What Cardiovascular Toxicities Are Germane to Oncology Drug Development?

VANDERBILT HEART

Javid J. Moslehi, M.D.
Director, Cardio-Oncology Program
Assistant Professor of Medicine
Vanderbilt School of Medicine
Nashville, TN
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
Cardiovascular Toxic Effects of Targeted Cancer Therapies

Javid J. Moslehi, M.D.

Cancer Treatment
- Radiation
- Traditional chemotherapies
- Targeted cancer therapies
- Other new cancer therapies

Vascular Toxic Effects
- Hypertension
- Venous and arterial thromboembolic events
- Peripheral-artery disease
- Pulmonary hypertension
- Vasospasm
- Proteinuria
- Accelerated atherosclerosis
- Metabolic derangements

Cardiac Toxic Effects
- Decline in left ventricular ejection fraction
- Congestive heart failure
- Arrhythmia
- Myocarditis
- Pericardial disease
- Pericardial effusion

Moslehi, NEJM. 2016. 375(15):1457-1467.
Cardio-Oncology in 2017: New Concepts

• Concept #1: Cardiovascular sequelae of cancer therapies are diverse. It is no longer just about heart failure
  – Systolic Heart Failure
  – Heart Failure with normal Ejection Fraction (CHF-nEF)
  – Hypertension
  – Vascular Events (Atherosclerosis)
  – Thrombosis
  – Arrhythmias
  – Metabolic Disorders
  – Myocarditis
  – etc....
Cardio-Oncology in 2017: New Concepts

- Concept #2: Weigh the toxicity against the benefit
- Cardiovascular toxicities that are identified with new cancer therapies must be juxtaposed against the prognosis of cancer, existing therapies in the same class (for the same cancer) and the net benefit of therapy
- The threshold for toxicity may be different for a first-in-class therapy for a cancer type that has a poor prognosis and has few existing treatment possibilities versus a later-generation drug in a cancer with multiple existing therapies and a generally good prognosis
TIME

There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like GLEEVAC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

Brian Druker, Nick Lydon, Charles Sawyers
Cardio-Oncology in 2017: New Concepts

- Concept #3: Multi-pronged approach is needed to understand mechanisms of toxicity, to define who is at risk of toxicity and to inform preventive and treatment strategies.
  - You can not be wed to your system and want to apply it to every aspect of cardio-oncology.
  - One system does not fit all!
Cardiovascular Nonclinical Screening

Immune-Checkpoint Inhibitor 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
    - Genetic risk factors
    - Tumor-specific 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??
Induced Pluripotent Stem Cells (iPSC), Rodent Models

Moslehi et al, Unpublished.
Cardio-Oncology in 2017: New Concepts

• Concept #4: Need to think outside the box with respect to generate data
  – Promoting multi-institutional collaborations
the link between
CANCER
and
CARDIOVASCULAR
DISEASE
Step 1 - Initial Information (contact form)

Please complete the survey below.

Thank you!

<table>
<thead>
<tr>
<th>1) First Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2) Last Name:</td>
<td></td>
</tr>
<tr>
<td>3) Email Address:</td>
<td></td>
</tr>
<tr>
<td>4) Phone Number:</td>
<td></td>
</tr>
<tr>
<td>* must provide value</td>
<td></td>
</tr>
</tbody>
</table>

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

| 5) Time 1:              |          |
| 6) Time 2:              |          |
Cardio-Oncology in 2017: New Concepts

• Concept #5: Need for cardiovascular adjudication in oncology clinical trials
Cancer immunotherapy-based combination studies underway in 2016
Definite Myocarditis:

1) Any pathology diagnostic of myocarditis
2) **Cardiac magnetic resonance imaging (CMR)** diagnostic of myocarditis, a clinical syndrome and one of the following:
   a) Elevated biomarker of **cardiac myonecrosis**
   b) ECG evidence of myo-pericarditis
3) New **wall motion abnormality (WMA)** on echocardiogram not explained by another diagnosis (e.g. ACS ruled out by angiography, trauma, stress induced cardiomyopathy, sepsis) and all of the following:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of **cardiac myonecrosis**
   c) ECG evidence of myo-pericarditis
   d) Negative angiography or other testing to exclude obstructive coronary disease

Probable Myocarditis: Any of the scenarios below that are not explained by another diagnosis (e.g. ACS, trauma, stress induced cardiomyopathy)

1) **CMR** with findings diagnostic of myocarditis without any of the following*:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of **cardiac myonecrosis**
   c) ECG evidence of myo-pericarditis
2) **Non-diagnostic CMR** findings suggestive of myocarditis with any 1 of the following:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of **cardiac myonecrosis**
   c) ECG evidence of myo-pericarditis
3) **New WMA on echocardiogram** and any 2 of the following:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of **cardiac myonecrosis**
   c) ECG evidence of myo-pericarditis
4) **18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)** imaging showing patchy cardiac FDG uptake, and any of the following:
   a) Clinical syndrome consistent with myocarditis
   b) Elevated biomarker of **cardiac myonecrosis**
   c) ECG evidence of myo-pericarditis
Cardio-Oncology in 2017: New Concepts

• Concept #6: Need for Educational Platforms
  – Web-Based Platforms
    • Educate patients
    • Educate health care providers
  – Training next generation of physicians and scientists (ideally physician-scientists)
Patients
We are here to help you get answers and find resources.

Providers
A database of emerging cardio-oncology issues for oncologists, cardiologists and primary care physicians.

Require Assistance?
Need advice in managing cancer immunotherapy cardiotoxicity?
Cardio-oncology is the evolving discipline focused on the intersection of cardiovascular disease and cancer.

CardioOnc.org serves as a comprehensive resource for providers who care for cancer patients and cancer survivors with the goal of promoting a greater understanding of the impact of cardiovascular disease in this growing population.

EXPLORE PROVIDER SECTIONS

Drug Database
Cancer Drugs and Risk of Cardiovascular Toxicity

Collaborative Network
Coming soon...
Vanderbilt Cardio-Oncology Fellows (2017-2018)

Wendy Bottinor, M.D.
Completing cardiology fellowship at University of Louisville
Funding: T32
Research Focus: Vascular effects of VEGF inhibitors

Joe-Elie Salem, M.D., PhD
Sorbonne University
Funding: Grant
Research Focus: Basic – Moslehi and Roden Laboratories

Kris Swiger, M.D.
Completing cardiology fellowship at Vanderbilt
Funding: 3rd year
Research Focus: Cardiovascular prevention
Vanderbilt Cardio-Oncology Program

Clinical Program
Heart Failure
JoAnn Lindenfeld
Thomas Wang
Lynne Stevenson
Genetics
Quinn Wells
Dan Roden
Arrhythmia/EP
Bill Stevenson
Greg Michaud
Roy John
Cardiac Surgery
Ash Shah
Vascular Medicine
Josh Beckman
Esther Kim
Jon Brown
Translational Core Lab
Yan-Ru Su

Basic Research Program
Moslehi Laboratory
Donald Okoye
Calvin Sheng
Mary Barber
Translational Research
Thomas Wang
Quinn Wells
Dan Roden
Vascular Biology
Jon Brown
Hind Lal
David Harrison
Richard Gumina
iPS/Zebrafish
Chaz Hong
Jason Becker
Bjorn Knollmann

Education
Vanderbilt Cardio-Oncology Fellowship
Javid.moslehi@vanderbilt.edu
Collaborations Across Institutions

Vanderbilt Cardio-Oncology Program
Moslehi Laboratory
Xiaoyu Wang
Weijuan Li
David Meoli
Calvin Sheng

Hong Laboratory
Adrian Cadar

Force Laboratory
Roden Laboratory
Tao Yang

Clinical Cardio-Oncology
Javid Moslehi
Daniel Lenihan
David Sloskey
Tom Force
JoAnn Lindenfeld

Vanderbilt Cancer
Carlos Arteaga
Jennifer Pietenpol
Scott Hiebert
Nishitha Reddy
Frank Cornell
Madan Jagasia
Dave Gailani
Michael Savona
Doug Johnson

OHSU
Brian Druker

Utah
Michael Deininger
Tom O’Hare

MSKCC
Lee Jones
Paul Cohen

Dana-Farber/Harvard
Paul Richardson
Ken Anderson
Jennifer Brown
George Demetri
David Steensma
Dan DeAngelo

Northwestern
Jeff Sosman

Harvard Medical School
Peter Sorger
Alfred Goldberg
Christine Seidman
Jon Seidman

FDA
Laleh Amiri-Kordestani
Todd Palmby
Geoffrey Kim
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 Pr 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

Stephane Ederhy

Stephane EDERHY, Privatien Hospitalier, Service de cardiologie – Pr Cohen
Hôpitaux Universitaires Est Parisien, Hôpital Saint Antoine, 184 Rue du Faubourg Saint-Antoine, 75571 Paris cedex 12
Ligne directe : 01 49 28 25 03, Secrétariat : 01 49 28 28 75, Fax : 01 49 28 24 35

720 Rutland Avenue
Ross building, #1049
Baltimore, MD 21205 USA
Phone (410) 614-3085
Fax (410) 367-2149
Appointments: (443) 997-0270
djudge@jhmi.edu