Imaging Modalities to Diagnose Cardiovascular Toxicities with Immunotherapy

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Second Annual Cardio-Oncology Workshop
December 1, 2017
Outline

• Potential Imaging Modalities for Immunotherapy Cardiotoxicity Evaluation
  – Echocardiography
  – Positron emission tomography/computed tomography (PET/CT)
  – Cardiac magnetic resonance (CMR) imaging

• Necessary Advances in Research
What are Our Diagnostic and Prognostic Imaging Targets?

- Myocardial Inflammation
- Cardiomyocyte Injury
- Contractile dysfunction and remodeling
- Establish disease severity
- “Rule-out” other disease states
- Myocardial fibrosis
- Recovery of function/resolution of injury

Acute: Diagnosis

Chronic: Prognosis
<table>
<thead>
<tr>
<th>Echocardiographic Measure</th>
<th>Phenotypic Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D/3D RA, RV, LA, &amp; LV size, shape</td>
<td>Cardiac structure</td>
</tr>
<tr>
<td>2D/3D LV &amp; RV strain, strain rate, ejection fraction</td>
<td>Systolic function</td>
</tr>
<tr>
<td>E/a, e’, a’, E/e’</td>
<td>Diastolic function, filling pressures</td>
</tr>
<tr>
<td>Ea, E_{es}, Ea/E_{es}, wall stress</td>
<td>Ventricular &amp; vascular Stiffness</td>
</tr>
<tr>
<td>Twist, torsion</td>
<td>Systolic &amp; diastolic deformation</td>
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<tr>
<td>Regurgitation, stenosis</td>
<td>Valvular disease</td>
</tr>
<tr>
<td>Pericardium</td>
<td>Pericardial effusion</td>
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<tr>
<td>Cardiac output, pulmonary pressures</td>
<td>Hemodynamics</td>
</tr>
</tbody>
</table>
Echocardiography

- **Advantages:** Safe, versatile, widely and readily available
- **Disadvantages:** Not sensitive or specific for the diagnosis of myocarditis or biologic disease activity
- **Potential role:** Screening tool, post-diagnosis for serial assessment of cardiac function and remodeling
Myocardial PET Can Be Used to Detect Inflammation

- Positron Emission Tomography (PET): Tool to evaluate myocardial perfusion, cardiac function, inflammation, metabolism, or cell death

- $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG): Quantitatively and qualitatively evaluate inflammation; increased glucose uptake hallmark of inflammatory activity

- Agreement with CMR for myocarditis diagnosis (N=55):
  - Kappa 0.73
  - Sensitivity 74% and Specificity 97%

Myocardial PET: Research Advances

• Small in vivo animal and human studies report the use of novel tracers in myocarditis diagnosis:
  – $^{11}$C-methionine: increased uptake in macrophages, T cells and B cells; no uptake in healthy myocardium
  – Somatostatin receptor based radiotracer: activated macrophages overexpress somatostatin receptor subtypes 1 and 2; concordance with CMR 85.3% (n=12)

Lapa, et al Int'l J Cardiol. 2015.

Increased somatostatin receptor uptake in septum in acute myocarditis
Myocardial PET

• **Advantages:** Insight into ‘active’ myocarditis

• **Disadvantages:** Radiation exposure, critical to ensure inhibition of physiological myocardial glucose uptake (~12% failed in one study), limited specificity

• **Potential (future) role:** Monitor response to therapy, localization of disease to guide biopsy, complement to CMR to enhance sensitivity

CMR Provides Detailed Characterization of Structure and Function

- Characterize with high reproducibility cardiac size and function
  - LVEF, volumes, mass, strain

- Gain unique qualitative and quantitative insight into intracellular and extracellular abnormalities
  - T1/T2 mapping, extracellular volume, delayed enhancement
  - Edema, inflammation, fibrosis


General Imaging Protocol for Myocardial Tissue Characterization
CMR and Myocarditis Diagnosis

• Lake Louise criteria (2 of 3):
  – Hyperemia (T1-weighted imaging w/early gadolinium enhancement)
  – Edema (T2-weighted imaging w/high signal intensity*)
    *Patchy, subepicardial/septal, transmural, global
  – Necrosis/cell injury and fibrosis (late gadolinium enhancement*)
  – Repeat CMR in 1-2 weeks if no findings are present but clinical suspicion high

• Additional supportive findings: LV dysfunction – regional or global; pericardial effusion

• Sensitivity 67%, Specificity 97% (pooled), although features can also observed in non-inflammatory cardiomyopathy

Advances in CMR to Improve Diagnostic Accuracy

- 129 patients with suspected myocarditis → CMR, biopsy (MyoRacer-Trial)
- T1 Native, ECV – elevated in acute group (edema, hyperemia, myocardial fibrosis/necrosis)
- T2 – Elevated in acute & chronic groups (free water content, edema); findings corroborated by others

**TABLE 3** CMR Imaging Techniques

<table>
<thead>
<tr>
<th></th>
<th>&lt;14 days symptoms</th>
<th>&gt;14 days symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Myocarditis</td>
<td>No Myocarditis</td>
</tr>
<tr>
<td>1.5-T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema ratio</td>
<td>1.97 ± 0.37</td>
<td>1.81 ± 0.42</td>
</tr>
<tr>
<td>Early enhancement</td>
<td>4.63 ± 2.23</td>
<td>5.69 ± 4.45</td>
</tr>
<tr>
<td>Presence of LE</td>
<td>77</td>
<td>63</td>
</tr>
<tr>
<td>LLC</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>Native T1</td>
<td>1,113 ± 67</td>
<td>1,044 ± 42</td>
</tr>
<tr>
<td>ECV</td>
<td>37.2 ± 6.5</td>
<td>31.8 ± 4.9</td>
</tr>
<tr>
<td>T2</td>
<td>62.2 ± 4.5</td>
<td>56.9 ± 7.2</td>
</tr>
</tbody>
</table>

Advances in CMR to Improve Diagnostic Accuracy

• 48 patients with myocarditis underwent repeated assessment by CMR (acute, 3 months, and 12 months)
• Initially increased, but native T1 and T2 decreased over time, potentially indicative of ability to differentiate “acute” versus “healed”
• LGE/ECV* parameter had highest diagnostic accuracies at all 3 timepoints (91%, 85%, 86%)

*LGE/ECV = Late gadolinium enhancement or ECV ≥27%

CMR

- **Advantages:** Structural and functional characterization, potential to differentiate acute versus healed

- **Disadvantages:** Less readily available, highly dependent upon adequate image quality, reproducibility/variability of T1, T2 derived parameters

- **Potential role:** Diagnosis, prognosis, response to cardiac therapy and/or to immunotherapy
CV Phenotyping with Imaging: Needs and Opportunities

• Improve upon the sensitivity, specificity, and diagnostic accuracy of imaging modalities

• Define subgroups and settings of highest utility for imaging---diagnosis or prognosis (guide further diagnostic testing, response to cardiac therapy, likelihood of recovery, or safety of immunotherapy)

• Establish an efficient infrastructure to ask impactful imaging questions of interest (Cancer Moonshot Initiative, Provocative Questions RFA)

• Develop evidence-based, consensus guidelines specific to immunotherapy and cardiotoxicity (White Paper)
THANK YOU
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