Cardiovascular Toxicities Associated with Checkpoint Inhibitors

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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

• Consultation (Not Paid)
  – AbbVie/Abbott, Janssen/J&J, Amgen, Deciphera
  – U.S. Federal and Drug Administration (FDA)

• Research Grants:
  – Pfizer, Bristol-Myers Squibb
Immune Checkpoint-Inhibitor 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

EKG changes:

T Cell Infiltrates in the Heart

CD3

CD4

CD8

CD20

CD68

CD138

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

H&E  

CD4  

CD8  

CD20  

Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

Clinical Questions

- Incidence?
- Clinical presentation?
- Treatment?

↑

Immune Checkpoint Inhibitor-Associated Myocarditis
Electrocardiographic (EKG) Disturbances with Immune-Checkpoint Inhibitor Associated Myocarditis

Courtesy of Olenchock, BWH. Ahmad, Yale
Incidence of myocarditis and myositis with ipilimumumab and nivolumub treatment

Table 1. Incidence of Myocarditis and Myositis in Patients Receiving Nivolumub or Ipilimumub plus Nivolumub.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nivolumub (N=17,620)</th>
<th>Nivolumub plus Ipilimumub (N=2974)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Myocarditis</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>Myositis</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>

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute
## Cardiac disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities</td>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest or with minimal activity or exertion; intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)</td>
<td>Death</td>
</tr>
<tr>
<td>Definition: A disorder characterized by inflammation of the muscle tissue of the heart.</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Atrioventricular block complete</td>
<td>-</td>
<td>Non-urgent intervention indicated</td>
<td>Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrioventricular block first degree</td>
<td>Asymptomatic, intervention not indicated</td>
<td>Non-urgent intervention indicated</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain - cardiac</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Pain at rest; limiting self care ADL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction disorder</td>
<td>Mild symptoms; intervention not indicated</td>
<td>Moderate symptoms</td>
<td>Severe symptoms; intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Definition: A disorder characterized by pathological irregularities in the cardiac conduction system.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

Clinical Questions
- Incidence?
- Clinical presentation?
- Treatment?

Who is at risk?
- Precision or Personalized Medicine
  - 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??
- Induced Pluripotent Stem Cells (iPSC), Rodent Models
Immune-Checkpoint Inhibitor Myocarditis: Defining a New Syndrome

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Immune Checkpoint Inhibitor-Associated Myocarditis

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

Moslehi et al, Unpublished.
Other cases of Immune checkpoint-inhibitor associated myocarditis?

From: EDERHY Stéphane <stephane.ederhy@aphp.fr>
Date: Monday, February 20, 2017 at 5:12 AM
To: Javid Moslehi <javid.moslehi@vanderbilt.edu>
Subject: Cardiotoxicity and Immune checkpoints inhibitors

Dear Dr Moslehi,

As you know we read with great interest your recent manuscript in the New England Journal of Medicine describing two cases of cardiotoxicity due to immune checkpoint inhibitors. I would like to have your expert opinion on a clinical case. One of my colleagues had received yesterday a 35 years old patient treated with a combination of immune checkpoints inhibitors for melanoma. She developed dyspnea, heart failure then cardiogenic shock despite prednisolone. This morning a Left ventricular assist device was implanted due to refractory cardiogenic shock. Cardiac magnetic resonance performed at admission was in favor of myocarditis (left and right ventricle). LVEF measured with echo found an LVEF of 20%. The ECG found an Right bundle branch block. Troponin was 200 ng/ml. Due to the severity of this clinical scenario, we would like to try to propose to this patient plasma exchange. Have you ever tried such management in this particular context, do you think this proposition is of interest?

Best regards,

Stéphane Ederhy

Stephane EDERHY, Praticien Hospitalier, Service de cardiologie – Pr Cohen
Hôpitaux Universitaires Est Parisien, Hôpital Saint Antoine, 184 Rue du Faubourg Saint-Antoine, 75 571 Paris cedex 12

Ligne directe : 01 49 28 25 03, Secrétariat : 01 49 28 28 75, Fax : 01 49 28 24 35
the link between CANCER and CARDIOVASCULAR DISEASE
# Step 1 - Initial Information (contact form)

Please complete the survey below.

Thank you!

## Requesting Physician Information

<table>
<thead>
<tr>
<th></th>
<th>First Name:</th>
<th></th>
<th>Last Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3)</td>
<td>Email Address:</td>
<td></td>
<td>4) Phone Number:</td>
<td>* must provide value</td>
</tr>
</tbody>
</table>

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

|   | Time 1:   |   | Time 2:   |   |
### Table 3. Selected Ongoing Phase 3 Trials of Combination Therapy with Immune Checkpoint Blockers and Vaccines as First-Line Treatment for Advanced Renal-Cell Carcinoma.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary End Point</th>
<th>Estimated No. of Patients Enrolled</th>
<th>Trial</th>
<th>ClinicalTrials.gov No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab–lenvatinib vs. everolimus–lenvatinib vs. sunitinib</td>
<td>Progression-free survival</td>
<td>735</td>
<td>CLEAR</td>
<td>NCT02811861</td>
</tr>
<tr>
<td>Nivolumab–ipilimumab vs. sunitinib</td>
<td>Progression-free survival and overall survival</td>
<td>1070</td>
<td>CheckMate 214</td>
<td>NCT02231749</td>
</tr>
<tr>
<td>Atezolizumab–bevacizumab vs. sunitinib</td>
<td>Progression-free survival and overall survival in PD-L1–detectable tumors</td>
<td>900</td>
<td>IMmotion151</td>
<td>NCT02420821</td>
</tr>
<tr>
<td>Avelumab–axitinib vs. sunitinib</td>
<td>Progression-free survival</td>
<td>583</td>
<td>JAVELIN Renal 101</td>
<td>NCT02684006</td>
</tr>
<tr>
<td>Pembrolizumab–axitinib vs. sunitinib</td>
<td>Progression-free survival and overall survival</td>
<td>840</td>
<td>KEYNOTE-426</td>
<td>NCT02853331</td>
</tr>
<tr>
<td>Autologous dendritic-cell immunotherapy–sunitinib vs. sunitinib</td>
<td>Overall survival</td>
<td>450</td>
<td>ADAPT</td>
<td>NCT01582672</td>
</tr>
</tbody>
</table>

Conclusions

• Myocarditis is a new clinical phenomenon that is a rare (but clinically significant) complication of cancer immunotherapy
  – myositis with rhabdomyolysis
  – early progressive and refractory cardiac electrical instability
• Initial mechanistic studies show that robust T cell and macrophage infiltrates
• Need for multi-institutional efforts to understand the pathophysiology of myocarditis and multi-pronged approach to understand who is at risk of developing myocarditis
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