Pharmacogenetics in Breast Cancer

Giampietro Gasparini, MD
San Filippo Neri Hospital- Rome
Few histotypes

but

more molecular
diseases

Pharmacogenomics

Pharmacokinetics

Pharmacodynamics

Pharmacogenetics

• Age and PS
• Comorbidities
• Compliance
• Ethnics
• Genetics
MOLECULAR PORTRAIT OF BREAST CANCER

476 cDNA clones

85 arrays

Above average
Average
Below average
Not determined

Basal like
HER2
Normal
Luminal B
Luminal A
...... Results

- Identification of 5 breast cancer subgroups with different prognosis
- Identification of nonresponder patients
  ....but

- No predictive activity of absolute value (different outcome in selected “responsive” patients)

- No predictive determinants of toxicity

?
Drugs Work Better for Some People Than for Others

Factors influencing different response:

- Pharmacokinetics
- Environmental
- Genetics
Toward Personalized Therapy

- Tumor genetic profiling
- Pharmacogenetics
- Therapeutic drug monitoring
  - Pharmacokinetics
  - Predictive indicators
  - Drug-to-drug interactions
Pharmacogenetics may help in understanding some of the differences in therapeutic activity and toxicity of anticancer drugs.
Interethnic Genetic Differences in Activity and Toxicity to Anticancer Drugs

**Polymorphisms**: Structural modifications of DNA with a frequency $\geq 1\%$
Pharmacogenetics
Study of Patient’s Genetic Polymorphisms

- 90% SNPs
  - (Single nucleotide polymorphisms)

- 10%
  - Insertions and deletions
  - Tandem repeats/microsatellites
    - short (2bp)
    - long (20-30 o più)
  - Genetic duplications
  - Pseudogenes
    - Untranscribed esonic sequences with high homology with expressed genes
Are the Results of Clinical Trials Really Valid Worldwide?

- Ethnic-related incidence of tumors or toxicity
  - Gastric cancer: Japanise vs Caucasian
  - Gefinitib pulmonary toxicity: Japanise vs Caucasian
- Ethnic-related frequency of SNPs
  - Tamoxifen
  - Taxanes

Careful interpretation of clinical results in a single ethnic population

Can we change the paradigm of clinical trials by using pharmacogenetics?
Perform the trial in different ethnic populations

Make the optimal biological characterization of each single tumor

Pharmacogenetics

Variability to drug activity/toxicity

Tailored therapy
Pharmacogenetics (Haplotype and Genotype)

- **Transport** (MDR1, MRP2, RFC,...)
- **Metabolism** → phase I (CYP)
  → phase II (UGT, GST,...)
- **Target** (EGFR, VEGFR, TS,)

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- **Drug**
- **Metabolite**
- **Target**
Pharmacogenetic and Pharmacogenomic Diagnostic Biomarkers (approved by FDA)

TOXICITY

UGT1A1*28 (irinotecan) [Invader Assay]
TPMT (6-MP, azatioprine) [pro-Predict Py]
CYP2C9 (warfarin) [Amplichip]
CYP2D6 (atomoxetine) [Amplichip]

EFFICACY/RESISTANCE

CYP2D6 (tamoxifen) [AmpliChipCYP450Test]
Expression levels of Her2/neu (trastuzumab)
Mutations of K-RAS (cetuximab, panitumumab)
Chromosome Philadelphia/ Bcr-abl (imatinib)
C-kit (imatinib)

Not approved
EGFR mutations (gefitinib, erlotinib)
Tamoxifen: The Key-Pharmacogenetic Step

CYPs-cytochrome P450 metabolism
Tamoxifen Biotransformation

CYP3A4
CYP3A5

Tamoxifen

CYP2B6
CYP2C9
CYP2C19
CYP1A2

CYP2D6

N-desmethyltamoxifen

CYP2D6

4-hydroxytamoxifen

4-hydroxy-N-desmethyltamoxifen (Endoxifen)

5-10 nM (average ~7 nM)

10-200 nM (average ~ 90 nM)

Tamoxifen and Polymorphisms

- Polymorphic genetic variations of tamoxifen-metabolizing enzymes (http://www.imm.ki.se/cyp)
- Concomitant administration of CYP2D6 inhibitors may affect tamoxifen-related clinical outcomes
- CYP3A4 promoter variant also involved in tamoxifen metabolism
- Polymorphism of the SULT1A1 gene (SULT1A*2 variant)
- ER genotypes (ESR-Xbal and ESR2-02) may be associated with tam-associated lipid changes and may contribute to interindividual variability to tamoxifen benefits
# Tamoxifen Polymorphisms

<table>
<thead>
<tr>
<th>POLYMORPHISM CLASSES</th>
<th>CYPs</th>
<th>Ethnical Frequency</th>
<th>Clinical Implication</th>
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</table>
| Poor metabolizer     | CYP2D6: *3, *4, *5, *6| CAUCASIANS (RARE IN ASIANS AND BLACK AFRICANS)          | Nonfunctional variants →
|                      |                       |                                                         | • worse DFS (Goetz MP, Schroth W)                               |
|                      |                       |                                                         | • Worse PFS (Schroth W)                                        |
| Intermediate         | CYP2D6 * 10, *17, *   | ASIANS (RARE IN EUROPEAN CAUCASIANS)                     | Worse recurrence, decreased RFS, worse PFS (in adjuvant setting) (Schroth W) |
| metabolizer          | 41                    |                                                         |                                                               |
| Extensive            | CYP2D6 * 2xn          | CAUCASIANS                                              | Favorable RFS, to be confirmed                                 |
| metabolizer          |                       |                                                         |                                                               |
Endoxifen, But Not 4-hydroxytamoxifen, Degrades The Estrogen Receptor In Breast Cancer Cells: A Differential Mechanism Of Action Potentially Explaining CYP2D6

SABCS 2008

John R. Hawse, Xianglin Wu, Malayannan Subramaniam,
Matthew P. Goetz, Thomas C. Spelsberg, James N. Ingle

Relapse-Free Time According to CYP2D6 Metabolizer Status

Pharmacogenetic (CYP2D6) And Gene Expression Profiles (HOXB13/IL17BR And Molecular Grade Index) For Prediction Of Adjuvant Endocrine Therapy Benefit In The ABCSG 8 Trial

SABCS 2008
MP Goetz, M Ames, M Gnant, M Filipits, H Heinzl, R Jakesz, R Greil, C Marth, H Samonigg, V Suman, S Safgren, M Kuffel, R Weinshilboum, M Erlander, X Ma, J Ingle
ABCSG Trial 8 Structure

Primary surgery → Randomize → Tamoxifen (2 years) → Tamoxifen (3 years)

Primary endpoint: event-free survival

Switching period

Relapse-Free Time According to CYP2D6 in Women Receiving Adjuvant Tamoxifen

### CYP2D6 and Risk of Breast Events

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk to EM</th>
<th>(P) Value</th>
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<tbody>
<tr>
<td><strong>ARM A: TAM for 5 Years</strong>&lt;br&gt;(n = 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>3.83 (1.27-11.55)</td>
<td>.017</td>
</tr>
<tr>
<td>CYP2D6 IM</td>
<td>0.87 (0.44-1.71)</td>
<td>.689</td>
</tr>
<tr>
<td><strong>ARM B: TAM to Anastrozole</strong>&lt;br&gt;(n = 55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 PM</td>
<td>1.02 (0.21-4.83)</td>
<td>.985</td>
</tr>
<tr>
<td>CYP2D6 IM</td>
<td>0.81 (0.40-1.61)</td>
<td>.538</td>
</tr>
</tbody>
</table>
Adjuvant Tamoxifen and CYP2D6

• **CYP2D6 associated with recurrence**
  - Goetz et al. 2005,1 20082 (USA)
  - Hawse et al. 20083 (AUSTRIA)
  - Schroth et al. 20074 (Germany)
  - Kiyotani et al. 20085 (Japan)
  - Newman et al. 20086 (UK)
  - Xu et al. 20087 (China)

• **CYP2D6 not associated with recurrence**
  - Wegman et al. 2005,8 20079 (Sweden)

Aromatase Inhibitors: The Key-Pharmacogenetic Step

CYPs-cytochrome P450 enzyme aromatase by CYP 19A1 or aromatase genes
POLYMORPHISMS ENVOLVED IN EXEMESTANE ACTIVITY

**CYP3A4*1B CYP3A5*3**

**CYP19**

**RIZ1**

**ER1**

**ER2**

**CYP17 CYP1B1*3 COMT UGT1A1*28**
**AIs Polymorphisms**

- > 80 CYP 19 polymorphisms resulting in 44 haplotypes from each of the 4 ethnic groups have been identified.

- **Arg^{39} variant OF CYP19A1**: Present in 6.7% Han Chinese American (rare in other ethnic groups);

- **Cys^{264} variant OF CYP19A1**: Higher frequencies in Han Chinese Americans and African Americans (11.7%-22.5%) than Caucasian or Mexican Americans (2.5%-5%)

- **CYP19A1 3’-untranslated region variant**: Associated to higher RR and TTP in postmenopausal ER+ metastatic disease treated with letrozole
ROLE OF THE CYP19 Ex11+410G>T AND OTHER GENETIC POLYMORPHISMS ON RESPONSE TO EXEMESTANE AS FIRST LINE TREATMENT IN PATIENTS WITH METASTATIC BREAST CARCINOMA

Giuseppe Toffoli, MD, Director Pharmacology CRO Aviano

Giampietro Gasparini, Study Coordinator CIPOMO
STUDY DESIGN

Patients enrollment and treatment

- 394 patients will be enrolled for pharmacogenetic analysis.
- In 100 patients will be done also PK analysis.
- Therapy: exemestane 25 mg/po/day. At least 8 weeks on therapy are required for evaluation.
Taxanes: The Key-Pharmacogenetic Step

Metabolism (CYP3A4, CYP3A5)

Transport-efflux (ABCB1) gene polymorphisms
Taxanes

- Docetaxel is metabolized by CYP3A4/5, while paclitaxel by CYP2C8/CYP3A4.

- There is controversy whether polymorphisms in the ABCB1 gene, encoding P-glycoprotein, correlate to efficacy of taxanes.

- In a prospective study with paclitaxel in metastatic breast cancer, the genotype ABCB1 2677 GG showed a significant correlation with resistance.

- In a retrospective analysis of the CALCB 9871 study (109 patients) no difference was found between Caucasian and African-American patients in terms of docetaxel toxicity regarding polymorphisms CYP3A4, CYP3A5, and ABCB1.

Taxanes

- Interethnic differences in docetaxel PK and toxicities exist between south-east populations (Chinese vs Indian vs Malays)\(^1\)
- CYP3A4*1B is a promoter polymorphism with different ethnic incidences: 45% in African-American, 2-9% in Caucasian; rare in Asian\(^2\)
- Caucasian patients harboring both CYP3A4*1B +/- CYP3A5*1\(^\circ\) alleles have higher docetaxel clearance\(^3,4\) ()
- In Caucasian patients treated with docetaxel, the polymorphism C1236T in the ABCB1 gene was significantly related to decreased clearance (-25%)\(^5\)
- Docetaxel-induced neuropathy, hematological toxicities, and OS are linked to ABCB1 allelic variants\(^6\)

Bevacizumab: The Key-Pharmacogenetic Step

VEGF as the Therapeutic Target

Bryan P. Schneider, Molin Wang, Milan Radovich, George W. Sledge, Sunil Badve, Ann Thor, David A. Flockhart, Bradley Hancock, Nancy Davidson, Julie Gralow, Maura Dickler, Edith A. Perez, Melody Cobleigh, Tamara Shenkier, Susan Edgerton, Kathy D. Miller

The VEGF-2578 AA genotype and the VEGF-1154 AA genotype predicted a favorable median OS for patients in the combination arm but did not predict an improved median OS for patients in the control arm and did not predict a superior PFS or RR for either arm. There was a significant incremental benefit from each addition of the VEGF-1154 A allele.

RESULTS

- Patients with VEGF-2578 AA and VEGF-1154 AA genotype have a superior OS compared with patients with alternative genotypes.

- The allele frequency of VEGF-2578 AA and VEGF-1154 AA in white population is frequent and ranges from 33% to 49%.

- The VEGF-634 CC and VEGF-1498 TT genotypes correlated with less grade 3 or 4 hypertension (0% and 8%, respectively) as compared to the combined alternate genotypes ($P = .005$ and $P = .022$, respectively).

- Patients with grade 3 or 4 hypertension have a superior OS as compared to pts with no hypertension (38.7 months vs 25.3 months, respectively; $P = .002$).

CRITICISMS

- The combination of paclitaxel/bevacizumab showed prolonged PFS (11.8 months vs 5.9 months) and RR (36.9% vs 21.2%) as compared to paclitaxel alone (E2100 Study), but....

- No significant difference was observed on OS (26.7 months vs 25.2 months; \( P = .16 \))

- The grade 3/4 toxicity was higher in the experimental arm (hypertension: 14.8% vs 0%; proteinuria: 3.6% vs 0%; cerebrovascular ischemia. 1.9% vs 0%)

- The RR and PFS observed in the control arm are worse than that usually observed in first-line therapy: Why?

- Retrospective analysis of pharmacogenetics on tumor specimens and not as usually performed on blood samples

TAKE HOME MESSAGE

• The results on pharmacogenetic studies are promising but mainly obtained in retrospective analysis

• Pharmacogenetic studies emphasize the relevance of ethnical diversities

• It is reasonable to hypothesize that pharmacogenetic analysis coupled with molecular characterization of each single tumor may lead to improved personalized therapy

• Data need to be validated in prospective clinical trials