Pharmacogenomics in the Treatment of Breast Cancer

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Indiana University School of Medicine
February 15th, 2008

The Consortium on Breast Cancer
Pharmacogenomics : COBRA
An Approach to Deciding what Pharmacogenetic Study To Do:

**Test Value Decreases when Current Predictive Ability is High**

Clinical Value of a Pharmacogenetic Test

- Cancer Therapy
- Antidepressants/5HTR
- $\beta$-blockade/$\beta$ Receptor

Current Clinical Ability to Predict Response

Meyer UA and Flockhart DA, 2003
Advances in Stratification that have already improved the Treatment of Breast Cancer

- Estrogen and Progesterone Receptors
- HER-2 and Herceptin
- Expression arrays that predict the value of chemotherapy
  - Oncotype Dx™
  - Mammaprint™

Anti-estrogen therapy for Breast Cancer

**Aromatase Inhibitors**
- Anastrozole (Arimidex™)
- Letrozole (Femara™)
- Exemestane (Aromasin™)

**Selective Estrogen Receptor Modulators**
- Tamoxifen
- Raloxifene
- Fulvestrant
Tamoxifen (for ~5 yrs) in Early Breast Cancer Reduced Recurrence for 15 years

Recurrence (%)

Years

15-year gain
11.8% (SE 1.3)
Logrank 2P<0.00001

Control
45.4%

About 5 years of tamoxifen
33.2%

15-year gain
11.8% (SE 1.3)
Logrank 2P<0.00001

Control
45.0%

About 5 years of tamoxifen
33.2%

NNT = 8
Absolute Benefit = 12%

*10,386 women

Central Anti-Estrogen Dogma
The ATAC trial: Aromatase Inhibition beat Estrogen Receptor Blockade by Tamoxifen

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The ATAC trial: Aromatase Inhibition beat Estrogen Receptor Blockade by Tamoxifen

Proportion with recurrence (%)

HR 95% CI p-value
AN vs TAM 0.78 0.65–0.93 0.007

NNT = 50
Absolute Change in Risk: 2.1%

AN vs TAM 0.78 0.65–0.93 0.007

NNT = 50
Absolute Change in Risk: 2.1%

AN 2617 2533 2436 2243 1258 602
TAM 2598 2516 2386 2180 1210 574

Howell A, EBCC Hamburg 3-18-2004

*Censoring non-BC deaths before recurrence
The ELPH (Exemestane and Letrozole Pharmacogenomics) Trial

Upfront or after Tamoxifen for 2-5 yrs

Letrozole
Exemestane

N=250/Arm

Indiana University
University of Michigan
Johns Hopkins

Germ line SNPs
Drug metabolites
Estrogen, estrogen metabolites
Measures of estrogen activity (Breast Density; TBG, lipids, bone density, etc.)
Symptoms (hot flashes, etc)

Case Report

• 39 yo woman with stage II breast cancer presents after surgery, chemotherapy and 3 months on letrozole or exemestane c/o diffuse musculoskeletal pain without tender points. She has done her own challenge/rechallenge 4 or 5 times, is becoming depressed and hopeless and is not willing to continue.
Aromatase Inhibitor Side Effects in the ELPh trial

- Of 100 patients enrolled:
  - 42 reported serious bone and joint problems
  - 38 referred to rheumatology
  - 15 dropped out because of musculoskeletal pain.
    - Rotator cuff tendonitis,
    - Carpal tunnel syndrome
- Most common Co-Medications used for pain and for vasomotor Symptoms:
  - ibuprofen
  - naproxen
  - celecoxib

Henry et al. ASCO 2007

Adverse Reactions from Tamoxifen and Aromatase Inhibitors are Different in Asia from Western Countries

SABCS 2007
No pain, no gain: Women who experience hot flashes have better outcomes.


No Pain, No Gain: Women with Hot Flashes do Better

Cusack J et al, SABCS 2008
In Endocrine Therapy for Breast Cancer

Compliance Matters

• 2,080 women were treated for breast cancer in Scotland between 1993 and 2002.
• 79% received prescriptions for tamoxifen as an adjuvant treatment after surgery.
• Women with fewer than 70% of their tamoxifen prescriptions filled showed a 16% increased risk of death

Thompson et al: ASCO 2007

Hypothesis

• Genetic factors that influence medication adherence may influence outcomes
• Could the pharmacogenetics of tamoxifen metabolism influence compliance or outcomes?
Central Anti-Estrogen Dogma
The ATAC trial: Aromatase Inhibition beat Estrogen Receptor Blockade by Tamoxifen

Proportion with recurrence (%)
0 6 12 18 24 30 36 42 48 54

HR 95% CI p-value
AN vs TAM 0.78 0.65–0.93 0.007

NNT = 50

Absolute Change in Risk: 2.1%

AN vs TAM 0.78 0.65–0.93 0.007

Tamoxifen
Anastrazole

How is tamoxifen metabolized to endoxifen?

Zeruesenay Desta PhD
Associate Professor of Medicine and Pharmacology
Indiana University School of Medicine
UGT1A10 is the most efficient catalyst of endoxifen O-glucuronidation

<table>
<thead>
<tr>
<th>UGT</th>
<th>$V_{\text{max}}$ (pmol·min$^{-1}$·µg$^{-1}$)</th>
<th>$K_M$ (µM)</th>
<th>$V_{\text{max}}/K_M$ (µl·min$^{-1}$·µg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>2.3 ± 0.3</td>
<td>333 ± 60</td>
<td>0.0069 ± 0.0005</td>
</tr>
<tr>
<td>1A3</td>
<td>2.9 ± 0.4</td>
<td>158 ± 29</td>
<td>0.018 ± 0.001</td>
</tr>
<tr>
<td>1A7</td>
<td>Low activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A8</td>
<td>11.6 ± 1.4</td>
<td>101 ± 13</td>
<td>0.12 ± 0.01</td>
</tr>
<tr>
<td>1A9</td>
<td>Low activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1A10</td>
<td>5.7 ± 0.7</td>
<td>39.9 ± 3.4</td>
<td>0.14 ± 0.005</td>
</tr>
<tr>
<td>2B7</td>
<td>3.0 ± 0.4</td>
<td>101 ± 17</td>
<td>0.030 ± 0.004</td>
</tr>
<tr>
<td>2B15</td>
<td>N.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B17</td>
<td>N.D.</td>
<td></td>
<td></td>
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</tbody>
</table>

Endoxifen and 4-OH-Tamoxifen are Equipotent as Inhibitors of Estrogen Stimulated Cell Proliferation

![Graph showing cell growth inhibition by Endoxifen, 4-OH Tamoxifen, and Tamoxifen at different concentrations.](image)

*Johnson M et al, 2003*

Endoxifen and 4-OH-tam effects on global gene expression are highly correlated

![Graph showing fold-changes in gene expression by Endoxifen and 4-OH-Tamoxifen.](image)

*Young-Chai Lim et al. 2005*
Paroxetine and CYP2D6 genotype change the plasma concentrations of endoxifen

Stearns, Desta, Hayes, Flockhart et al. JNCI, December 2003
Pharmacokinetic changes result in changes in efficacy? Impossible

- Tamoxifen and its metabolites saturate the estrogen receptor in the breast.

Serum Concentrations of Tamoxifen and Metabolites Predict that Endoxifen is more active in vivo.

Johnson M et al, 2003
Inhibition of CYP2D6 Lowered Endoxifen Concentrations

**Jin Y et al:** J Natl Cancer Inst 97:30, 2005

**Plasma Endoxifen (nM)**

- **Wt/Wt, no inhibitor**
- **Venlafaxine**
- **Sertraline**
- **Paroxetine**
- ***4/*4, no inhibitor**

**Relapse-free Survival**

- **CYP2D6 WT/WT**
- **CYP2D6 *4/WT**
- **CYP2D6 *4/*4**

*P*=0.020

**Goetz et al J Clin Oncol. 2005;23(36):9312-8.**
Goetz et al JCO 2005

Biobank data showed the opposite result.

...patients were identified as taking tamoxifen if the drug was prescribed at least once in the two years after diagnosis.

Databank Studies vs Randomized Prospective Randomized Controlled Trials for Pharmacogenomic Questions

- PRCT are very expensive
- DNA in a bank is very stable
- DNA in a tumor paraffin block is very stable

- Medication data attached to biobanks have to be well annotated. In general it is not.

Influence of CYP2D6 genotype on tamoxifen response in German ER+ breast cancer patients

<table>
<thead>
<tr>
<th></th>
<th>Relapse-Free Time</th>
<th>Event-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability</td>
<td>Probability</td>
</tr>
<tr>
<td>EM</td>
<td>1.67 (1.16-2.41 95% CI)</td>
<td>1.50 (1.10-2.05 95% CI)</td>
</tr>
<tr>
<td>EM/het</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM+IM</td>
<td></td>
<td></td>
</tr>
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</table>

Schroth et al. JCO 2007
Korean CYP2D6 *10/*10 Carriers Experienced Faster Metastatic Breast Cancer Progression on Tamoxifen


A 5-fold Increased Rate of Breast Cancer Recurrence in Japanese Women carrying the CYP2D6 *10 allele

Clinical Consequences

- Tamoxifen should not be used with CYP2D6 inhibiting drugs
  - Fluoxetine
  - Paroxetine
  - Quinidine
  - Diphenhydramine

- Post menopausal women who are documented CYP2D6 poor metabolizers should consider an aromatase inhibitor as endocrine therapy for breast cancer

- No data are available to recommend CYP2D6 testing in premenopausal women

### CYP2D6 Genotype altered

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% of patients who developed moderate or severe hot flashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>*CYP2D6 *4/*4</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>*CYP2D6 *4/WT or Wt/WT</td>
<td>20% (36/177)</td>
</tr>
</tbody>
</table>

Germline Variants in Estrogen Receptor β Associate With a low risk for Hot Flashes


Odds ratio for hot flashes

No pain, no gain: Women who Experience Hot Flashes have Better Outcomes

Low CYP2D6 Score Associates with high Tamoxifen Compliance

![Graph showing the relationship between CYP2D6 Score and Tamoxifen Compliance]

Rae JM et al, SABCS 2007.

Larger Lessons from the Tamoxifen Experience

- Rodent Drug Metabolism ≠ Human Drug Metabolism
- Tissue Drug Concentrations are Hard to Interpret, Serum much easier
- Effective drugs usually have side effects, No Pain, No Gain
- Genetic factors that influence adherence to medications may influence outcomes
Bevacizumab significantly improved PFS

HR = 0.60
Log Rank Test   p<0.001

Pac. + Bev. 11.8 months
Paclitaxel     5.9 months

Bevacizumab increased grade 3/4 toxicity

Serious, frequent, & unique
Likely related to duration of taxane exposure

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>P (%)</th>
<th>P+B (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>2.9</td>
<td>9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.9</td>
<td>9.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17.7</td>
<td>23.5</td>
<td>0.05</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>0</td>
<td>1.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>14.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Miller et al. NEJM 357:2666; 2007
Improvement in PFS/ORR did not translate into OS benefit

Miller et al. NEJM 357:2666; 2007

ORR (measurable disease)
49.2% vs. 25.2%
P<0.001

GOOD NEWS AND BAD NEWS

Miller et al. NEJM 357:2666; 2007
Advisory Panel Rejects New Use for Cancer Drug

A federal advisory committee voted yesterday that Genentech’s drug Avastin should not be approved as a treatment for breast cancer.

By a 1-4 vote, the committee decided that Avastin’s ability to delay the worsening of cancer did not outweigh the drug’s toxic side effects, especially since women getting Avastin did not live significantly longer in the end.

“Absolutely, it’s a very painful reality that metastatic breast cancer is not curable,” said Natalie Compagni Forte, a patient representative on the committee, who voted against an

Schneider et al; SABCS, 2007

VEGF -2578 AA & -1154 AA tagSNPs associated with improved OS in combination arm

p=0.023

p=0.001

Schneider et al; SABCS, 2007
Genetic variability of VEGF predicts clinically significant hypertension in E2100

<table>
<thead>
<tr>
<th>SNP</th>
<th>% Grade 3/4 hypertension (#/%) by genotype</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-634</td>
<td>CC=0% (n=27;15.3%) vs. GC=22% (n=82; 46.3%) vs. GG=19% (n=68; 38.4%)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>CC vs. GC+GG</td>
<td>0.005</td>
</tr>
<tr>
<td>VEGF-1498</td>
<td>TT=8% (n=60; 33.9%) vs. CT=22% (n=82; 46.3%) vs. CC=23% (n=35; 19.8%)</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>TT vs. CC+CT</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Future Elements in Precision Prescribing for Breast Cancer

- Somatic: Estrogen and Progesterone Receptors to decide on endocrine treatment/not. Her-2 for Herceptin decision.
- Germline Genomics: CYP2D6 and UGT and ER genetic variant assessment to determine tamoxifen or aromatase inhibitor.
- Environment and Lifestyle Integration: Careful drug interaction and herbal assessment in each patient.
- Somatic Genomics: Expression and SNP arrays to determine whether to use chemotherapy and then the type and duration of chemotherapy