Skin Cancer in Organ Transplant Recipients

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Agenda

• Overall incidence and mortality
• Kaposi sarcoma, Merkel cell carcinoma, Melanoma
• In depth discussion of nonmelanoma skin cancer (NMSC) in organ transplant patients (OTRs)
Skin Cancer in OTRs

- Long-term utilization of immunosuppression in OTRs leads to decreased immune-mediated tumor surveillance and development of malignant tumors
- Skin cancers account for 40–50% of all posttransplant malignancies (highest)
- Significant morbidity and mortality
  - More aggressive than skin cancers in the general population
## Skin Cancer Incidence in OTRs vs. the General Population

<table>
<thead>
<tr>
<th>Type of skin cancer</th>
<th>Cell of origin</th>
<th>Increased incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>Epidermal keratinocyte</td>
<td>65-250 fold</td>
</tr>
<tr>
<td>BCC</td>
<td>Epidermal keratinocyte</td>
<td>10-16 fold</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Lymphatic endothelial cells</td>
<td>84-500 fold</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>Neuroendocrine cells</td>
<td>24-fold</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanocytes</td>
<td>3-8 fold</td>
</tr>
</tbody>
</table>

Adapted from Mittal and Colegio. *Am J Transplantation* 2017
Mortality

• Skin cancer-specific post-transplantation mortality of 35.27 per 100,000 person-years
  – MM- 23.07 per 100,000
  – SCC- 16.53 per 100,000
  – MCC- 16.18 per 100,000
• 3-fold elevation of melanoma-specific mortality in OTRs
• Risk factors in OTRs for skin cancer death
  – Male, Caucasian, thoracic transplant and age over 50 years

Garett et al.  JAAD 2016
Skin cancer-specific mortality stratified by transplantation era. Kaplan-Meier plot showing the proportion of organ transplant recipients dying of skin cancer 1 to 23 years after transplantation, stratified by transplantation era. Total N = 531,000.
Kaposi Sarcoma in OTRs

• Immunosuppression allows reactivation of HHV-8 infection in lymphatic endothelial cells
• Mean time to development of KS after transplant is approximately 13 months
• Presents on the skin and mucosa
  – Lower extremity involvement is common
• Visceral involvement has been reported to be as high as 25–30% in kidney recipients and 50% in heart and liver patients
Kaposi Sarcoma in OTRs
Kaposi Sarcoma in OTRs

- Decreasing the intensity of the anti-rejection drugs or switching agents to incorporate mTOR inhibitors is primary mode of therapy
- Other treatment is based on extent of disease
  - Local – imiquimod, IL vinblastine, cryo, excision, XRT
  - Visceral: doxorubicin, vinblastine, paclitaxel, and etoposide.

Merkel Cell Carcinoma in OTRs

• MCC is an aggressive, rare, neuroendocrine, skin tumor induced by Merkel cell polyomavirus
• 24-fold increased risk in OTRs
• Azathioprine plus cyclosporine is associated with the highest risk
Merkel Cell Carcinoma in OTRs
Merkel Cell Carcinoma in OTRs

• Primary treatment is surgical excision
• In the largest MCC cohort study (6900)
  – Adjuvant RT was associated with improved OS in stages I-II
  – Neither adjuvant RT nor chemotherapy was associated with improved OS in stage III
  – Suggest benefit with adjuvant RT
  – Do not support the routine use of adjuvant chemotherapy
• Systemic chemotherapy for advanced and metastatic MCC

Merkel Cell Carcinoma in OTRs

- OTRs have poorer MCC outcomes
  - Higher rates of disease progression
  - Diminished overall and disease-specific survival

<table>
<thead>
<tr>
<th></th>
<th>IC</th>
<th>OTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free</td>
<td>69.6%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Disease-specific</td>
<td>97.4%</td>
<td>56.2%</td>
</tr>
<tr>
<td>Overall</td>
<td>88.6%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

IC, Immunocompetent; OTR, organ transplant recipients

Organ transplant recipients with Merkel cell carcinoma have reduced progression-free, overall, and disease-specific survival independent of stage at presentation. Arron S, et. Al. JAAD 2014
Melanoma in OTRs

- MM in OTRs presents in three different scenarios
  - De novo MM after transplantation (most common)
  - Pre-transplant MM
  - Donor-derived MM (0.2%)
<table>
<thead>
<tr>
<th>Pre-transplant MM Stage</th>
<th>Recommended wait time</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-situ, Stage 0</td>
<td>No wait</td>
</tr>
<tr>
<td>Stage Ia</td>
<td>2 years</td>
</tr>
<tr>
<td>Stage Ib/Ic</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Stage IIb/Iic</td>
<td>5 years</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>Not eligible for transplantation</td>
</tr>
</tbody>
</table>

Melanoma in OTRs

• Although the risk for MM is only moderately increased (3-8 fold in adults, higher in peds), the prognosis is especially poor
  – Among all skin cancers in OTRs, MM has the highest mortality
• 5-year survival for T1/T2 post-transplantation melanoma is similar to AJCC control population
• ≥ Stage T3, prognosis is significantly worse in OTRs

Immunosuppression is an independent prognostic factor associated with aggressive tumor behavior in cutaneous melanoma. Donahue T, et al. *JAAD 2015*
Melanoma in OTRs

• Higher melanoma-specific mortality is reported among OTRs as compared with the immunocompetent population (HR 2.98)

Melanoma in OTRs

• Management of MM in OTRs mirrors management in immunocompetent patients with similar staging
• Adjustment of immunosuppression is individualized based on extent of melanoma and graft survival
• Immunotherapy in OTRs with advanced melanoma is new and largely undefined
  – Reports of PD-1 blockade leading to renal allograft rejection
  – Limited number of case reports of CTLA-4 inhibition (ipilimumab) show it to be safe and effective

Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. Lipson EJ, Bodell MA, Kraus ES, Sharfman WH. *J Clin Oncol*, 2014

Basal Cell Carcinoma in OTRs

- BCC is a locally destructive keratinocyte tumor affecting people with light phenotypes (red/blonde, blue/green, fair/freckled)
- Ratio of BCC:SCC is 4:1 in the general population reversed in OTRs
- OTRs are 10 - 16 times more likely to develop BCC

Basal Cell Carcinoma in OTRs
Basal Cell Carcinoma in OTRs

- BCC in OTRs are more frequent but not more aggressive than in the immunocompetent population
- Patients with post-transplant BCC often continue to develop additional lesions over time

Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: Cumulative incidence and risk factors. Wisgerhof HC, Edelbroek JR, de Fijter JW. Transplantation, 2010
Basal Cell Carcinoma in OTRs

• The current standard of care for BCC is surgical excision
  – Often MMS for OTRs with head and neck lesions
• In very rare instances, BCC may be locally advanced or metastasize
• Newer targeted therapies are promising
  – Hedgehog pathway inhibitors

Basal cell carcinoma with metastasis to the lung in an African American man
Jahan-Tigh R.R., Alston J.L., Umphlett M. JAAD 2010
Squamous Cell Carcinoma in OTRs
SCC in OTRs – Risk Factors

• Pretransplantation SCC is the strongest predictor of posttransplantation SCC risk
• Actinic keratoses and viral warts at or before transplantation
• Type of transplant
  – Lung, heart, and combined pancreas–kidney transplant recipients higher risk
  – Vs. kidney and liver transplant recipient
• Age, male gender, light phenotype, cumulative UV
Squamous Cell Carcinoma in OTRs

- The risk of SCC development increases with time post-transplant
- SCCs are more aggressive in OTRs
  - Display more “high risk features”
    - Poorly differentiated pathology
    - Spindle cell epithelial component is present in 20%
  - Higher rate of recurrence
  - Higher rate of metastasis

Incidence and clinical course of de-novo malignancies in renal allograft recipients
Squamous Cell Carcinoma in OTRs

• In a study of in-transit metastases of SCCs in OTRs
  – 33% of OTRs died
  – 33% had nodal disease
• Another study found 14.1% local recurrence
  – on average within the first 19 months
• Risk of distant metastases in this population is between 3% and 8% (vs. 0.5-5%)

Cutaneous squamous cell carcinomas in organ transplant recipients
Pathogenesis of SCC in OTRs

• Complex interplay of many factors
• UV radiation is most potent carcinogen
  – Causes both local and systemic immunosuppression
• In combo with chronic immunosuppression, significantly reduced capacity for immune-mediated tumor surveillance
• Resulting in increased risk of carcinogenesis
Immune-mediated

- Immunosuppressive medication

  Decreased response to tumor-specific antigens

  Inhibition of APCs and dysregulation of Treg

  HPV activation and E6 degradation of Bak

Immune suppressive mediators, e.g. IL-10

Non-immune-mediated

- Sensitization to UV-induced damage

  Calcineurin/NFAT inhibition, ATF3 induction, and p53 suppression

  Significantly increased p53 mutations

  Genetic predisposition

UV radiation

Production of pyrimidine dimers
Genetics and Immunosuppression

- Genetic variation affecting pharmacokinetics and pharmacodynamics may contribute to differences in skin cancer rates.
- Genetic polymorphisms in genes encoding the prednisolone receptor, GST enzyme, MC1R, MTHFR enzyme and COX-2 enzyme have been shown to increase the risk of NMSC in OTRs.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism</th>
<th>Risk of NMSC</th>
<th>Dermatologic side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic glucocorticoids</strong></td>
<td>Inhibit antigen presentation, induce lymphocyte toxicity, alter cytokine production</td>
<td>+</td>
<td>Acne, striae, skin fragility, ecchymosis</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibits purine synthesis</td>
<td>+++</td>
<td>Hypersensitivity reaction including urticaria, maculopapular and vasculitic eruptions</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits guanine nucleotide synthesis</td>
<td>+++</td>
<td>Nonspecific rash</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor Decreases T cell activation and IL-2 production</td>
<td>+++</td>
<td>Hirsutism, sebaceous hyperplasia, gingival hyperplasia</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor</td>
<td>+++</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Inhibits mammalian target of rapamycin Abrogates IL-2 signal transduction</td>
<td>+ (decreased skin cancer in clinical trials)</td>
<td>Impaired wound healing, acne/folliculitis, edema</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Inhibits mammalian target of rapamycin Abrogates IL-2 signal transduction</td>
<td>+ (similar to sirolimus)</td>
<td>Mouth ulcers, stomatitis</td>
</tr>
</tbody>
</table>
Specific Drugs and NMSC Risk

• Aziathioprine appears to have the largest impact on carcinogenesis
• Retrospective data suggests that immunosuppression with mycophenolate mofetil may be associated with lower risk for skin malignancy compared with azathioprine-based regimens

Specific Drugs and NMSC Risk – Nonimmununologic Pathways

• Mutagenic effects have been observed following cellular exposure to the combination of ultraviolet light and azathioprine

• Changes in cell morphology and inhibition of DNA repair, apoptosis, and p53 function have been associated with exposure to cyclosporine
Specific Drugs and NMSC Risk

• mTOR inhibitors (sirolimus and everolimus)
  – Sirolimus is associated with lower risk for skin cancers in OTRs
  – Prospective randomized trials showed reduced NMSC in OTRs after switching to mTOR-inhibitors

Sirolimus and NMSC Risk

• Sirolimus treatment significantly increased absolute numbers of CD4+ T cells, memory CD8+, and CD4+ T cells, and Tregs in sun-exposed skin in renal transplant patients
  – Vs. paired samples of non-SE skin
• No differences were found in the absolute number of any T cell subset in the blood

Voriconazole Exposure

• Independent risk factor for developing SCC
• A retrospective single-institution study of 455 lung transplant patients voriconazole use was associated with a 73% increased risk of developing SCC
• Usually affects cystic fibrosis patients

The Oncogenic Role of HPV in OTRs

- SCC has been hypothesized to originate from a co-carcinogen etiology
  - DNA damage induced by both UV and HPV
- No significant association between HPV and BCC
- Up to 90% of cutaneous SCCs in OTRs contain HPV DNA
  - Compared with 11–32% in normal skin

The Oncogenic Role of HPV in OTRs

• β-PV E6 protein
  – Inhibits p53 phosphorylation
  – Blocks the transactivation of p53 target genes (i.e., MDM2, p21 and pro-apoptotic genes)
  – Targets the pro-apoptotic protein Bak
  – Favors accumulation of UV damaged cells
    • Delays DNA repair (via abrogation of ATR activity)
    • Impairs the telomere/telomerase system

HPV Vaccination for OTRs

• Preclinical data shows that HPV immunization works
  – In immunosuppressed subjects
  – And in the presence of an established infection

• Evidence exists of cross-neutralization in response to vaccination
  – Neutralizing antibodies form against additional HPV subtypes

HPV vaccination for prevention of skin cancer. Vinzón SE, Rösl F. *Hum Vaccin Immunother.* 2015
HPV Vaccination for OTRs

- Vaccine against cutaneous HPV can effectively prevent naturally and experimentally induced skin tumors
- Argument for vaccination against cutaneous HPVs in OTRs
- Fairly common practice among specialty MDs

Management of NMSC in OTRs

• The most important risk factor for the development of skin cancer is exposure to UV radiation
  – Extreme intermittent
  – Cumulative exposure

• Essential that OTRs be educated about UV avoidance and skin protection
Managing SCCs in Transplant Recipients

- **Metastatic SCC**
  - In transit Metastases

- **Recurrent SCC**
  - Poorly Differentiated
  - Perineural Invasion

- **Well Differentiated SCC in situ**

- **Actinic Damage**

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**Aggressiveness of SCC**

**Number of SCCs**

- AKs
- SCCs 1–4/yr
- SCCs 5–10/yr
- SCCs > 10/yr

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**Reduction or Discontinuation of Immunosuppression**

**Systemic Chemoprophylaxis**
- Acitretin, 5-FU, Nicotinamide

**Switch to mTOR Inhibitor**
- Topical Treatment of Fields of AKs
  - 5-FU, PDT, Diclofenac
  - Topical Retinoids
  - Imiquimod

**Treat Isolated AKs**
- Preventative Measures
  - Regular Skin Screenings
  - Strict Sun Protection

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*Mittal and Colegio*
Management of NMSC in OTRs

- Field cancerization refers to entire anatomic units with widespread epidermal dysplasia.
Management of NMSC in OTRs

- Field treatments
- Topical 5-FU
- Imiquimod
- Topical diclofenac
- Topical retinoids
- Photodynamic therapy (PDT)
Management of NMSC in OTRs
Management of NMSC in OTRs

• Individual invasive SCC
  – Surgery is mainstay of care
  – MMS (highest cure rate 98%)
  – Excision with POMA
  – Primary radiation therapy in inoperable settings
  – Adjuvant radiation therapy for perineural involvement or positive margins
Management of NMSC in OTRs

- Expert consensus guidelines on when to modify immunosuppression

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 NMSC per year or Development of high-risk SCC</td>
<td>Mild reduction of immunosuppression</td>
</tr>
<tr>
<td>≥ 25 NMSC per year or Tumors with a 3-yr mortality risk of 10%</td>
<td>Moderate reduction of immunosuppression</td>
</tr>
<tr>
<td>Life threatening tumor(s)</td>
<td>Severe reduction or withdrawal of immunosuppression</td>
</tr>
</tbody>
</table>

Management of NMSC in OTRs

- Many synchronous, invasive SCCs and BCCs
Management of NMSC in OTRs

• Multidisciplinary combination strategies
  – Surgical management of invasive tumors
  – Field treatments
  – Modification of immunosuppression
  – Chemoprophylaxis
    • Oral retinoids (target hyperproliferative keratinocytes)
    • Nicotinamide (enhances DNA repair post-UV damage)
    • Capecitabine (oral prodrug of 5-FU)

A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention
Chemoprophylaxis - Nicotinamide

- Nicotinamide replenishes cellular ATP levels in keratinocytes after UV exposure
- Energy-replenishing effect is key mechanism by which nicotinamide enhances DNA repair

Nicotinamide prevents ultraviolet radiation-induced cellular energy loss. Park J. *Photochem Photobiol* 2010
Management of NMSC in OTRs

• The role of sentinel lymph node biopsy (SLNB)
  – May be indicated in patients with a BWH T2b or AJCC T2 lesions >2cm
  – Patients with positive SLNB are eligible for adjuvant therapy trials
Management of NMSC in OTRs

• Radiologic evaluation of high-risk SCC
  – It is suggested that patients with high-risk tumors get imaging
  – Studies have shown that imaging in this cohort results in change in management plan for 1/3
  – One study associated such imaging driven management changes with 50% reduction in disease-related morbidity

The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. Ruiz ES, Karia PS, Morgan FC, Schmults CD. *J Am Acad Dermatol*, 2017
Management of NMSC in OTRs

- Metastatic SCC – in transit, local and distant
Management of NMSC in OTRs

• Systemic chemotherapy is indicated but specific algorithms do not exist
• Cisplatin+/- 5-FU shown efficacy
• Cetuximab is often used
• In one study, after 2 months of treatment, ORR was 47%
  – 80% for cetuximab with RT
  – 37.5% for cetuximab with carboplatin
  – 33% for cetuximab monotherapy

Management of NMSC in OTRs

• Immune checkpoint inhibitors have produced tumor regressions in multiple cancer types
• However, these therapies are largely untested in patients treated with long-term immunosuppressive medications
• Unclear if augmented adaptive immunity will induce graft rejection

Antagonists of PD-1 and PD-L1 in cancer treatment. Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, Topalian SL. *Semin Oncol* 2015
Management of NMSC in OTRs

• Higher PD-L1 expression observed in high risk cutaneous SCC

• Several recent case reports of dramatic responses in patients with advanced/metastatic SCCs treated with the PD-1 inhibitors
  – 1 patient with ongoing CR for >16 months
  – Subject was immunocompetent

Management of NMSCs in OTRs

• PD-1 antibody was administered to an OTR with metastatic cutaneous SCC
• The patient had a robust antitumor response
• Along with allograft rejection

Tumor regression and allograft rejection after administration of anti-PD-1
Management of NMSC in OTRs

• The PD-1 pathway may be critical in maintaining partial tolerance, preventing T cell–mediated rejection

• Renal OTRs reportedly tolerate CTLA-4 inhibitors without allograft rejection
  – In melanoma, as discussed earlier
  – Also 1 report of a treated patient with graft rejection

• This may suggest that the CTLA-4 pathway plays a lesser role than the PD-1 pathway in transplant tolerance

Management of NMSC in OTRs

- Requires multidisciplinary approach
- Surgical - Mohs, ENT, Plastics
- Medical – Transplant, Medical Oncology, Dermatology and Pathology
- Radiation Oncology
Thank you.