Where Do We Need Biomarkers?

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Disclosures

Consultation: Astute Medical, Alere Medical, Abbott Medical, Covidien Medical, Gambro Medical, NxStage Medical, Sanofi-Aventis
Outline

• A Brief History of Breast Cancer
• Lessons for Renal Disease
A Brief History of Breast Cancer

• Well codified histopathology
  – Ductal, tubular, mucinous, papillary, cribiform, lobular
  – Bloom-Richardson Grading > aggressive v. non aggressive

• Good staging system
  – Tumor, Node, Mets (TNM)
Breast Cancer Treatment

• Localized, no nodes
  – Breast-conserving surgery, R/T, adjuvant chemo

• Localized, Positive nodes
  – Breast-conserving surgery, R/T, adjuvant chemo

• Metastatic
  – Bigger surgery, R/T, adjuvant chemo

• Chemotherapy – taxane and anthracycline containing chemo
Outcomes

• **Standard Therapy**
  – Improvement in outcomes was marginal

• **Modern Therapy**
  – Based on receptor status
  – HER2, Estrogen, Progesterone
  – Dreaded triple negative
Oncology Renaissance

• Diagnosis and Treatment linked to molecular pathways
Oncology Hospital

Breast Cancer

Lung Cancer

Hematologic Cancer

Skin Cancer
Future Oncology Hospital

JAK-2

HER-2

kras

p53
Acute Kidney Injury Classification
Phenotype(s)

- Pre Renal
- Renal
- Post Renal
Acute Kidney Injury Classification

- Sepsis
- Post Cardiac Surgery
- ACRD
- Contrast
- Nephrotoxic
Value of Phenotyping

1. Enrich event rate for clinical trial design
2. Identification of patients at risk: early diagnostic
3. Identification of patients with poor outcomes: prognostic
4. Identification of patients for therapies: theragnostic
Facets of a Syndrome
Breast Cancer

Estrogen

Prog

HER2
KIM-1

IL-18

TIMP-2

AKI
AKI Staging System

KDIGO Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
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<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase</td>
<td>&lt;0.5 ml/kg/h for 6–12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients &lt;18 years, decrease in eGFR to &lt;35 ml/min per 1.73 m²</td>
<td>&lt;0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>
AKI – Why we can’t

• We need kidney biopsy data
• We need more money
• Complex disease/syndrome
• We need better biomarkers
Current Classification System

AKI

Sepsis - 47%
Hyovolemia 25%
Surgery - 34%
Card. Shock - 27%
Drug - 19%
Other - 12%

AKI Stage
Comorbidities

Interactions

Host Response Treatment Effects

Outcomes

Chawla – Curr Opinion Crit Care - 2012
Kidney Disease Advantage

• Access to fluid that is proximate to injury

• Urine
What can I do?
The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Christina Curtis1,2,*, Sohrab P. Shah3,4,*, Suet-Feung Chin1,2,*, Gulisa Turashvili3,4,*, Oscar M. Rueda1,2, Mark J. Dunning2, Doug Speed2,5†, Andy G. Lynch1,2, Shamith Samarajiwa1,2, Yinyin Yuan1,2, Stefan Gräf1,2, Gavin Ha3, Gholamreza Haffari3, Ali Bashashati3, Roslin Russell2, Steven McKinney3,4, METABRIC Group†, Anita Lægerød6, Andrew Green7, Elena Provenzano8, Gordon Wishart8, Sarah Pinder9, Peter Watson3,4,10, Florian Markowitz1,2, Leigh Murphy10, Ian Ellis7, Arnie Puri and Dam2,11, Anne-Lise Børresen-Dale6,12, James D. Brenton2,13, Simon Tavaré1,2,5,14, Carlos Caldas1,2,8,13 & Samuel Aparicio3,4

The elucidation of breast cancer subgroups and their molecular drivers requires integrated views of the genome and transcriptome from representative numbers of patients. We present an integrated analysis of copy number and gene expression in a discovery and validation set of 997 and 995 primary breast tumours, respectively, with long-term clinical follow-up. Inherited variants (copy number variants and single nucleotide polymorphisms) and acquired somatic copy number aberrations (CNAs) were associated with expression in ∼40% of genes, with the landscape dominated by cis- and trans-acting CNAs. By delineating expression outlier genes driven in cis by CNAs, we identified putative cancer genes, including deletions in PPP2R2A, MTAP and MAP2K4. Unsupervised analysis of paired DNA–RNA profiles revealed novel subgroups with distinct clinical outcomes, which reproduced in the validation cohort. These include a high-risk, oestrogen-receptor-positive 11q13/14 cis-acting subgroup and a favourable prognosis subgroup devoid of CNAs. Trans-acting aberration hotspots were found to modulate subgroup-specific gene networks, including a TCR deletion-mediated adaptive immune response in the ‘CNA-devoid’ subgroup and a basal-specific chromosome 5 deletion-associated mitotic network. Our results provide a novel molecular stratification of the breast cancer population, derived from the impact of somatic CNAs on the transcriptome.
Discovery set

Logrank $P = 1.2 \times 10^{-14}$

Disease-specific survival probability vs. Months

Legend:
- IntClust1: 74(18)
- IntClust2: 45(20)
- IntClust3: 150(19)
- IntClust4: 164(32)
- IntClust5: 91(48)
- IntClust6: 44(14)
- IntClust7: 109(21)
- IntClust8: 140(34)
- IntClust9: 67(24)
- IntClust10: 96(30)
Disentanglement Process

- L-FABP
- NGAL
- IL-18
- KIM-1
- IGBP7
- TIMP2

Enroll → Measure BM → Initiate Intervention → Good Outcome

Enroll → Measure BM → Initiate Intervention → Poor Outcome
Phenotyping Does Not Always Lend Itself to Multivariate Analysis
Treatment A

Biomarker [X]

Biomarker [Y]
Testing Candidate Classes

<table>
<thead>
<tr>
<th>NGAL  -</th>
<th>KIM-1 -</th>
<th></th>
<th>KIM-1 +</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL  +</td>
<td></td>
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</tbody>
</table>
Topographic Phenotype Testing

- Pajek
- NodeXL
- Python iGraph

- Disclaimer – I do not have a PhD in statistics
Biomarkers are not tissue receptors

- Temporal Effects – BM kinetics
- Non-linear relationships with disease
- Comorbidities (e.g. sepsis)
- Assay related issues
Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185HER2 Monoclonal Antibody in Patients With HER2/neu-Overexpressing Metastatic Breast Cancer

By José Baselga, Debasish Tripathy, John Mendelsohn, Sharon Baughman, Christopher C. Benz, Lucy Dantis, Nancy T. Sklarin, Andrew D. Seidman, Clifford A. Hudis, Jackie Moore, Paul P. Rosen, Thomas Twaddell, I. Craig Henderson, and Larry Norton

Purpose: Breast cancer frequently overexpresses the product of the HER2 proto-oncogene, a 185-kd growth factor receptor (p185HER2). The recombinant humanized monoclonal antibody (rhuMAb) HER2 has high affinity for p185HER2 and inhibits the growth of breast cancer cells that overexpress HER2. We evaluated the efficacy and toxicity of weekly intravenous administration of rhuMAb HER2 in patients with HER2-overexpressing metastatic breast cancer.

Patients and Methods: We treated 46 patients with metastatic breast carcinomas that overexpressed HER2. Patients received a loading dose of 250 mg of intravenous rhuMAb HER2, then 10 weekly doses of 100 mg each. Patients with no disease progression at the completion of this treatment period were offered a maintenance phase of 100 mg/wk.

Results: Study patients had extensive metastatic disease, and most had received extensive prior anticancer therapy. Adequate pharmacokinetic levels of rhuMAb HER2 were obtained in 90% of the patients. Toxicity was minimal and no antibodies against rhuMAb HER2 were detected in any patients. Objective responses were seen in five of 43 assessable patients, and included one complete remission and four partial remissions (overall response rate, 11.6%; 95% confidence interval, 4.36 to 25.9%). Responses were observed in liver, mediastinum, lymph nodes, and chest wall lesions. Minor responses, seen in two patients, and stable disease, which occurred in 14 patients, lasted for a median of 5.1 months.

Conclusion: rhuMAb HER2 is well tolerated and clinically active in patients with HER2-overexpressing metastatic breast cancers that had received extensive prior therapy. This is evidence that targeting growth factor receptors can cause regression of human cancer and justifies further evaluation of this agent.

Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That Has Progressed After Chemotherapy for Metastatic Disease

By Melody A. Cobleigh, Charles L. Vogel, Debu Tripathy, Nicholas J. Robert, Susy Scholl, Louis Fehrenbacher, Janet M. Wolter, Virginia Paton, Steven Shak, Gracie Lieberman, and Dennis J. Slamon

Purpose: Overexpression of the HER2 protein occurs in 25% to 30% of human breast cancers and leads to a particularly aggressive form of the disease. Efficacy and safety of recombinant humanized anti-HER2 monoclonal antibody as a single agent was evaluated in women with HER2-overexpressing metastatic breast cancer that had progressed after chemotherapy for metastatic disease.

Patients and Methods: Two hundred twenty-two women, with HER2-overexpressing metastatic breast cancer that had progressed after one or two chemotherapy regimens, were enrolled. Patients received a loading dose of 4 mg/kg intravenously, followed by a 2-mg/kg maintenance dose at weekly intervals.

Results: Study patients had advanced metastatic disease and had received extensive prior therapy. A blinded, independent response evaluation committee identified eight complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% confidence interval, 11% to 21%). The median duration of response was 9.1 months; the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of patients, were infusion-associated fever and/or chills that usually occurred only during the first infusion, and were of mild to moderate severity. These symptoms were treated successfully with acetaminophen and/or diphenhydramine. The most clinically significant adverse event was cardiac dysfunction, which occurred in 4.7% of patients. Only 1% of patients discontinued the study because of treatment-related adverse events.

Conclusion: Recombinant humanized anti-HER2 monoclonal antibody, administered as a single agent, produces durable objective responses and is well tolerated by women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. Side effects that are commonly observed with chemotherapy, such as alopecia, mucositis, and neutropenia, are rarely seen.

Don’t Dismiss Early Signal

• Story of Herceptin
Table 1. Comparison of breast cancer and acute kidney injury disease management variables

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer</th>
<th>AKI</th>
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</thead>
<tbody>
<tr>
<td>Baseline data</td>
<td>Demographics</td>
<td>Well characterized</td>
</tr>
<tr>
<td></td>
<td>Genomics</td>
<td>Well characterized</td>
</tr>
<tr>
<td></td>
<td>Epigenetics</td>
<td>Well characterized</td>
</tr>
<tr>
<td>Staging system</td>
<td>TNM</td>
<td>KDIGO</td>
</tr>
<tr>
<td>Disease type</td>
<td>Histopathology</td>
<td>Functional/structural classification</td>
</tr>
<tr>
<td>Disease characteristic that directs therapy</td>
<td>Receptor status</td>
<td>AKI biomarkers (proposed)</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; TNM, tumor, node, metastasis.
Summary

• AKI and CKD needs to move toward molecular diagnostics

• Urinary biomarkers should be tested for use as:
  – Diagnostic panels > no more pre-renal/renal/ATN
  – Therapeutics
    • Profile to treat
    • Profile to select therapeutic(s)
• Process is iterative
• Requires collaboration and broad sharing of data

• This same approach should be applied to sepsis and to ARDS
Acknowledgments