Geographic Variations in Response and Toxicity of Anticancer Agents

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Japan-SWOG “Common Arm Analysis” of Paclitaxel/Carboplatin Therapy in Advanced NSCLC: A Model for Prospective Comparison of Cooperative Group Trials

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SWOG 0003: Phase III Trial of Paclitaxel/Carboplatin +/- Tirapazamine in Advanced NSCLC

→ Paclitaxel/Carboplatin

→ Paclitaxel/Carboplatin + Tirapazamine

Paclitaxel: 225 mg/m² & Carboplatin: AUC = 6
Tirapazamine: 260 (1ˢᵗ cycle) → 330 mg/m²
Four Arm Cooperative Study (FACS) in Advanced NSCLC

→ Irinotecan/Cisplatin

→ Paclitaxel/Carboplatin

→ Gemcitabine/Cisplatin

→ Vinorelbine/Cisplatin

Paclitaxel : 200 mg/m2 & Carboplatin : AUC = 6
## Toxicity Analysis

<table>
<thead>
<tr>
<th></th>
<th>FACS (N=145)</th>
<th>S0003 (N=186)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (gr 4)</td>
<td>102 (69%)</td>
<td>48 (26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Febrile Neutropenia (gr 3-4)</td>
<td>26 (18%)</td>
<td>6 (3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anemia (gr 3-4)</td>
<td>22 (15%)</td>
<td>12 (6.5%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Platelets (gr 3-4)</td>
<td>16 (11%)</td>
<td>14 (8%)</td>
<td>0.270</td>
</tr>
<tr>
<td>Myalgias (gr 3-4)</td>
<td>3 (2%)</td>
<td>11 (6%)</td>
<td>0.084</td>
</tr>
<tr>
<td>Neuropathy (gr 3-4)</td>
<td>5 (3%)</td>
<td>30 (16%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
## Treatment Delivery

<table>
<thead>
<tr>
<th></th>
<th>FACS</th>
<th>S0003</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles delivered (median)</td>
<td>3</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>% receiving &gt; 3 cycles</td>
<td>35 (24%)</td>
<td>100 (54%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% receiving 6 cycles</td>
<td>16 (11%)</td>
<td>68 (36.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% patients dose reduced</td>
<td>pending</td>
<td>26%</td>
<td>--</td>
</tr>
</tbody>
</table>
# Efficacy

<table>
<thead>
<tr>
<th></th>
<th>FACS (N=145)</th>
<th>S0003 (N=182)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>1 (0.7%)</td>
<td>3 (1.6%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>46 (31.7%)</td>
<td>59 (32.4%)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>CR + PR</strong></td>
<td>47 (32%)</td>
<td>62 (34%)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>MST (months)</strong></td>
<td>12</td>
<td>9</td>
<td>NA</td>
</tr>
<tr>
<td><strong>1 year survival</strong></td>
<td>51%</td>
<td>37%</td>
<td>0.009</td>
</tr>
</tbody>
</table>
CONCLUSION

• Variable results are not due to study design or conduct

• Variable results may be due to biologic and/or environmental differences
Pharmacogenetics

• Inherited variations in genes encoding:
  – Drug targets
  – Transport proteins
  – Metabolic enzymes

• And their contribution to the toxicity and/or efficacy of therapeutic agents.
Human Genetic Variation

• Each human person carries millions of normal variations in our DNA
  – Germline = inherited
  – Common variations = polymorphism
  – Stable in person during lifetime
    • except in reproductive organs and with errors in cell division (e.g. cancer)
  – Each parent passes $\frac{1}{2}$ of their variations to their children
Human Genetic Variation

.1 SNP in every 500-1000 nucleotides

.Homo sapiens 99.6-99.8% identical

.Human variation ~0.2 – 0.4% (3 billion nucleotides) gives ~10 million DNA variants

.10% variation between population groups gives 1 million DNA variants
Single Nucleotide Polymorphisms

- A Single substitution in the DNA sequence
  - $A \to C$
  - $A \to T$
  - $A \to G$
Insertion (Deletion)
VNTR (Variable Number Tandem Repeats) Microsatellite

A.

Possible sites of additional repeat insertion.

B.

site of repeat insertion

'new' repeat
Copy Number Variants

- A duplication or deletion involving > 1kb of DNA
- If > 1% in reference population, Copy Number Polymorphism
- Non-homologous end joining
- Non allelic homologous recombination
- Can affect expression levels, function
Polymorphisms can alter function through multiple mechanisms.
Polymorphisms can alter function through multiple mechanisms.
Pharmacogenetics and FDA

Genes involved in PK
- Drug Absorption/Transport
- Activation/Metabolism/Excretion

Genes involved in PD
- Drug mechanism of action.
- targets/downstream effectors

Hematology/Oncology Drugs with FDA label modifications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genetic Variation</th>
<th>Involved in:</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MP and AZA</td>
<td>TPMT</td>
<td>PK</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>PK</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Coumadin</td>
<td>CYP2C9 &amp; VKORC1</td>
<td>PK and PD</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>CYP2D6</td>
<td>PK</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>
Tamoxifen

Approved since 1970s

Used widely in breast cancers - metastatic, adjuvant, prevention

Complex metabolic pathway

Difficult to directly measure drug effects
4-hydroxy: potent - antagonist >100% rel. to E2

3,4-hydroxy: potent - antagonist 100% rel. to E2

4-hydroxy, N-desmethyl: potent - antagonist 100% rel. to E2

Tamoxifen Metabolism

Endoxifen
## Distribution of CYP2D6 alleles in different populations

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>*4</th>
<th>*10</th>
<th>*17</th>
<th>Duplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Caucasians</td>
<td>589</td>
<td>0.207</td>
<td>0.015</td>
<td>--</td>
<td>0.021</td>
</tr>
<tr>
<td>American Caucasians</td>
<td>464</td>
<td>0.181</td>
<td>0.040</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Turkish</td>
<td>404</td>
<td>0.113</td>
<td>0.061</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Chinese</td>
<td>127</td>
<td>0.012</td>
<td>0.700</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Japanese</td>
<td>206</td>
<td>--</td>
<td>0.386</td>
<td>--</td>
<td>0.01</td>
</tr>
<tr>
<td>Malays</td>
<td>107</td>
<td>0.028</td>
<td>0.495</td>
<td>0.005</td>
<td>--</td>
</tr>
<tr>
<td>Koreans</td>
<td>212</td>
<td>--</td>
<td>0.463</td>
<td>--</td>
<td>0.01</td>
</tr>
<tr>
<td>Ethiopians</td>
<td>122</td>
<td>0.012</td>
<td>0.086</td>
<td>0.09</td>
<td>0.136</td>
</tr>
<tr>
<td>Tanzanians</td>
<td>106</td>
<td>0.009</td>
<td>0.038</td>
<td>0.17</td>
<td>0.042</td>
</tr>
<tr>
<td>Zimbabwean</td>
<td>80</td>
<td>0.025</td>
<td>0.056</td>
<td>0.34</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*Bradford et al. Pharmacogenomics 2002, 3: 229-43
CYP2D6 variant genotype and CYP2D6 inhibitors lower Endoxifen levels

Figure 3

N = 80

A Trial where Tamoxifen Outcomes and Germline DNA were collected: NCCTG 89-30-52

Postmenopausal women
Early ER$^+$ breast cancer
541 women accrued

Randomization

5 years of Tamoxifen
5 yrs of Tamoxifen + 1 yr of Fluoxymesterone (10 mg po bid)

5 years total therapy
Relapse-free Survival

**CYP2D6 and tamoxifen**

Convincing association between *CYP2D6* genotype/phenotype with tamoxifen-related outcome

*CYP2D6* testing commercially available

Proposal to update tamoxifen label to incorporate *CYP2D6* testing

No clinical guidelines or algorithm on management of patients with intermediate or poor metabolizer phenotypes

- *Increase dose?*
- *Use alternative agent (eg aromatase inhibitor)?*
Metabolism of Tamoxifen
Bridging studies

• Supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region

• Additional pharmacokinetic information may be included
Pharmacogenomics

The convergence of advances in pharmacogenetics and human genomics
Incorporating Pharmacogenomics into Clinical Care

- **Prognostic Predictors**
  - Somatic and germline genome
  - Dictate tumor behavior

- **Efficacy Predictors**
  - Somatic genome
  - Dictate tumor sensitivity

- **Toxicity Predictors**
  - Germline genome
  - Dictate patient sensitivity

- **Exposure Predictors**
  - Germline genome
  - Dictate drug exposure
Ethnic sensitivity (FDA E5)

- Nonlinear pharmacokinetics
- Steep dose-response curve for efficacy and safety
- Narrow therapeutic window
- Highly metabolized, especially through a single pathway (drug-drug interaction)
- Metabolism by enzymes known to show genetic polymorphism
- Prodrug, with the potential for ethnically variable enzymatic conversion
- High intersubject variation in bioavailability
- Low bioavailability, thus more susceptible to dietary absorption effects
- High likelihood of use in a setting of multiple co-medications
- High likelihood for inappropriate use e.g., analgesics and tranquilizers
Issues in using race/ethnicity to study drug response

- Social, cultural and political classification
- Correlation with geographical location
- Correlation with population genetic structure (ancestry)
- Issues of self reporting
- Population admixture
- Do genetic factors affect ethnic/racial groups similarly?