Pharmacogenomics of Chemotherapy induced nausea & vomiting

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Dr Sandip Mukhopadhyay

• MBBS, Burdwan University (1995) Gold medal in Pharmacology
  • MD in Pharmacology, Christian Medical College-Ludhiana
  • Fellowship in Palliative Medicine – IPM-Calicut

• Assistant Professor of Pharmacology & Coordinator of Pharmacovigilance at Burdwan Medical College

• Research interest of supportive Oncology

• Received 8 international awards in last five years

• “Young Investigator” 2017 by the “Multinational Association of Supportive Care in Cancer (MASCC)” in Washington DC, USA to receive his award

• “MASCC Ambassador” for India 2017-18 for Supportive care
Conflict of interest

• None
Overview

• Introduction
• Pharmacogenomic angles in CINV
  – Background sensitivity
  – PGx of antiemetics
  – PGx of chemotherapy drugs
  – PGx of Opioids
• Implementing PGx strategies
  – Success of PGx in CINV
  – The grey areas
  – Barriers in implementation
• Future direction
• Conclusions
"Here's my sequence..."

New Yorker, 2000
• **Pharmacogenetics** - alteration of drug action due to single gene

• **Pharmacogenomics** - alteration of drug action due to effect of number of genes (genome)

• Because drug responses - determined by multiple proteins, rather than single proteins
  – Recent trends - *shifted from pharmacogenetics to pharmacogenomics.*
Cell → Chromosome → DNA → Gene

https://kintalk.org/genetics-101/
Normal Gene

Mutated Gene

Normal Protein

Abnormal Protein

No Protein

https://kintalk.org/genetics-101/
Why?

- Growing research in genomics - now explained many areas in the health including cancer treatment
- Genomic input - possible in supportive care/ CINV

Unable to explain the grey areas
Pharmacogenetic angles in CINV

Background Genomic sensitivity

PGx of Chemotherapeutic drugs

PGx of Antiemetics

PGx of Opioids
Background genomic sensitivity

- BRCA gene mutation
- Low expression of BRCA gene protein

Less CINV
Pharmacogenomics of Antiemetic drugs
Antiemetic drugs act commonly on:

- Serotonin
- Neurokinin
- Dopamine

Possible PGx angles:

- Receptors
- Transporters
- Metabolizing enzymes
A. Pharmacogenetic prediction from metabolizing enzyme
Biotransformation

Inactive drug ➔ Active drug

Active drug ➔ Inactive drug

Active drug ➔ Active metabolite
Phases of biotransformation

**Phase 1**
Non-synthetic reaction

**Phase 2**
Synthetic reaction
• CYP 3A4
• CYP 1A1
• CYP2D6
• CYP2C9
• CYP 2C19
• CYP2E1
# 5HT3RA metabolism by CYP

<table>
<thead>
<tr>
<th>5HT₃-RA</th>
<th>Major P450(s)</th>
<th>Minor P450(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolasetron (a prodrug, must be converted to reduced dolasetron by carbonyl reductase)</td>
<td>CYP2D6</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Granisetron</td>
<td>CYP3A</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>No dominant P450</td>
<td>CYP1A1, CYP1A2, CYP2D6, CYP2E1, CYP3A4</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>CYP2D6</td>
<td>CYP3A, CYP1A2</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>CYP2D6</td>
<td></td>
</tr>
<tr>
<td>Tropisetron</td>
<td>CYP2D6</td>
<td></td>
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</table>

Trammel, et al, 2013
CYP 2D6 genetic variation

- 100+ documented alleles
- number of variants more common in different ethnicities
- Duplications, deletions, or rearrangement constitutes a major source of interindividual variation in the human genome
- Normal Function- CYP2D6*1, *2

https://www.pharmvar.org/gene/CYP2D6
CYP2D6 phenotype

Poor metabolizer (PM)
- *3
- *4, *5 (deletion)
- *6
- Non functioning allele

Intermediate metabolizer (IM)
- *29
- Decreased activity

Extensive metabolizer (EM)
- *1
- *2

Ultra rapid metabolizer (UM)
- Northeast Africa, Oceania, including the Saudi Arabian-20%
- Black Ethiopian populations- 29%
- Caucasians - 1 to 10%

CYP2D6 activity
- None
- Low
- Normal
- High
Prospective cohort study

N= 270, five emetogenic level

CINV prophylaxis with Ondansetron & tropisetron

CYP2D6 genotyping

Plasma tropisetron concentration

Acute emesis (0-24 hours)

- Two time frames
  - 0-4 hr
  - 5-24 hr
• **CYP2D6 genotyping**
  
  – Poor metabolizer - (7.8%)- No functional allele
  
  • *Tropisetron serum conc.* (6 hours after administration) ↑↑
  
  – Extensive metabolizers – (58.1%)- two active alleles
  
  – Ultra rapid metabolizer- (1.58%) - 3 alleles
Mean values (SD) of vomiting as function of number of active CYP2D6 genes

Patients with three active genes had significantly more vomiting at both observation periods than all other patients ($P < .001, P < .03$)
Tropisetron Vs. Ondansetron
(Number of functional gene with & N & V)
• Ondansetron
• Partly metabolized by CYP3A4
  -CYP 3A4 - relatively more stable
“Because of the low frequency (1.5% to 2%) of genetically defined UM in the German population, it would be necessary to genotype approximately 50 patients for CYP2D6 to prevent one case of severe vomiting or nausea”
• Higher proportion of UM other regions - may influence the efficacy of antiemetic treatment in cancer patients

• Genotyping for CYP2D6
• before start of the chemotherapy or
• use of alternative antiemetic drugs not metabolized by CYP2D6
  - may further ↓ CINV
CYP3A4 pharmacogenetics
Aim: to clarify genetic polymorphism effects in the three main races in Malaysia i.e., Malay, Chinese and Indian, on the clinical antiemetic effects of granisetron.

- Prospective observational study, breast cancer patients
- n=158
- CINV in the first 24 hours after chemotherapy administration

High CINV in Chinese- linked to CYP3A4 polymorphism

Penang, Malaysia
“…Chinese patients with breast cancer should be treated with a different type of 5-HT3RA such as tropisetron and dolasetron, since they are predominantly metabolized by CYP2D6 only” (Hassan et al, 2011)
B. Pharmacogenetic prediction from transport proteins
# ABCB1 transporter

<table>
<thead>
<tr>
<th>Author</th>
<th>Gene</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babaoglu et al., 2005</td>
<td>ABCB1 transporter</td>
<td>3435C &gt; T associated with treatment efficacy</td>
</tr>
<tr>
<td>He et al., 2014</td>
<td>ABCB1 transporter</td>
<td>3435C &gt; T associated with <strong>higher risk for CINV</strong></td>
</tr>
<tr>
<td>Perwitasari et al., 2011</td>
<td>ABCB1 transporter</td>
<td>CTG haplotype associated with <strong>higher delayed phase CINV</strong></td>
</tr>
<tr>
<td>Zoto et al., 2015</td>
<td>ABCB1 transporter</td>
<td>3435TT variant with <strong>significantly less CINV</strong></td>
</tr>
</tbody>
</table>
OCT1

<table>
<thead>
<tr>
<th>Author</th>
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<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzvetkov et al., 2012</td>
<td>OCT1</td>
<td>May increase efficacy of tropisetron (Navoban®) by limiting hepatic uptake</td>
</tr>
</tbody>
</table>

Present status:
No validated chip available for routine clinical use for transporters
C. Pharmacogenetic prediction from CINV- the Pharmacodynamic angle
Genetic variation of receptor
No antagonist function

CINV

Antagonist Drug

Enhanced cellular activity

Abnormal 5HT receptors

Normal receptor function

Codes for 5HT receptors
<table>
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<th>Author</th>
<th>Drug</th>
<th>Gene</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser et al.</td>
<td>Tropisetron (n=242)</td>
<td>5-HT3A receptor</td>
<td>21 polymorphism No significant association with CINV</td>
</tr>
<tr>
<td>(2004)</td>
<td>Same</td>
<td>5-HT3B gene</td>
<td>13 polymorphism 30% of the patients suffered from CINV</td>
</tr>
<tr>
<td>Fasching et al.</td>
<td>Ondansetron (n=120)</td>
<td>5-HT3C receptor</td>
<td>Variant genotype of K163 N was associated with vomiting (RR = 2.62)</td>
</tr>
<tr>
<td>(2008),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremblay et al.</td>
<td>Ondansetron &amp; tropisetron (n=286)</td>
<td>5-HT3B gene</td>
<td><strong>5-HT3B receptor gene may serve as genetic predictor</strong> for anti-emetic therapy with the _AAG deletion variant (OR = 32). after adjusted with other risk factors of emesis.</td>
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<tr>
<td>Author</td>
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<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hammer et al. (2010)</td>
<td>Ondansetron n=110 Ca Breast (EC/ E chemo-Rx)</td>
<td>HTR3A, HTR3B, HTR3D and HTR3E</td>
<td>Along with previously identified HTR3 polymorphisms, the <strong>HTR3D polymorphism</strong> may be a <strong>predictor of CINV</strong>. G allele of <em>HTR3D p.G36A</em> - over-represented in nonresponders - individual risk predictions</td>
</tr>
<tr>
<td>Ward et al., 2008</td>
<td>Dolasetron or tropisetron (n=70)</td>
<td>5-HT3C, 5-HT3B, CYP 2D6</td>
<td><strong>No SNPs significant</strong> One patient with polymorphism and higher CINV</td>
</tr>
</tbody>
</table>
NK1 receptor gene

- **TACR1 gene**
  - tachykinin receptor 1 (also known as neurokinin 1 receptor or substance P receptor)
- *Not been examined in relation to CINV*

- Laugsand *et al.*
  - genotyped ten SNPs
  
  However, *none of the investigated SNPs was significantly associated with nausea and vomiting*
Pharmacogenetics of anticancer drugs- partial linkage

Pharmacogenetics of opioid-induced nausea & vomiting during chemotherapy
: Needs further evaluation
Implementing PGx strategies in CINV
• The clinical implementation process has 3 distinct phases:
  – pre-implementation,
  – developmental, and
  – clinical implementation stage.
• Research and finding solutions to challenges:
  – required within each phase
• In addition, suitable and feasible solutions are required to overcome education, ELSI, reimbursement, and scientific barriers
Success

• Acute emesis link
  • 5HT3B gene – Pharmacodynamic modulation
  • CYP2D6 – Metabolism modulation
  • CYP3A4 – Metabolism modulation
  • ABCB1 (Pgp) - Transporter

• Data about all 1st generation 5HT3RA (ondansetron, tropisetron, dolasetron, granisetron)
The grey areas

• Little or no data
  • Delayed emesis
  • Dopamine receptor & CINV
  • Palonosetron
  • NK1 antagonist
  • Olanzapine

• Studies- mostly on candidate gene approach
• Small study population
• Isolated patients (e.g. breast cancer)
• Animal models- difficult pre-clinical research
Barriers for Clinical Implementation of PGx

- **IT infrastructure** (infrastructure, IT PGx integration)
- **Scientific** (e.g. turnaround time of PGx test, gene-drug pair selection)
- **Educational** (awareness)
- **Ethical, regulatory, legal issues**
Barriers for Clinical Implementation

- Translation of data into clinical practice
- Cost
- Availability of test facility
- No valid tests for transporters and receptors for routine use
- High expectations
Complex Phenotypes – What Can We Expect?

Few genes and environmental factors each contributing a large risk

Many genes and environmental factors each contributing a small risk
An individualized antiemetic treatment algorithm using the cytochrome P450 (CYP) 2D6 genotype

Trammel et al, 2013

Diagram:

1. Diagnosis
2. Treatment with a Highly or Moderately Emetic Risk Chemotherapy according to ASCO, MASCC, ESMO and NCCN guidelines
3. CYP2D6 Genotyping
4. UM
   - Consider using maximum doses of the 5HT\textsubscript{3}-RA
   - Moderate Emetic Risk: Consider using NK\textsubscript{1}-RA and corticosteroids
5. IM, EM
   - Consider not using 5HT\textsubscript{3}-RAs
   - High Emetic Risk: Consider using 3-day aoptiant course and larger doses of corticosteroids
6. PM
   - Continue with ASCO, MASCC, ESMO and/or NCCN Guidelines for Anti-Emetic 5HT\textsubscript{3}-RA Dosing
   - Consider using a reduced dose of 5HT\textsubscript{3}-RAs to avoid toxicities

Curr Oncol Rep
DOI 10.1007/s11912-013-0312-x
Future perspective

• Interindividual differences in susceptibility to CINV-partly explained

• Tech support- Next-generation DNA sequencing-revolutionary

• Necessary to shift the research paradigm in CINV from a candidate gene approach to GWAS (Genome wide association studies)
  – Number of genes in the human genome exceeds 20,000, and the number of SNPs might be hundreds to thousands times larger
Conclusion

Advances in pharmacogenetics and pharmacogenomics related to CINV will contribute to future personalized cancer therapy strategies
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