Can Biomarkers be Used to Assess Risk of Vascular Cardiotoxicity?

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- St. Jude Medical: advisory board, speaker
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- Medicine Company: advisory board, speaker

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- None
Outline

• Inflammatory pathobiology of vascular disease

• Endothelial dysfunction – cardiovascular pathology

• Mechanisms of ischemic vascular events

• Biomarkers of cardiovascular events
  - biochemical biomarkers
  - imaging biomarkers
  - physiologic biomarkers

• Monitoring for vascular toxicity and CV events in oncology trials
Arterial Thrombosis: Not Unique to Targeted Novel Cancer Therapies

- 55 y.o female under treatment for pancreatic cancer
- On FOLFIRINOX - includes fluorouracil (5-FU), a pyrimidine analog antimetabolite (non targeted)

- Presented with chest pain and ST elevation MI
- Treated with coronary stenting, recovered, now starting alternate cancer therapy

Mechanism: possible 5-FU effect on endothelial function
Arterial Thrombosis is Complicated: Inflammation and Thrombotic Pathways Intertwine in Vascular Pathobiology

Molecular and cellular pathways link thrombotic and inflammatory processes.

- Atherogenesis
- Plaque stability
- Atherothrombosis
- Restenosis
- Vasculitis
- Vasospasm

Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Unclear:
• On target vs. off target effects?
• Clinical vascular events can be triggered by effects on:
  - endothelial cells
  - smooth muscle cells
  - platelets
  - monocytes
  - clotting proteins
Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Heterogeneous Mechanisms: atherogenic, plaque destabilizing, prothrombotic

Atherosclerotic Vasculopathy

Atherothrombotic Vasculopathy

75% MIs
- Rupture of Fibrous Cap
- Superficial Erosion

25% MIs
- DM
- Females
- Erosion of Calcium Nodule
- Intraplaque Hemorrhage

Libby, P. Scientific American 2002
Novel Cancer Therapies: Mechanisms of Vascular Toxicity

Heterogeneous Mechanisms: proliferative, vasospastic

Proliferative Vasculopathy

Vasospastic Vasculopathy

Nilotinib PAOD

Initial Angio

After IC Nitro

Endothelial Dysfunction: Central in the Pathobiology of Vascular Disease

Main Factors That Affect Endothelial Function

- Age
- Dyslipidemia
- Gender
- Hypertension
- Family History
- Obesity
- Physical Activity
- Visceral Fat
- Insulin Resistance
- Smoking
- Hyperglycemia
Endothelial Dysfunction: Central in the Pathobiology of Vascular Disease

Endothelial injury - inciting event predisposes to atherosclerosis and thrombosis

- Decreased NO bioavailability indicative of endothelial dysfunction and damage.
- NO dysregulation one of the earliest events in all types of vascular pathology.
Biomarkers and Vascular Cardiotoxicity

Biomarker (WHO):
- Substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*

- Measurement reflecting an interaction between a biological system and a potential hazard - not just incidence and outcome of disease, but also the effects of treatments, interventions, and exposure**

Assess underlying mechanisms of CV disease

*Clin Pharmacol Therapeutics. 2001;69:89–95

**WHO International Programme on Chemical Safety Biomarkers in Risk Assessment: Validity and Validation. 2001
Biochemical Biomarkers:

- Proteomic markers
- Phosphoprotein markers
- Epigenetic markers
- Multimarker strategies
Inflammatory Biomarkers Predict Risk of Cardiovascular Events

IL-6 and Risk of Future MI in Apparently Healthy Men

Ridker PM. Circulation, 2000
Inflammatory Biomarkers Predict Risk of Cardiovascular Events

Plasma Concentration of Soluble ICAM-1 and Risks of Future Myocardial Infarction

Baseline level of sICAM-1 (ng/ml)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Range</th>
<th>Relative Risk</th>
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<tr>
<td>1</td>
<td>&lt;45.5</td>
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<td>4</td>
<td>&gt;81.6</td>
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Soluble P-Selectin and the Risk of Future Cardiovascular Events: The Women’s Health Study

P-trend = 0.007

Baseline level of sICAM-1 (ng/ml)
Inflammatory Biomarkers Predict Risk of Cardiovascular Events

**Novel Risk Markers for Cardiovascular Events in Apparently Healthy Middle Aged Women**

- Lp(a)
- tHcy
- IL-6
- TC
- LDLC
- sICAM-1
- SAA
- Apo B
- TC: HDLC
- hs-CRP
- hs-CRP + TC: HDLC

**Novel Risk Markers for Myocardial Infarction in Apparently Healthy Middle Aged Men**

- Lp(a)
- D-dimer
- tHcy
- TC
- fibrinogen
- sICAM-1
- tPA:ag
- TC: HDLC
- Il-6
- hs-CRP
- hs-CRP + TC: HDLC

Relative Risk of Future Cardiovascular Events

Ridker PM et al, NEJM 2000

Ridker PM. Advances in Int Med 2000;45:391-418
Myocardial Necrosis Biomarker: cTroponin in Cancer Chemotherapy

Risk of CV death, by cTnT

deFilippi C et al. JAMA 2010;304:2494-2502.

Risk of LV dysfunction by cTnT

* cTnI increased in 114/473 pts receiving high dose chemo

Cardinale et al. Circulation 2006;114:2474-81
Clinical Phenotyping to Identify Novel CV Biomarkers

- Platelet mRNA Profiling
- Acute MI patients vs stable CAD patients
- Find genes responsible for plaque rupture/MI
- 24 differentially regulated genes
- Lead candidate = MRP-14 (elevated in MI)
  - CVD biomarker (preclinical and humans)
  - regulates atherosclerosis
  - activates platelets through CD36

MRP-14 and Risk of CV Disease

Healy, A. Circulation 2006
Croce, K. Circulation 2009
Schmizu, K. Circulation 2011
Maiseyeu A. ATVB 2012
Wang, Y. J Clin Invest 2014
Micro RNAs: Novel Circulating Biomarkers of Cardiovascular Disease

- miR-181b novel inhibitor of atherosclerosis, regulates EC inflammation
- inhibited the expression of importin-α3 which supports NF-κB inflammatory function

Icli, B. Circ Res 2014
Imaging Biomarkers:

- **Structural**

- **Structural / functional**
  - Inflammation imaging
  - Ischemia / perfusion imaging
Coronary Artery Calcium Score:

Report: Agatston calcium score

Multi-Ethnic Study of Atherosclerosis

Heinz Nixdorf Recall Study

Cumulative Incidence of Coronary Events (%) vs. Years to Event

- Coronary-artery calcium score categories: >300, 101-300, 1-100, 0
- CAC Categories:
  - 1-99: Meta-Analysis 1.9 (1.3 - 2.8), HNR-Study 1.7 (0.8 - 3.5)
  - 100-399: Meta-Analysis 4.3 (3.1 - 6.1), HNR-Study 4.0 (2.0 - 8.1)
  - 400-999: Meta-Analysis 7.2 (5.2 - 9.9), HNR-Study 5.4 (2.4-12.3)
  - ≥1000: Meta-Analysis 10.8 (4.2-27.7), HNR-Study 16.1 (8.0-32.2)

Relative Risk (versus CAC = 0) vs. Relative Risk

[Graph showing cumulative incidence and relative risk across different calcium score categories]
CT Angiography of Coronary Arteries:

Extent of disease

- Minimal (0-25%)
- Mild (25-49%)
- Moderate (50-69%)
- Severe (>70%)
Coronary CT Angiography: Disease Burden Predicts Outcomes

CONFIRM Registry 23,854 patients

MGH/BWH Registry N=3242 patients
mean f/u 3.6 years
1st outcome: CV death / MI

Non-obstructive plaque → increased risk of CV death / MI

Min JACC 2011

Survival free from CV death or Myocardial Infarction

Bittencourt, Circulation CV Imaging 2014
Myocardial Perfusion and FDG PET: Functional and Structural Imaging

**Normal Study**
Normal myocardial perfusion and no FDG uptake

**Cardiac Sarcoidosis**
Abnormal myocardial perfusion and focal FDG uptake
Physiologic Cardiovascular Biomarkers:

- Blood pressure / heart rate
- Heart rate recovery after exercise
- Endothelial function
Quantifying Endothelial Function in Humans

Brachial artery flow-mediated dilation
• Metric of endothelial dysfunction.
• Correlates with coronary flow-mediated dilation.
• Predicts long-term CV events.

Charakida, M European Heart Journal (2010) 31, 2854–2861
Quantifying Endothelial Function in Humans

- Endo-PAT
  - endothelial mediated vasodilation
  - reactive hyperemia index
The pathobiology of vascular disease is a complex process that involves multiple cell types. Inflammation and endothelial dysfunction are common to all vascular pathologies. Vascular events can arise from dysregulation of several homeostatic processes (athero, spasm, intimal obliteration).

The complex pathobiology of vascular disease creates challenges in predicting whether a targeted cancer therapy will have adverse cardiovascular effects. Cardiovascular biomarkers track the molecular and structural processes that underlie the pathobiology of vascular disease. Biomarkers predict risk of vascular events and can in some cases inform about vascular disease mechanism. Biomarker limitations include poor ability to identify individual patients who will experience a vascular event.