Biomarkers of Acute Kidney Injury in Cancer Patients: From Bench to Bedside

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Harvard Medical School
Past-President, American Society of Nephrology
Disclosures
Joseph V. Bonventre

Advisory Board/Consultant: Janssen, Merck, Sarepta, Seattle Genetics

Equity: Coegin, Medibeacon, Goldfinch, Autonomous Medical Devices, Oisin

Co-Inventor on KIM-1 and kidney organoid patents assigned to Partners Healthcare
Outline

• Onconephrology: Historical Perspectives
• AKI Biomarker Needs
• Inadequacy of Creatinine as a Marker of AKI
• FDA Qualification of a Biomarker Composite for Kidney Safety
• A Safety Biomarker may also be a Prognostic Marker
• AKI Biomarker Roadmap
Onconephrology (History)

Onconephrology Forum, ASN (2010)

Seminars in NEPHROLOGY

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Onco-Nephrology: Kidney Disease in the Cancer Patient
Benjamin D. Humphreys, MD, PhD
Guest Editor

Onconephrology References (Pubmed)
Onconephrology: The Latest Frontier in the War against Kidney Disease

Abdulla K. Salahudeen* and Joseph V. Bonventre†

*Nephrology Section, Department of General Internal Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas, and †Renal Division, Brigham and Women's Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts


Several nephrologists working with patients with cancer believe that nephrologists caring for cancer-related nephrologic problems are indispensable members of the multidisciplinary cancer care team; a multidisciplinary model for cancer care is increasingly adopted by larger cancer centers, such as MDACC in Houston, Memorial Sloan-Kettering Cancer Center in New York, and Dana-Farber/Brigham and Women's Hospital Cancer Center in Boston. These centers have instituted this approach to improve cancer outcomes. Furthermore, several...
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- AKI Biomarker Roadmap
AKI Biomarker Needs

1. Diagnose and monitor kidney injury early during its course

FDA-NIH Biomarker Categories: Diagnostic, Monitoring, Safety

2. Predict which patients are more likely to develop AKI as a response to a drug or procedure

FDA-NIH Biomarker Categories: Predictive, Susceptibility/Risk

3. Predict AKI progression to CKD and/or ESKD

FDA-NIH Biomarker Categories: Susceptibility/Risk, Prognostic

4. Measure efficacy of a drug or intervention for AKI

FDA-NIH Biomarker Categories: Pharmacodynamic/Response

5. Predict which patients will have a positive therapeutic response to a drug or intervention to prevent or treat AKI

FDA-NIH Biomarker Categories: Predictive

Roadmap for Accelerating the Development of Biomarkers for Acute Kidney Injury

- Diagnostic
- Monitoring
- Pharmacodynamic/response
- Predictive
- Prognostic
- Safety
- Susceptibility/Risk

Biomarker Data Repository
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Acute kidney injury is defined when one of the following criteria is met:

- Serum creatinine rises by $\geq 26\mu\text{mol/L}$ (0.3 mg/dl) within 48 hours or
- Serum creatinine rises $\geq 1.5$ fold from the reference value, which is known or presumed to have occurred within 7 days or
- Urine output is $< 0.5 \text{ ml/kg/hr}$ for $\geq 6$ consecutive hours

KDIGO = Kidney Disease to Improve Global Outcomes
What Has Held Up Progress

Definition of AKI relies on $\Delta$ sCreat

- Serum creatinine rises by $\geq 26\mu$mol/L (0.3 mg/dl) within 48 hrs or
- Serum creatinine rises $\geq 1.5$ fold from the reference value, which is known or presumed to have occurred within one week, or
- Urine output is $< 0.5$ml/kg/hr for $\geq 6$ consecutive hours

**BUT**

Acute kidney injury $\neq$ Acute tubular/interstitial injury

We want biomarkers that measure **tubular-interstitial injury**

Modified from
Sharma, Mucino and Ronco
Nephron Clin Pract
127:94-100, 2014
Mean Urinary KIM-1 and NAG Levels During Cisplatin Treatments
In 12 Patients with Testicular Cancer

SCr did not change
Reduced GFR (↑Creatinine) Leads to Better Outcomes


DAPA CKD

Heerspink et al. NEJM 383:1436-46, 2020
Abemaciclib increases sCr 10-40% due to inhibition of Tubular Secretion

Plasma Metformin Concentration (ng/ml)

Abemaciclib

Placebo

Time post-dose of metformin (hr)

Clearance of Metformin

Iohexol Clearance

Wang and Kestenbaum
CJASN, 2018

Chappell...Bonventre. Clin Pharm and Therapeutics 105, 2019
Summary of Kim-1, NAG, SCr, BUN Data with 10 Toxicants

Composite Tubular Severity Score:

Grade 0  Grade 1  Grade 2  Grade 3

Kim-1 mRNA levels

Kim-1 protein levels

Urinary Kim-1 (Fold change)

Urinary NAG (Fold change)

Cisplatin  Vancomycin  Puromycin  Lithium  Methapyrilene
Gentamicin  Tacrolimus  Doxorubicin  Furosemide  ANIT

Vaidya et al. Nature Biotech, May 2010
Sensitivity and Specificity of Kim-1, NAG, BUN, SCr

Vaidya et al.
Nature Biotechnology,
May, 2010

Predictive Safety Testing Consortium Rat Toxicity Studies
Evaluation of 14 Urinary Biomarkers Across 22 Rat Renal Safety Studies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>Sens*</th>
<th>Fold Cut Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim-1</td>
<td>0.98</td>
<td>97</td>
<td>1.5</td>
</tr>
<tr>
<td>Clusterin</td>
<td>0.96</td>
<td>86</td>
<td>1.8</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.96</td>
<td>90</td>
<td>1.8</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>0.95</td>
<td>85</td>
<td>1.7</td>
</tr>
<tr>
<td>Osteoactivin</td>
<td>0.94</td>
<td>88</td>
<td>1.9</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.92</td>
<td>83</td>
<td>1.6</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>0.89</td>
<td>69</td>
<td>1.6</td>
</tr>
<tr>
<td>NAG</td>
<td>0.88</td>
<td>73</td>
<td>1.4</td>
</tr>
<tr>
<td>RBP4</td>
<td>0.84</td>
<td>73</td>
<td>1.8</td>
</tr>
<tr>
<td>B2M</td>
<td>0.80</td>
<td>67</td>
<td>1.6</td>
</tr>
<tr>
<td>Total Protein</td>
<td>0.77</td>
<td>55</td>
<td>1.8</td>
</tr>
<tr>
<td>GST-α</td>
<td>0.57</td>
<td>45</td>
<td>1.8</td>
</tr>
<tr>
<td>BUN</td>
<td>0.81</td>
<td>68</td>
<td>1.2</td>
</tr>
<tr>
<td>sCr</td>
<td>0.73</td>
<td>56</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Sensitivity values at 95% specificity.

AUC: area under the ROC curve
How to qualify a biomarker or group of biomarkers without using creatinine

Context of Use

A safety biomarker (s).... to detect kidney tubular injury in phase 1 trials in healthy volunteers ....
Early Data on 8 Biomarkers Show Superior Sensitivity over Serum Creatinine for the Identification of Patients Exposed to Cisplatin

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mesothelioma Patients: Number/N (%) $&gt; T_{SS}^*$</th>
<th>Normal Healthy Volunteers: % $&gt; T_{SS}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients With Medically Relevant Increases in sCr</td>
<td>Patients Without Medically Relevant Increases in sCr</td>
</tr>
<tr>
<td>Clusterin</td>
<td>19/20 (95.0%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>20/20 (100.0%)</td>
<td>30/31 (96.8%)</td>
</tr>
<tr>
<td>Microalbumin</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>Total Protein</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>NAG</td>
<td>20/20 (100.0%)</td>
<td>27/30 (90.0%)</td>
</tr>
<tr>
<td>Kim-1</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>Cystatin-C</td>
<td>19/20 (95%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>NGAL</td>
<td>19/20 (95%)</td>
<td>24/30 (80.0%)</td>
</tr>
</tbody>
</table>

W. Glaab on behalf of FNIH Biomarkers Consortium KSP Team
NEDMDG Summer Symposium, Burlington MA June 2016
Two Prospective Clinical Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>(adults with cystic fibrosis)</td>
<td>100 patients, 50 controls</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>(Adult Head and Neck Cancer)</td>
<td>100 patients, 50 controls</td>
</tr>
<tr>
<td>Acronym</td>
<td>Name (Unique ID (Uniprot))</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>CLU</td>
<td>Urinary Clusterin (P10909)</td>
<td>A heterodimeric highly conserved secreted glycoprotein expressed in the proximal and distal tubules, glomerulus and collecting duct.</td>
</tr>
<tr>
<td>CysC</td>
<td>Cystatin-C (P01034)</td>
<td>A small serum protein produced by all nucleated cells and found in most tissues and body fluids. CysC is freely filtered by the glomerulus and completely reabsorbed and catabolized in healthy renal tubular epithelium.</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Kidney Injury Molecule -1 (O96042)</td>
<td>A type I transmembrane glycoprotein containing an ectodomain consisting of an immunoglobulin-like domain and a mucin domain that is strongly induced by ischemic and toxic insults to the kidney.</td>
</tr>
<tr>
<td>NAG</td>
<td>N-acetyl-beta-D-glucosaminidase (O60502)</td>
<td>A large lysosomal enzyme with two isoforms and is mainly expressed in proximal tubules.</td>
</tr>
<tr>
<td>NGAL</td>
<td>Neutrophil gelatinase-associated lipocalin (P80188)</td>
<td>Expressed in various tissues at low levels with upregulated transcription in tubulopithelial cells following ischemic and nephrotoxic kidney injuries.</td>
</tr>
<tr>
<td>OPN</td>
<td>Osteopontin (P10451)</td>
<td>A highly acidic glycoprotein expressed by many tissues that acts as a macrophage adhesion and chemotactic molecule.</td>
</tr>
</tbody>
</table>
Two Arm New Cohort of Normal Healthy Volunteers

1. For each subject, calculate the uCr-normalized fold-change from baseline for each biomarker. Define this as $FC_i$ for subject $i$ and biomarker $j$ where $j = 1, 2, ..., 6$.

2. For each subject $i$, calculate the Composite Measure:

$$CM_i = \exp \left\{ \sum_{j=1}^{6} \frac{1}{6} \log(FC_{ij}) \right\}$$

3. Calculate the geometric mean of the Composite Measure for cohort $k$ ($k = \text{Drug, Control}$):

$$\overline{CM}_k = \exp \left\{ \frac{1}{m} \sum_{i=1}^{m} \log(CM_i) \right\}$$

4. Calculate the ratio of the geometric means for the two cohorts:

$$GM_{\text{Ratio}} = \frac{\overline{CM}_{\text{Drug}}}{\overline{CM}_{\text{Control}}}$$

FDA Qualification Decision and Executive Summary, 2018
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Other Things to Consider

- A kidney toxicity marker becomes more difficult to use as a drug toxicity marker if the cancer itself generates the biomarker.

- If the cancer cells generate the biomarker then the biomarker may be useful as a prognostic marker.
KIM-1 is Expressed in Renal Cell Carcinoma and Lymphatic Metastases

“Normal” tissue is non-malignant ischemic tissue

Han......Bonventre JASN 16:1126-34, 2005
Overall Survival by Plasma KIM-1 Quartile in DF/HCC RCC Cohort

Sabbisetty, Xu…Bonventre. Submitted

133 patients
Progression Free Survival by Plasma KIM-1 Quartile in DF/HCC RCC Cohort

Sabbisetti, Xu...Bonventre. Submitted
Plasma KIM-1 Related to Staging and Nephrectomy in DF/HCC RCC Cohort

Sabbisetti, Xu...Bonventre. Submitted
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Roadmap for Accelerating the Development of Biomarkers for Acute Kidney Injury

Purpose and Overview

April 2022
Overview of Key Roadmap Components

- The Need for AKI Biomarkers
- Vision for Accelerated Biomarker Development
- Action Items for Achieving Roadmap Strategy
- Challenges to Accelerating AKI Biomarker Development
- AKI Biomarker Use Cases
Roadmap for Accelerating Biomarker Development

UNDOABLE TO ACHIEVE ROADMAP GOALS:
- Establish Biomarker Development and Standardization
- Data Sharing and Interoperability
- Establishment of Regulatory Pathways
- Establishment of Clinical Pathways
- Implementation of Implementation Strategies
- Overcome Challenges:
  - Regulatory Challenges
  - Clinical Challenges
  - Technical Challenges

ENHANCE DISCOVERY, BUILD EVIDENCE, AND ACCELERATE IMPLEMENTATION OF BIOMARKERS THAT:
- Enhance efficacy and safety of treatments
- Predict efficacy and safety of treatments
- Provide early detection of disease
- Improve patient outcomes
- Reduce healthcare costs

KHI KIDNEY HEALTH INITIATIVE
NEXIGHT GROUP
UNDEARTAKE THESE ACTIVITIES TO ACHIEVE ROADMAP GOALS:

1. **Optimize Biomarker Testing and Integrate Appropriate Biomarker Use into New and Ongoing Studies**
   Study data can help answer critical questions about biomarkers to make them more actionable and further drive their development.

2. **Collaborate on Biobanking, Data Collection, and Data Sharing**
   Use existing resources such as biobanks and clinical trial datasets to support AKI biomarker studies and create a repository of AKI samples to support generation of data and validation assays for AKI biomarker development.

3. **Use Biomarkers to Better Define and Predict AKI and its Phenotypes**
   An improved definition of AKI that maps closely with true kidney injury at a cellular level could support the development of clear AKI phenotypes and help enable efficient development of treatment for AKI.

4. **Support Coordinated Biomarker Development and Qualification**
   Organize a more systematic data collection effort that leverages the activities of different stakeholder groups and seeks to answer specific key questions and fill high-priority data gaps.

5. **Develop AKI Biomarker Guidance and Best Practices to Facilitate Adoption**
   The development of guidance and resources that target common questions and pain points for AKI biomarker use can help accelerate adoption by the community.

6. **Increase Awareness of Biomarker Benefits**
   Education campaigns targeted at clinicians, hospital administration, therapeutic developers, payors, and patients could help them to become active proponents of biomarkers and increase adoption of biomarkers as a standard part of risk evaluation, diagnosis, and care.

7. **Focus Community Efforts**
   Attention should be focused on 1–2 of the highest-priority use cases, with research focused on 5–10 biomarkers within each use case to prevent dilution of community effort.
ENHANCE DISCOVERY, BUILD EVIDENCE, AND ACCELERATE IMPLEMENTATION OF BIOMARKERS THAT:

- Diagnose and monitor kidney injury at an early stage
- Predict which patients are more susceptible to developing AKI in response to a therapeutic or procedure
- Identify AKI patients who are likely to progress to CKD and/or ESKD
- Predict which patients will have a positive response to an intervention to prevent or treat AKI
- Measure response to a therapeutic intervention for AKI
Learn more about the roadmap on the KHI website

Kidney Health Initiative (KHI) | Current Projects (asn-online.org)
Biomarker Qualification Does not Imply FDA Clearance of an Assay

Pre-Analytical and Analytical Challenges with AKI Biomarkers
Two Paths to Faulty Results

Suspect Samples → Validated Assay → Misleading Inconsistent Results
Perfect Samples → Faulty Assay

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Summary

- There are multiple unfulfilled needs for AKI biomarkers
- There are a number of very promising candidate biomarkers
- ∆ serum creatinine is inappropriate as a gold standard
- A composite of 6 biomarkers has been qualified by the FDA for use to detect acute tubular injury in Phase 1 studies in normal volunteers.
- The FDA, ASN, (Kidney Health Initiative), AST, Pharma and Critical Path Institute are working together to advance AKI biomarkers to use in drug development and in clinical use.
Thank You