the rapid decline of our patient from widespread metastasis. Our patient was treated with temozolomide, an oral prodrug of dacarbazine. There are scarce outcome data regarding the use of dacarbazine or temozolomide specifically in SOTRs.[7,8]

Immunotherapy with interleukin-2 has not been studied in SOTRs. However, the risk of organ rejection and potentially life-threatening capillary leak syndrome and the small percentage of patients who achieve durable remission may limit its use in SOTRs.

Our patient did not qualify for treatment with mitogen-activated protein kinase (MAPK) pathway inhibitors because of wild-type BRAF status. The 3 FDA-approved MAPK pathway inhibitors could potentially be used in SOTRs, although data regarding their safety and efficacy are lacking.

We are aware of a single publication describing the use of an immune checkpoint inhibitor in SOTRs.[12] The authors report 2 cases of metastatic melanoma in kidney transplant recipients who were treated with ipilimumab. Both patients had partial responses, remained on low-dose prednisone monotherapy, and maintained stable kidney function. The use of ipilimumab and pembrolizumab in SOTRs remains uncertain, as immunosuppressed patients were excluded from the clinical development of both therapies. The theoretic concern for their use in SOTRs is the risk for organ rejection caused by the immunostimulatory effects of these 2 agents.

This case report illustrates a current practice gap regarding the safety and efficacy of systemic therapies to treat metastatic melanoma in SOTRs and the need for additional study in this field. Because immunosuppression excludes SOTRs from most clinical trials for adjuvant and systemic chemotherapy, initial experience with these drugs in SOTRS may occur outside of the clinical trials setting. Currently, we evaluate each SOTR patient individually, with treatment decisions based on careful consideration of the risks and potential benefits of systemic therapy options in the context of their immune suppression.

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