Immunotherapy Associated with Cardiotoxicity

Global Cardio-Oncology Summit 2018, Tampa

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Disclosures

• Takeda Inc – Consulting
  – Unrelated to current presentation
Lecture Structure

• A brief case

• What we think we know:
  – Incidence
  – Presentation
  – Outcomes
  – Pathology
  – Possible mechanisms
  – Potential diagnostic and treatment approaches

• Some of the many remaining questions

• Partnerships/thinking ahead
Immune Therapies for Cancer: A Paradigm Shift

Cancer's Newest Miracle Cure

Alice Park
Aug 10, 2017

For more, visit TIME Health.

New immunotherapy drug behind Jimmy Carter's cancer cure

Former president given pembrolizumab, one of the most promising new drugs in the treatment of cancer.
ICI Clinical Usage – MGH

Doses of ICI’s given at MGH
Immune Checkpoint Inhibitors: Adverse Events

- Encephalitis, aseptic meningitis
- Hypophysitis
- Thyroiditis, hypothyroidism, hyperthyroidism
- Pneumonitis
- Thrombocytopenia, anemia
- Hepatitis
- Adrenal insufficiency
- Nephritis
- Vasculitis
- Arthralgia
- Neuropathy
- Uveitis
- Dry mouth, mucositis
- Rash, vitiligo
- Myocarditis
- Pancreatitis, autoimmune diabetes
- Colitis
- Enteritis

Postow, NEJM, 2018
Why is it relevant to us?
Consult

FF: 49 year old male with metastatic renal cell
- Past Medical History: Hyperlipidemia, mild CKD
- Diagnosed 2015; Nivolumab late in March 2018
- On 4/28/18 (Saturday night) he consumed “a lot of booze” “I have cancer”
- On 4/29 (Sunday) he was at lunch and had diaphoresis, nausea, and fatigue
- This is how he feels when he drinks heavily
- He was brought to the ED against his will by his significant other
- No chest pain and SOB

- Cardiac set 1 TnT-hs 5th gen 15.
- Cardiac set 2 TnT-hs 5th gen 14.
- Cardiac set 3 TnT-hs 5th gen 18.
- NTproBNP was 29
Case Presentation: Testing

- He underwent stress test on 4/30/18 (Monday).
- This found that he had excellent exercise capacity (10 METS).
- ECG was negative for ischemia.
- Myocardial images were normal without evidence of ischemia or infarction and normal LV contractile function (LVEF 72%).
- He was discharged
Case Presentation: Clinical course

- On Tuesday, 4/31/18 attends his regular Oncology appointment.
- He tells his story and they repeat the EKG.
Case Presentation: Clinical course

- An echocardiogram is suggested despite the normal LV size, EF and no wall motion on the nuclear.

Left ventricular cavity size is normal.
Left ventricular systolic function is normal.
The estimated ejection fraction is 58%
Case Presentation: Next Steps?

1. Pretend you did not hear the page or see the email
2. Reassure and continue cancer treatment
3. Say you have not a clue and suggest another test
Case Presentation: Another Test

- Normal T2 imaging for myocardial edema
- Normal LGE images for Fibrosis

- Resting systolic LV function is borderline (LVEF = 55%)
- There is mild hypokinesia without regional variations
- No Edema or Fibrosis, no evidence of myocarditis.
Case Presentation: Next Steps?

1. Reassure and continue cancer treatment
   • Patient feels fine, no HF or arrhythmias
   • Troponin relatively unremarkable
   • No MRI features of myocarditis
   • Occasional significant alcohol intake
   • No prior EKG or cardiac studies
2. Biopsy
Case Presentation: Biopsy Result

Lymphocytic myocarditis
Similar to grade 3B transplant rejection
Case Presentation: Outcome

- Methylprednisone 1000 mg per day
- After 3 days transitioned to prednisone 60 mg with an outpatient taper
Incidence – a random week

Thanks.

Two in one week - saw in follow up too. Other than AF, the most common CUA consult diagnosis....

Sent from my iPhone
ICI Myocarditis:
What we think we know
## Incidence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumab (N=17,620)</th>
<th>Nivolumab plus Ipilimumab (N=2974)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any*</td>
<td>10 (0.06)</td>
<td>8 (0.27)</td>
</tr>
<tr>
<td>Fatal events</td>
<td>1 (&lt;0.01)</td>
<td>5 (0.17)</td>
</tr>
<tr>
<td><strong>Myositis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>27 (0.15)</td>
<td>7 (0.24)</td>
</tr>
<tr>
<td>Fatal events</td>
<td>2 (0.01)</td>
<td>1 (0.03)</td>
</tr>
</tbody>
</table>

* The number of patients with myocarditis includes six patients with concurrent myocarditis and myositis.
Incidences – conflicting data

- Meta-analysis of 22 clinical trials of PD-1 and PD-L1 inhibitors for treatment of lung neoplasms with 4828 patients.
- All single agent, no combination studies.
- Occurrence rates:
  - 1.0% of cardiac arrest
  - 2.0% cardiac failure
  - 1.0% of myocardial infarction
  - 0.5% myocarditis
  - 0.7% tamponade
  - Cumulative rate of significant cardiac events: 5.2%
## Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>
CTC Cardiac Events: A Broad Menu

Which of these in the setting of a recent ICI start is not some manifestation of an “-itis”?

Myocarditis
- Heart failure
- Left ventricular systolic dysfunction
- Ventricular tachycardia
- Ventricular fibrillation
- Ventricular arrhythmia
- Conduction disorder

Pericarditis
- Pericardial tamponade
- Atrial fibrillation
- Atrioventricular block first degree
- Mobitz (type) II atrioventricular block
- Asystole
- Conduction disorder
Registry

Mahmood, JACC, 2017
Myocarditis Definition

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Diagnostic criteria for clinically suspected myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentations</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Acute chest pain, pericarditic, or pseudo-ischaemic &lt;br&gt;New-onset (days up to 3 months) or worsening of dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs &lt;br&gt;Subacute/chronic (&gt; 3 months) or worsening of: dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs &lt;br&gt;Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death &lt;br&gt;Unexplained cardiogenic shock</td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td>I. ECG/Holter/stress test features &lt;br&gt;Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td>II. Myocardiocytolysis markers &lt;br&gt;Elevated TnT/TnI</td>
</tr>
<tr>
<td></td>
<td>III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR) &lt;br&gt;New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi</td>
</tr>
<tr>
<td></td>
<td>IV. Tissue characterization by CMR &lt;br&gt;Oedema and/or LGE of classical myocarditic pattern (see text)</td>
</tr>
</tbody>
</table>

Clinically suspected myocarditis if ≥ 1 clinical presentation and ≥ 1 diagnostic criteria from different categories, in the absence of (1) angiographically detectable coronary artery disease (coronary stenosis ≥ 50%); (2) known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.) (see text). Suspicion is higher with higher number of fulfilled criteria.

<sup>a</sup>If the patient is asymptomatic ≥2 diagnostic criteria should be met.
## Single vs. Combined Therapy

<table>
<thead>
<tr>
<th></th>
<th>Myocarditis (n = 35)</th>
<th>Control (n = 105)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent vs. combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination (ever received)</td>
<td>12 (34.3)</td>
<td>10 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combination (current regiment)</td>
<td>12 (34.3)</td>
<td>2 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monotherapy (current regimen)</td>
<td>23 (65.7)</td>
<td>103 (96.0)</td>
<td></td>
</tr>
<tr>
<td>Combined ICI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab (anti-CTLA4) + nivolumab (anti-PD1)</td>
<td>9 (26.0)</td>
<td>9 (8.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ipilimumab (anti-CTLA4) + pembrolizumab (anti-PD1)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Tremelimumab (anti-CTLA4) + avelumab (anti-PDL1)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Tremelimumab (anti-CTLA4) + durvalumab (anti-PDL1)</td>
<td>1 (2.9)</td>
<td>1 (1.0)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Median time to onset of myocarditis from first ICI was early with 81% presenting within 3 months of starting therapy.
ICI’s and myocarditis: Presentation

Symptoms at Presentation

- Chest Pain
- SOB
- Palpitations
- Sudden Cardiac Death

* Could have more than 1
Testing at Presentation

- Nearly all myocarditis cases had a troponin elevation (94%).
- Most had a BNP or NT-proBNP elevation (66%).
- Abnormal EKG changes were noted in 83% of myocarditis cases.
- The LVEF was normal in 45% of cases and abnormal in 55%.
ICI Myocarditis: Outcomes

• 46% of myocarditis cases experienced a MACE (16/35):
  • cardiovascular death (n=6)
  • cardiogenic shock (n=3)
  • cardiac arrest (4)
  • complete heart block requiring pacing (n=3)

• Of the 16 MACE, 6 (38%) occurred in patients with a normal LVEF.
MACE vs. no MACE: Treatment

Steroids were the initial treatment of myocarditis in 31 (89%) cases.

Other immunosuppression therapies were also administered:

- Intravenous immunoglobulin (n=2)
- Mycophenolate (n=2)
- Anti-thymocyte globulin (n=1)
- Infliximab (n=3)
Summary of Findings

- Clinical myocarditis with ICI therapies has a high rate of major adverse cardiac events.
- LVEF is not a good predictor of outcomes among patients with ICI myocarditis.
- High dose steroids reduce the rate of major adverse events in ICI myocarditis.
- Earlier treatment may reduce the rate of major adverse events in ICI myocarditis.
ICI Myocarditis: Pathology
Biopsy/Pathology

Cases

Pathologically Similar to Transplant Rejection with a CD4+ and CD8+ T cell infiltrate

Normal Cardiac Biopsy

Not Normal Cardiac Biopsies

Norwood, JITC, 2017; Ganatra/Neilan, The Oncologist, In Press
ICI Myocarditis: Potential Mechanisms
In models of T-cell-mediated myocarditis, PD-L1 up-regulation in cardiac myocytes appears to be a cytokine-induced cardio-protective mechanism.

Grabie, Circulation, 2007
Animal Models – PD-L1 in Mouse Models of Myocarditis

Up-regulation of PD-L1 regulates PMN infiltration and prevents lethal cardiac injury.

Grabie, Circulation, 2007
Animal Models – PD-L1 in Mouse Models of Myocarditis

Blocking PD-L1 with a monoclonal antibody increased cardiac injury.

Grabie, Circulation, 2007
Preliminary Suggestions for an Approach
Checkpoint Inhibitor-induced Myocarditis: Surveillance

Check a troponin/EKG at baseline and with each cycle.
Prospective Biomarker Screening Studies

- Serial Study of 59 NSCLC Patients on single agent Nivolumab
- 4\textsuperscript{th} Generation Troponin I assay
- Troponin became detectable in 6 patients (10%).
- Troponin elevation in 5 occurred among those with cardiovascular disease
- Troponin elevation in 1 occurred in a patient without cardiovascular disease
- Range of incidence of 1.7\% to 12\%
Prospective Biomarker Study: MSKCC

<table>
<thead>
<tr>
<th>Combination</th>
<th>Number of Patients</th>
<th>Troponin Checked</th>
<th>Troponin Newly Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab/Tremelimumab</td>
<td>108</td>
<td>46</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Ipi/Nivo</td>
<td>883</td>
<td>343</td>
<td>18 (5.2%)</td>
</tr>
</tbody>
</table>

Preliminary Data: Courtesy Dr. Richard Steingart, MSKCC
Myocarditis – Assessment of Potential Cases

- EKG
- Serum Biomarkers
- Symptoms
- Pathology
- LVEF/GLS
- Cardiac MRI
Checkpoint Inhibitor-induced Myocarditis: Suggested Management

- **Myocarditis**

  - **LVEF normal/no malignant rhythm**
    - 1 gram Solumedrol 3-5 days
    - Myocarditis persists
    - Infliximab (5 mg/kg) vs. Mycophenolate
    - Myocarditis persists
    - Repeat Infliximab (5 mg/kg) vs. Biopsy

  - **LVEF reduced/Patient unstable**
    - Recommend Cardiac Biopsy/HF consult
    - Biopsy positive
    - High Dose Steroids, or anti-thymocyte globulin
Some of the Additional Questions
GLS in patients with ICI-Myocarditis - anecdote

Normal Patient

One of my ICI Myocarditis Patient with a Normal LVEF and Sudden Death

GLS: - 24

GLS: - 11
GLS in patients with ICI-Myocarditis – some early data

All patients

Preserved LVEF

Number at risk
GLS ≥ 10.5  37  31  24  22  19  17  17
GLS < 10    36  20  7   6   5   5   5

Number at risk
GLS ≥ 10.5  10  10  8   22  6   5   5
GLS < 10    20  11  5   4   3   3   3

p value < 0.001
p value = 0.0046 log-rank test
Table 1: Description of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Flu Vaccine</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of influenza vaccination</td>
<td>28 (31)</td>
<td>75 (39)</td>
<td>0.23</td>
</tr>
<tr>
<td>Time of vaccination prior to ICI, days [IQR]</td>
<td>88 [47, 126]</td>
<td>58 [25, 91]</td>
<td>0.22</td>
</tr>
</tbody>
</table>
# Myocarditis ICI’s – Need for a Definition

<table>
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<tr>
<th>Definitive Myocarditis</th>
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<tbody>
<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Syndrome + abnormal troponin + diagnostic cardiac MRI findings</td>
</tr>
<tr>
<td>Abnormal troponin + ventricular arrhythmias/high grade conduction system disease + diagnostic cardiac MRI findings</td>
</tr>
<tr>
<td>Abnormal troponin + diagnostic cardiac MRI findings</td>
</tr>
<tr>
<td>Ventricular arrhythmias/high grade conduction system disease + diagnostic cardiac MRI findings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probable Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death – no autopsy</td>
</tr>
<tr>
<td>Syndrome + abnormal troponin + ventricular arrhythmias/high grade conduction system disease</td>
</tr>
<tr>
<td>Abnormal troponin + new LVEF reduction</td>
</tr>
<tr>
<td>Abnormal troponin + ventricular arrhythmias/high grade conduction system disease + no alternate diagnosis</td>
</tr>
<tr>
<td>New heart failure + diagnostic cardiac MRI findings</td>
</tr>
<tr>
<td>Syndrome + diagnostic cardiac MRI findings</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible Myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>New LVEF reduction/heart failure + no alternate diagnosis</td>
</tr>
<tr>
<td>Elevated troponin + no alternate diagnosis</td>
</tr>
<tr>
<td>New ventricular tachycardia/high grade conduction system disease + no alternate diagnosis</td>
</tr>
<tr>
<td>Consistent cardiac MRI findings</td>
</tr>
</tbody>
</table>
Partnerships are Key
The Future is Immune Therapy

- There are now 164 agents targeting PD-1/L1, of which 50 are currently in clinical stages with five having already received FDA approval.
- In 2017, there were 940 immuno-oncology agents being tested in 3042 clinical trials with a target enrollment of 577,076 patients.
Expanding Cancer Treatments + Increasing Cancer Survivors

= Job Security + Research Opportunities

DeSantis C, Cancer Survivorship Statistics, 2014; Image Courtesy: GM Murtagh, MD;
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