Where Do We Need Biomarkers?

Lakhmir Chawla, M.D.

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
- Post Renal
- Renal

Acute Kidney Injury Classification

- Sepsis
- Post Cardiac Surgery
- Contrast
- Nephrotoxic
- ACRD
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
Breast Cancer

- Estrogen Receptor
- Prog Receptor
- HER2

AKI

- KIM-1
- IL-18
- TIMP-2

AKI Staging System

KDIGO Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urea output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-2.0 times baseline</td>
<td>&lt;8.0 mg/dL for 4-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.5 times baseline</td>
<td>&gt;8.0 mg/dL for &gt;12 hours</td>
</tr>
<tr>
<td>3</td>
<td>&gt;3.0 times baseline</td>
<td>Needs for &gt;12 hours</td>
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Definition of end stage therapy

UO is patients <18 years, decrees in K/FR < 0.050/min per 1.73 m²
AKI – Why we can’t

- We need kidney biopsy data
- We need more money
- Complex disease/syndrome
- We need better biomarkers

Kidney Disease Advantage

- Access to fluid that is proximate to injury
- Urine
Phenotyping Does Not Always Lend Itself to Multivariate Analysis

Untreated

Treatment A
Testing Candidate Classes

<table>
<thead>
<tr>
<th>KIM-1 -</th>
<th>KIM-1 +</th>
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<tbody>
<tr>
<td>NGAL -</td>
<td></td>
</tr>
<tr>
<td>NGAL +</td>
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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-neo-Overexpressing Metastatic Breast Cancer

By Jun Bradle, Deborah Tipton, John Henschel, Sharon Buchanan, Christopher C. Bees, Lucy Dwyer, Nancy S. Milner, Andrew D. South, Clifford A. Hudis, Jackie Auer, Paul F. Baur, Thomas Twaddle, J. Craig Hendrickson, and Jerry Hughes

Purpose: Breast cancer frequently overexpresses the product of the HER2 proto-oncogene, a 185-kDa growth factor receptor (185HER2). The recombinant humanized monoclonal antibody (mAb) received orphan drug designation for 185HER2 and inhibits the growth of breast cancer cells that overexpress HER2. We evaluated the efficacy and safety of weekly intravenous administration of Herceptin (mAb 185HER2) to patients with 185HER2-overexpressing metastatic breast cancer.

Patients and Methods: We treated 46 patients with metastatic breast cancer that overexpressed HER2. Patients received a loading dose of 330 mg of intravenous Herceptin, then 13 weekly doses of 100 mg each. Patients with no disease progression at the completion of 16 weeks may have received additional courses of weekly Herceptin for a maximum of 14 months.

Results: Study patients had extensive metastatic disease, and most had received extensive prior anti-cancer therapy. Adequate pharmacokinetic levels of Herceptin were obtained in 90% of the patients. Toxicity was minimal and no antibodies against Herceptin were detected in any patients. Objective responses were seen in 14 patients, 8 of which were surprising, and 12 patients not previously treated with chemotherapy. Four patients had stable disease for 16 weeks or longer, and short-term benefit was seen in 12 patients. Median duration of survival was 15 months. Overall survival was 10 months.

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 Melissa A. Cattanugh, Charles L. Vogel, Deb Tipton, Nicholas J. Baker, Tony Schom, and Hari Frantinokou

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. Herceptin, a recombinant humanized monoclonal antibody, has been shown to reverse the growth of breast cancer cells in women who overexpress HER2 compared with chemotherapy-alone treatment. This multinational study further assessed the efficacy and safety of Herceptin in women whose breast cancer had progressed after chemotherapy for metastatic disease.

Patients and Methods: Two hundred twenty-three women with HER2-overexpressing metastatic breast cancer were treated with Herceptin, in addition to continuing chemotherapy. Patients received a loading dose of 330 mg of intravenous Herceptin, then 13 weekly doses of 100 mg each. Patients were monitored for clinical benefit, and adverse events were recorded. The median duration of response was 5.3 months, and the median duration of survival was 15 months. The most common adverse events, which occurred in approximately 40% of patients, were infusion-related reactions. These included fever, chills, and headache. The most common adverse events that occurred in 10% of patients were diarrhea, rash, and fatigue. Overall survival was 10 months.
Don’t Dismiss Early Signal

• Story of Herceptin

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