Malignancy and Solid Organ Transplant

By Patrick Klem
Posttransplant Malignancy: Sources of Information

• Posttransplant cancer rates can vary greatly
• Large registries (IPITTR, ANZDATA, OPTN/UNOS, EDTA-ERA)
  – Common limitations: voluntary participation, subset of entire population, some tumor types excluded (NMSC), short follow-up periods/only 1st-cancer cases
• Single-center or clinical trials
  – Generally retrospective (underestimate true frequency)
  – Single cases can greatly ↑ rates for rare tumors
  – Insufficient #s to detect differences in incidence/mortality
  – Generally short follow-up
• Estimate cancer risk vs general population (SEER)

IPITTR=Israel Penn International Transplant Tumour Registry; ANZDATA=Australia and New Zealand Data Registry; OPTN/UNOS=Organ Procurement and Transplantation Network/United Network for Organ Sharing; EDTA-ERA=European Dialysis & Transplantation Association—European Renal Association; ; NMSC=non-melanoma skin cancers; SIR=standardized incidence ratio

Gutierrez-Dalmau A, Campistol JM. Drugs. 2007;67:1167-98
Skin and Lip Cancers: Characteristics

- Skin cancer is by far the most common posttransplant malignancy, particularly nonmelanoma skin cancer (BCC and SCC)
- Exposed areas most commonly affected
  - Head and neck and arms
- More common in lightly complected individuals
- BCC : SCC ratio is reversed in the transplant population
  - General population (5:1); Transplant recipients (1:1.9)
- Risk of lip cancer is ↑ in transplant recipients

BCC=basal cell skin cancer; SCC=squamous cell skin cancer

Cancer Risk In Kidney Transplant Recipients: ANZDATA Registry

Clinical Behavior of Skin Cancers

• Skin cancers tend to behave more aggressively in transplant recipients than the general population
  – 5% of transplant recipients with skin cancers die from the skin cancer (vs 1-2% in the general population)

• Incidence of multiple skin cancers is high (44%)
  – Subset of patients appear to have a widespread cutaneous abnormality with areas of unstable epithelium that gives rise to locally recurrent tumors
  – Some patients may develop dozens of skin cancers

Skin and Lip Cancers: Prevention and Therapy

Prevention
- Regular follow-up with an experienced dermatologist
- Skin care education
- Conversion to sirolimus in patients with multiple skin cancers
- Immunosuppression reduction when feasible

Treatment
- Topical imiquimod or 5-FU can be effective treatment for basal cell cancers
- Immunosuppression reduction
- Topical or systemic retinoids (use limited due to toxicity)
- Conversion to sirolimus
## Relative Risk of Overall and Selected Posttransplant Malignancies

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Observed cases</th>
<th>Expected cases</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>778</td>
<td>313.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Lip</td>
<td>54</td>
<td>1.7</td>
<td>31.3</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>125</td>
<td>14.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>71</td>
<td>9.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Vulva</td>
<td>3</td>
<td>0.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Thyroid</td>
<td>23</td>
<td>4.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>13</td>
<td>3.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Lung</td>
<td>108</td>
<td>51.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>20</td>
<td>10.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Colorectal</td>
<td>51</td>
<td>37.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Breast</td>
<td>52</td>
<td>39.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Prostate</td>
<td>37</td>
<td>40.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Canadian Organ Replacement Registry (recipients of a kidney transplant between 1981-1998)  


### Increased Cancer Rates

Table 1. Cancer risk after renal transplantation in Australia and the United States

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Cumulative Incidence (/100,000) Australia</th>
<th>Cumulative Incidence (/100,000) United States</th>
<th>SIR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>213</td>
<td>140</td>
<td>21.30</td>
</tr>
<tr>
<td>Kidney/ureter</td>
<td>139</td>
<td>1010</td>
<td>10.39</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>189</td>
<td>80</td>
<td>7.40</td>
</tr>
<tr>
<td>Bladder</td>
<td>90</td>
<td>126</td>
<td>5.03</td>
</tr>
<tr>
<td>Esophagus</td>
<td>40</td>
<td>70</td>
<td>4.00</td>
</tr>
<tr>
<td>Cervix</td>
<td>35</td>
<td>180</td>
<td>3.85</td>
</tr>
<tr>
<td>Liver</td>
<td>20</td>
<td>220</td>
<td>2.99</td>
</tr>
<tr>
<td>Melanoma</td>
<td>129</td>
<td>320</td>
<td>2.14</td>
</tr>
<tr>
<td>Lung/bronchus/trachea</td>
<td>85</td>
<td>690</td>
<td>1.89</td>
</tr>
<tr>
<td>Colorectal</td>
<td>169</td>
<td>510</td>
<td>2.51</td>
</tr>
<tr>
<td>Breast</td>
<td>100</td>
<td>1050</td>
<td>0.98 (female)</td>
</tr>
<tr>
<td>Prostate</td>
<td>40</td>
<td>1740</td>
<td>0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Australia Male</th>
<th>United States Male</th>
<th>SIR&lt;sup&gt;b&lt;/sup&gt; United States Male</th>
<th>Australia Female</th>
<th>United States Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi sarcoma</td>
<td>17.4</td>
<td>62.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney/ureter</td>
<td>14.1</td>
<td>14.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6.9</td>
<td>29.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>1.6</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
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<td>2.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>4.2</td>
<td>4.5</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>1.6</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is PTLD?

• An **EBV-related disease** - B cell proliferation induced by EBV infection
  – EBV naïve patient receiving EBV + organ has a 25-50x increase risk of developing PTLD
  – Most common cause of cancer related death

**Reactive Hyperplasia**
  – Post-transplant infectious mononucleosis
  – Plasma cell hyperplasia

**Neoplasia**
  – Polymorphic B cell hyperplasia
  – Polymorphic lymphoma
## PTLD: Therapeutic Approaches

<table>
<thead>
<tr>
<th></th>
<th>Primary EBV Infection</th>
<th>Benign PTLD</th>
<th>Malignant PTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Mononucleosis-like syndrome</td>
<td>Solid tumors</td>
<td>Solid Tumors</td>
</tr>
<tr>
<td>Histology</td>
<td>Polymorphic</td>
<td>Polymorphic</td>
<td>Monomorphmic</td>
</tr>
<tr>
<td>Clonality Studies</td>
<td>Polyclonal</td>
<td>Polyclonal</td>
<td>Monoclonal</td>
</tr>
<tr>
<td>Therapy</td>
<td>ISR Acyclovir</td>
<td>ISR +/- Rituximab</td>
<td>ISR/ISD Surgery/XRT Chemotherapy Rituximab</td>
</tr>
</tbody>
</table>

ISR=immunosuppression reduction; ISD=immunosuppression discontinuation; XRT=radiotherapy
**EBV and PTLD**

- 95% of population is EBV IgG+
- ~5% of KTx recipients are EBV- recipients of EBV+ kidneys
- PTLD occurs in ~1% overall
- 80% of PTLD occurs in EBV- recipients
- Incidence of PTLD in EBV- recipients is as high as 20%!

1000 recipients:

- 50 EBV+-/-
- 950 EBV++/+  

10 cases PTLD:

- 8 PTLD EBV+-/-
- 2 PTLD EBV++/+
Risk for PTLD/Lymphoma is increased with ATG (Thymoglobulin) and OKT3.
Treatment of PTLD: Immunosuppression reduction

- Limited Disease:
  - 25% reduction
  - if triple therapy, may D/C antiproliferative (i.e. mycophenolate) medication

- Extensive Disease:
  - Critically ill:
    - Stop all immunosuppression
    - Prednisone at 7.5-10 mg/d
    - Frequent biopsies, avoid rejection
    - Bolus with steroids prn rejection

  - Not critically ill:
    - D/C antiproliferative agent,
    - decrease calcineurin inhibitor by 50%,
    - maintain prednisone at 7.5-10 mg/d
PTLD: Rituximab or Chemotherapy?

- Of 117 patients treated for PTLD from 1996-2005 at a single center, 35 failed immunosuppression dose reduction and survived to receive rituximab, chemotherapy, or both:

- 22 received rituximab:
  - 13 had complete response (59%), those without response received chemotherapy
  - Median survival 31 months

- 23 received chemotherapy:
  - 13 had complete response (57%)
  - Median survival 42 months
  - 26% died due to toxicities of therapy

Elstrom R et al, Am J Transplantation 2006; 6: 569
PTLD: Take-home points

- EBV related lymphoma

- Anti-Thymocyte Globulin (ATG) and OTK3 use increase risk

- Know your patient’s EBV serostatus, consider more rapid IS taper in EBV+-/- recipients

- If PTLD develops:
  - Reduction in immunosuppression is 1st line
  - Rituximab +/- chemotherapy next step
Pro- and Anti-Oncogenic Effects of Immunosuppressive Drugs
Proposed Risk Factors for Posttransplant Malignancy

- Immunosuppression
  - duration
  - intensity
  - type

- Exposure to UV light*
  - total sun burden
  - geographical region

- Increasing recipient age

- Genetic predisposition

- History of malignancy

- Previous exposure to carcinogens

- Chronic viral infection†

*RMSC; †predominantly PTLD and Kaposi’s sarcoma

Adapted from Valantine H. J Heart Lung Transplant. 2007;26:557-64.
mTOR Inhibitors—Immunosuppressive Drugs with Anti-Oncogenic Properties

- Sirolimus (Rapamune)
  - only mTOR inhibitor currently approved in the US for use in transplant recipients
  - also known as rapamycin

- Everolimus (Certican)
  - approved in Europe for use in transplant recipients
  - also known as RAD

- Temsirolimus (Torisel)
  - IV formulation, FDA approved for stage IV RCC

mTOR=mammalian target of rapamycin
Mechanism of Action of mTOR Inhibitors

- Sirolimus (and other mTOR inhibitors) inhibit mTOR, a downstream effector important in signaling pathways for cell growth and proliferation.

- Other growth factors use these same pathways to stimulate proliferation of various cells.
  - The anti-oncogenic effects of sirolimus are thought to relate (in part) to disruption of these pathways via mTOR inhibition.

- Sirolimus also inhibits VEGF production and angiogenesis, a critical process in tumor development or progression.
## Sirolimus Registration Trials

<table>
<thead>
<tr>
<th>Study*</th>
<th>Year</th>
<th>F/U (mo)</th>
<th>IS</th>
<th>Limbs</th>
<th>#Pt</th>
<th>PTLD (%)</th>
<th>Skin CA</th>
<th>Total CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>US De Novo Phase III</td>
<td>Kahan</td>
<td>2000</td>
<td>12</td>
<td>Cy Pred</td>
<td>Aza Cy Sir 2 mg Sir 5 mg</td>
<td>159 281 269</td>
<td>0.6 0.4 0.7</td>
<td>3.1 0.8 3.6</td>
</tr>
<tr>
<td>European De Novo Phase II</td>
<td>Groth</td>
<td>1999</td>
<td>12</td>
<td>Aza Pred</td>
<td>Cy Sir</td>
<td>41 42</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>European De Novo Phase II</td>
<td>Kreis</td>
<td>2000</td>
<td>12</td>
<td>MMF Pred</td>
<td>Cy Sir</td>
<td>38 40</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>European Convert Phase III</td>
<td>Kreis</td>
<td>2004</td>
<td>36</td>
<td>MMF Pred</td>
<td>Cy Sir</td>
<td>215 215</td>
<td>1.4 0.5</td>
<td>6.5 3.7</td>
</tr>
</tbody>
</table>

* Induction therapy was not used in any trial  
IS=Immunosuppression; CA=cancer

# mTOR Inhibition: Prevention of Posttransplant Malignancies

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr</th>
<th>Data Source</th>
<th>#Pts Analyzed</th>
<th>FU (mo)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walter Reed¹</td>
<td>2005</td>
<td>USRDS</td>
<td>25,127</td>
<td></td>
<td>MVA: MMF reduced PTLD risk Sirolimus no effect</td>
</tr>
<tr>
<td>SRTR²</td>
<td>2005</td>
<td>SRTR</td>
<td>33,249</td>
<td>32</td>
<td>MVA: Sirolimus* reduced risk of nonskin de novo (RR 0.45) or any de novo Ca (RR 0.40)</td>
</tr>
<tr>
<td>UT Houston³</td>
<td>2005</td>
<td>Single Center</td>
<td>1,008</td>
<td>62</td>
<td>3.6% Ca incidence 0.4% PTLD, 2.4% skin</td>
</tr>
<tr>
<td>Mathew⁴</td>
<td>2004</td>
<td>5 Sirolimus Trials</td>
<td>1,671</td>
<td>24</td>
<td>Skin Ca incidence: Sirolimus 0%, CNI 5%</td>
</tr>
<tr>
<td>Campistol⁵</td>
<td>2006</td>
<td>Randomized open-label</td>
<td>430</td>
<td>60</td>
<td>Reduced risk of SCC, BCC, any skin Ca w/ early conversion from CyA- to SRL-based therapy</td>
</tr>
</tbody>
</table>

*Included pts treated with either sirolimus or everolimus. All studies were of kidney transplant recipients only. FU=follow-up; MVA=multivariate analysis; Ca=cancer; CyA=cyclosporine; SRL=sirolimus.

Kaposi’s Sarcoma

- Risk in transplant recipients is markedly increased over general population (84- to 500-fold)\(^1\)
- Uncommon in children\(^2\)
- Observed mainly in kidney transplant recipients\(^2\)
- Ethnic predisposition\(^2\)
  - Most patients are Arabic, African, Italian, Jewish, Greek, or Turkish
- Mean age at diagnosis 43 years (range 4.5–67)\(^2\)
- Most patients HIV negative\(^2\)

#mTOR Inhibition: Treatment of Posttransplant Kaposi’s Sarcoma#

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>#Pts</th>
<th>Tumor ↓ (% pts)</th>
<th>FU (mos)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stallone</td>
<td>2005</td>
<td>Italy</td>
<td>15</td>
<td>100*</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Gutierrez-Dalmau</td>
<td>2005</td>
<td>Spain</td>
<td>7</td>
<td>100†</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Boratynska</td>
<td>2007</td>
<td>Poland</td>
<td>4</td>
<td>100‡</td>
<td>7-48</td>
<td>100</td>
</tr>
<tr>
<td>Zmonarski</td>
<td>2005</td>
<td>Poland</td>
<td>2</td>
<td>100§</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>Campistol</td>
<td>2004</td>
<td>Spain</td>
<td>2</td>
<td>100*</td>
<td>&gt;3–18</td>
<td>100</td>
</tr>
<tr>
<td>Mohsin</td>
<td>2005</td>
<td>Oman</td>
<td>1</td>
<td>100*</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Gheith</td>
<td>2007</td>
<td>Egypt</td>
<td>1</td>
<td>100*</td>
<td>NR</td>
<td>100</td>
</tr>
<tr>
<td>Volkow</td>
<td>2007</td>
<td>Mexico</td>
<td>1</td>
<td>100</td>
<td>4+</td>
<td>100</td>
</tr>
</tbody>
</table>

*All lesions in all patients showed complete regression.
†Most lesions showed complete regression; partial ↓ hyperpigmented atrophic (HA) skin lesions.
‡Complete regression most skin and all lung lesions; partial ↓ HA skin lesions.
§Smaller skin lesions disappeared; lung & the biggest skin lesions partial ↓.

Posttransplant Cancer Screening

- **Breast**
  - Women >50 yrs: mammogram every 1–2 yrs
  - Women <50 yrs at high risk (family history or prior cancer): mammogram every 1–2 yrs

- **Cervical**
  - Women >18 yrs: Pap smear every year

- **Prostate**
  - Men >40 yrs: Rectal exam and PSA every year

- **Colorectal**
  - Recipients >50 yrs: fecal blood test yearly, flexible sigmoidoscopy every 5 yrs, or colonoscopy every 10 yrs

- **Skin**
  - Annual self exam and physician exam and biopsy of all suspicious lesions
Cancer after transplant

• Skin/lip most common – 40-50% of all malignancies
  – More squamous cell (as much as 250x higher vs general pop) vs. basal cell (10x higher vs. general pop)
• Anogenital- 2-3% of all malignancies
• Renal carcinomas- 0.5 -3.9% of malignancies
• PTLD- 1 -5% of malignancies
  – EBV with causative role