WHY CARDIOLOGISTS MUST CARE ABOUT CANCER IMMUNOTHERAPY

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Immune-Checkpoint Inhibitor (ICI) Associated Myocarditis: Defining a New Clinical Syndrome

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Disclosures

• Consultation (Paid)
  – Novartis, Pfizer, Bristol-Myers Squibb, Takeda/Millennium, Ariad, Acceleron, Vertex, Incyte, Rgenix, Verastem, Pharmacyclics, StemCentRx, Heat Biologics, Daiichi Sankyo, Regeneron, Myokardia

• Consultation (Not Paid)
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  – U.S. Federal and Drug Administration (FDA)

• Research Grants:
  – Pfizer, Bristol-Myers Squibb
Anthracyclines
Radiation
Heart Failure
CAD

Anti-metabolites (5FU)
Ischemia
Vasospasm

Anthracyclines
Radiation
Heart Failure
CAD
Her2 Targeted Therapies
Cardiomyopathy
MEK/RAF TKI
Cardiomyopathy
Drugs Affecting UPS
Immunomodulators (IMiDs): thrombosis
Proteasome inhibitors (e.g. bortezomib, carfilzomib): vascular

Cancer Immunotherapies (Chekpoint Inhibitors) ????
Cancer Survivorship

Antimetabolites (5FU)
Ischemia
Vasospasm

PI3K Inhibitors
Hyperglycemia
Metabolic
?Myocardial/Arrhythmia

CML TKIs
Imatinib: protective
Dasatinib/Nilotinib/
Bosutinib/Ponatinib:
PAH/Vascular/Atherosclerosis

CDK4/6 inhibitors
?Arrhythmia

BTK Inhibitors
Ibrututinib:
Arrhythmia/Atrial Fibrillation

Immune Checkpoint Inhibitors (ICI)
Targeting Immune Checkpoints for Cancer Treatment

- **CTLA-4 Inhibitors**
  - Ipilimumab (Yervoy)

- **PD-1 Inhibitors**
  - Nivolumab (Opdivo)
  - Pembrolizumab (Keytruda)

- **PDL-1 Inhibitors**
  - Atezolizumab (Tecentriq)
  - Durvalumab (FDA breakthrough designation)

- **Combination Therapy**

Cancer immunotherapy-based combination studies underway in 2016

Slide Courtesy of Dr. Jeff Sosman, Northwestern
Immune Checkpoint-Inhibitor (ICI) Associated Myocarditis

• 65 yo F metastatic melanoma (lung, liver, brain, adrenal) presents with chest pain and SOB x 3 days – 12 days after Ipilimumab 3 mg/kg and Nivolumab 1 mg/kg

• Labs Troponin I: 4.72, 9.6, 17, 24.72 – CK: 8178, 16903 – arrhythmias, death

the link between
CANCER
and
CARDIOVASCULAR DISEASE
**Step 1- Initial Information (contact form)**

Please complete the survey below.

Thank you!

---

**Requesting Physician Information**

1) **First Name:**

2) **Last Name:**

3) **Email Address:**

4) **Phone Number:**
   * must provide value

---

**Requested time for call-back (please offer 5, 30-minute time periods.)**

5) **Time 1:**

6) **Time 2:**
Rapid Increase in Reporting of Fatal ICI-Associated Myocarditis

- Fatality rates:
  - Anti-PD-1/PD-L1 plus anti-CTLA-4: 78%
  - Anti-PD-1/PD-L1 monotherapy: 42% – p=0.004

### Table: Characteristics of patients with immune checkpoint inhibitor associated myocarditis (n=101)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>66</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>40</td>
</tr>
<tr>
<td>NSCLC</td>
<td>30</td>
</tr>
<tr>
<td>Renal</td>
<td>7</td>
</tr>
<tr>
<td>Other*</td>
<td>23</td>
</tr>
</tbody>
</table>

- **Concomitant medications**
  - Aspirin: 11%
  - Statin: 11%
  - Beta blocker: 7%
  - ACE/ARB: 12%
  - Diabetes medication: 6%

- **Regimen**
  - Anti-PD-1 monotherapy: 43%
    - Nivolumab: 43%
    - Pembrolizumab: 15%
  - Anti-PD-L1 monotherapy: 3%
  - Anti-CTLA-4 (Ipilimumab) monotherapy: 5%
  - Combination anti-PD-1/PD-L1 + anti-CTLA-4: 27%
  - Combination anti-PD-1/PD-L1 + other agents: 0%

- **Timing (median, range)**: 25 days (5-120)

- **Concurrent AEs**
  - Myositis/rhabdomyolysis: 25
  - Myasthenia gravis: 10
  - Colitis: 4
  - Severe cutaneous events: 4
  - Other: 5

- **Fatal outcome**: 52

- **Reporting outcome**
  - 2010 – 2014: 3
  - 2015: 6
  - 2016: 45
  - 2017 (through Dec. 6): 76

Cardiovascular Complications of Immune Checkpoint Inhibitors (ICI)

• Myocarditis
• Arrhythmias
  – supraventricular tachycardia
  – atrial fibrillation
• Pericardial disease
  – including pericarditis
• Vasculitis

Salem, Manouchehri, Moey...Johnson, Moslehi. Unpublished.
Fatal Vasculitis in Lung Cancer Patient Treated with anti-PD1 Therapy

perivascular lymphocytic infiltrates

necrotizing vasculitis

Slides courtesy of Dr. Robert Padera, Harvard Medical School.
Immune-Checkpoint Inhibitor (ICI) Myocarditis: Defining a New Syndrome

Clinical Questions
Incidence?
Clinical presentation?
Treatment?

Immune Checkpoint Inhibitor-Associated Myocarditis

Who is at risk?
Precision or Personalized Medicine
- CV risk factors
- Autoimmune risk factors
- Tumor risk factors
- ?Genetic risk factors
T Cell Infiltrates in the Heart

CD3

CD4

CD8

CD20

CD68

CD138

Johnson…Sosman, Moslehi NEJM. 2016.
T Cell Infiltrates in the Skeletal Muscle

Insights into Mechanisms of Toxicity
Insights into Mechanisms of Toxicity

A. Patient 1

Pretreatment Tumor

No. of T-Cell Clones in Tumor

Post-treatment Tumor

No. of T-Cell Clones in Cardiac Muscle

Skeletal Muscle

No. of T-Cell Clones in Cardiac Muscle

A. Inflammatory gene transcripts

B. Muscle-specific gene transcripts

FPKM transcript counts

pre-tx tumor  skeletal diseased  esophagus normal
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Immune Checkpoint Inhibitor-Associated Myocarditis

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  - CV risk factors
  - Autoimmune risk factors
  - Tumor risk factors
  - Genetic risk factors

Basic biology of PD-1/PD-L1 in the heart
How does the heart interact with the immune system??
Generation of Mouse Models for ICI-Associated Myocarditis and Vasculitis

Vanderbilt Cardio-Oncology Program
Moslehi Laboratory
Immune-Checkpoint Inhibitor (ICI) Myocarditis: Defining a New Syndrome

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- Incidence?
- Clinical presentation?
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Immune Checkpoint Inhibitor-Associated Myocarditis

Who is at risk?
- Precision or Personalized Medicine
  - CV risk factors
  - Autoimmune risk factors
  - Tumor risk factors
  - Genetic risk factors

Partnership with...
- Other academic centers
- FDA
- Pharma

Basic biology of PD-1/PD-L1 in the heart
How does the heart interact with the immune system??
?Implications for other forms of myocarditis, cardiac transplant

Moslehi et al, Unpublished.
Conclusions

• Myocarditis is a new clinical phenomenon that is a rare (but clinically significant) complication of cancer immunotherapy
  – Variable presentation
    • myositis with rhabdomyolysis
  – Early progressive and refractory cardiac electrical instability

• Other cardiovascular sequelae (arrhythmia, vasculitis)

• Need for multi-institutional efforts to understand the pathophysiology of myocarditis and multi-pronged (basic, translational, clinical) research approach to understand who is at risk of developing myocarditis and how to diagnose and treat
  – Example of cardioonc.org website
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Vanderbilt Cardio-Oncology Program

Clinical Program
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Dan Roden
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Translational Core Lab
Yan-Ru Su

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Education
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Vanderbilt Cardio-Oncology Program

**Clinical Program**

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Dan Roden

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Ash Shah

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