Genomics in patients with Japanese Ancestry

Yoshiaki Uyama, Ph.D.
Pharmaceuticals & Medical Devices Agency (PMDA)
Visiting Professor, Graduate School of Medicine, Chiba University
Visiting Professor, Graduate School of Medicine, Nagoya University
Examples of PGx implementation
-Ethnic differences-
CBZ-induced SJS/TEN & HLA-B*1502
CBZ-induced SJ S/TEN & HLA-B*1502

- HLA-B*1502 screening could provide a benefit in countries, in which HLA-B*1502 is relatively prevalent

<table>
<thead>
<tr>
<th></th>
<th>HLA-B*1502-positive with alternative medication (N=215)</th>
<th>HLA-B*1502-Negative with CBZ (N=4120)</th>
<th>Estimated historical incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ-induced SJ S/TEN</td>
<td>0% (0/0)</td>
<td>0% (0/0)</td>
<td>0.23%</td>
</tr>
</tbody>
</table>


- However, CBZ-induced SJ S/TEN patients carrying HLA-B*1502 have not been found in Japanese

Biomarker for CBZ-induced SJS/TEN in Japanese

- In Japanese, association with a different allele, HLA-A*3101, has been reported
  
  Ozeki T et al, Human Molecular Genet, 2010

- Interestingly, similar results were found in European population
  
Results of Genome-Wide Association Study (GWAS) in Japanese population

- **HLA-A*3101** is associated with CBZ-induced serious cutaneous adverse events including SJS/TEN

The association with **HLA-B*1502** is revealed in Han-Chinese, but **not in Japanese**

Clinical meaningfulness of **HLA-A*3101** on patient selections is still unknown
Other Examples
Higher EGFR mutation rate in Asian population

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>30–40%</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>5–10%</td>
</tr>
</tbody>
</table>

Mitsudomi T et al., Cancer Sci. 12:1817-24, 2007

Higher efficacy of gefitinib has been confirmed in non-small cell lung cancer patients with EGFR mutation, mainly in Asian population

Irinotecan & UGT1A1 Alleles

- Higher prevalence of UGT1A1*6 (lower activity) in Japanese
- The Japanese Label includes the information of *6 in addition to *28

Kaniwa N et al. Drug Metab Dispos (2005)

*6: 0%
*28: 44.6%

*6: 17.1%
*28: 10%
Comparison of the label between Japan and US
Comparing grading levels of the contexts between Japan and the US

Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012
## Examples of grading differences of drug/BM-context between Japan and the US

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene/Marker</th>
<th>Japan</th>
<th>USA</th>
<th>Possible reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>CYP2C9</td>
<td>Information only</td>
<td>Indication and Usage</td>
<td>Clinical evidence in Japanese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Clinical Pharmacology)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*1502</td>
<td>Information only</td>
<td>Boxed Warning</td>
<td>Genetic difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Other precaution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>DPD</td>
<td>Information only</td>
<td>Contraindication</td>
<td>Genetic difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Other precaution)</td>
<td></td>
<td>Availability of diagnostic agent</td>
</tr>
</tbody>
</table>

Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012
## Factors to cause similarities/differences

<table>
<thead>
<tr>
<th></th>
<th>Number of contexts with grading difference (%)</th>
<th>Number of contexts without grading difference (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ME (n = 30)</td>
<td>24 (80%)</td>
<td>6 (20%)</td>
<td>0.0048</td>
</tr>
<tr>
<td>PT (n = 18)</td>
<td>6 (33%)</td>
<td>12 (67%)</td>
<td></td>
</tr>
<tr>
<td>Others (n = 6)</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of biomarker use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy (n = 21)</td>
<td>7 (33%)</td>
<td>14 (67%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Safety (n = 33)</td>
<td>26 (79%)</td>
<td>7 (21%)</td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic area</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology (n = 20)</td>
<td>7 (35%)</td>
<td>13 (65%)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Others (n = 34)</td>
<td>26 (76%)</td>
<td>8 (24%)</td>
<td></td>
</tr>
<tr>
<td><strong>Year of outcome in Japan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1993 (n = 18)</td>
<td>16 (89%)</td>
<td>2 (11%)</td>
<td>0.0104</td>
</tr>
<tr>
<td>1994 - 2003 (n = 11)</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
<td></td>
</tr>
<tr>
<td>After 2004 (n = 25)</td>
<td>11 (44%)</td>
<td>14 (56%)</td>
<td></td>
</tr>
<tr>
<td><strong>Company type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU&amp;US-based company (n = 33)</td>
<td>18 (55%)</td>
<td>15 (45%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Japan-based company (n = 21)</td>
<td>15 (71%)</td>
<td>6 (29%)</td>
<td></td>
</tr>
<tr>
<td><strong>PGx evidence for the Japanese in Japanese PIs</strong></td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Data on clinical endpoints (n = 13)</td>
<td>2 (15%)</td>
<td>11 (85%)</td>
<td></td>
</tr>
<tr>
<td>PK data only (n = 6)</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>None (n = 35)</td>
<td>28 (80%)</td>
<td>7 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

Otsubo Y et al, Drug Metab Pharmacokinet, 27: 144-151, 2012
Challenges in PGx-guided drug development & Ethnic factors
PGx-based data evaluation in Multi-Regional Clinical Trials (MRCTs)

Can data in biomarker (+) patients from various regions be considered in a single population?
MRCTs with PGx

- In the era of globalization of drug developments
  - Encourage a sponsor to
    - Use PGx in global clinical trials
    - Include major ethnicities from an early stage of drug developments
    - Discuss with PMDA about a development strategy with PGx

Conduct a confirmatory trial after having grasped impacts of PGx in drug responses
PGx information in a drug label

- What evidence is needed to describe a practical guidance for a safety biomarker, such as dose adjustment and patient selection?
  - Which section and what level of warning?:
    - contraindication, indication, dosage, clinical pharmacology, etc.
    - requirement, recommendation, information only

- How to describe PGx information/data relating to ethnicities?
  - Include more data in a stratified population in terms of race, nationality, and/or ethnicities?
Expanding PMDA Scientific Consultations

Non-Clinical

IND

Pre P-I

Clinical

Phase I

Phase II

End of P-II

Phase III

Pre NDA

Review

NDA

Post-Market

Phase IV

Pre-post marketing

End of Re-evaluation period

Special Consultation on PGx/Biomarker Qualification

Pharmaceutical Affairs Consultation

Prior-Assessment Consultation

Revised from Figure by Ichimaru K et al, Clin Pharmacol Therapeut, 88: 454-457, 2010
Advancing Regulatory Science

Stronger & More Complete Regulatory Science Bridge will help us for the future drug developments

- SMART Global -

- Sharing data/experiences/knowledge globally

- Managing projects/issues globally

- Advancing regulatory science globally

- Respect for other idea/views globally

- Transparent process globally

WORKING TOGETHER FOR PATIENTS
Information

- PMDA HOMEPAGE (English)

- E-mail:
  uyama-yoshiaki@pmda.go.jp

Thank you for your attention