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. Renal transplant recipients have an incidence of melanoma up to 8 times greater than the comparison immunocompetent population. Posttransplant melanomas diagnosed at a later stage (Breslow depth 1.51-3.00 mm and T3/T4 stage tumors) 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.

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.

CASE REPORT

A 43-year-old woman with a history of non-melanoma 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 mm² (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...
observation without adjuvant therapy. Mycophenolate
mofetil was discontinued, but tacrolimus and predni-
sone 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 axil-
lary nodes. Fine-needle aspiration showed melano-
ma. 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 me-
tastases 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 out-
comes compared with immunocompetent patients
for posttransplant melanomas diagnosed at Breslow
depths $\geq 1.5$ mm.\textsuperscript{3,4} Even in the absence of
transplant-associated immunosuppression, the tumor
characteristics for our patient portended an unfavor-
able prognosis. Reduction of immunosuppression,
which was done in our patient, is recommended in
the setting of postransplant melanoma.\textsuperscript{6} However, it
is unknown how this affects survival.\textsuperscript{6}

Since 2011, the number of FDA-approved sys-
temic therapies for melanoma has proliferated from
3 to 8 drugs (Table I).\textsuperscript{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 clin-
ical trials.\textsuperscript{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,\textsuperscript{3,4} effective adjuvant treatment would be
useful. Interferon alfa (IFN-$\alpha$) is the only FDA-
approved adjuvant systemic therapy. The landmark
clinical trials for IFN-$\alpha$\textsuperscript{15,16} did not include immuno-
suppressed patients, and the use of IFN-$\alpha$ in this
population causes concern for organ rejection.
Indeed, the few cases reported in the literature
for IFN-$\alpha$ in kidney transplant recipients with IFN-$\alpha$ either in conjunction with
withdrawal of immunosuppression or removal of the
transplanted kidney.\textsuperscript{7,10,11} Because of a marginal
survival benefit for IFN-$\alpha$ and the possibility to enroll
patients in clinical trials with more effective medica-
tions, its use has declined. Immunosuppression

| Table I. FDA-approved systemic treatments for melanoma |
|-----------------------------------------------|------------------|-------------------|------------------|
| Therapeutic options                  | Year of approval | Mechanism          | Indications                                      |
|-----------------------------------------------|------------------|-------------------|-------------------------------------------------|
| Cytotoxic chemotherapeutic agents          |                  |                   |                                                 |
| Dacarbazine\textsuperscript{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-$\alpha$\textsuperscript{9,11}         | 1996, 2011       | 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\textsuperscript{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.
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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