Individualized Treatment in Breast Cancer

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Outline
- Impact of pharmacogenomics on drug therapy
- Application of gene-expression profiling in the treatment of breast cancer
- Future development of breast cancer treatment

What is Pharmacogenomics?
- Genomic-wide analysis of genetic determinants of drug efficacy and toxicity ⇒ Identification of drug targets
- Differ from pharmacogenetics = study of causes of individual variations in drug response due to genetic variation which usually looks at a few genes of interest at most
Why is pharmacogenomics important

We are all different...
- Most of us are treated in the same way
- Trial and error indicated that majority of us do not respond in the same way to the same therapy

Pharmacogenomics attempt to understand why people respond differently to different drugs.

Solution: Personalized Medicine

- Increase response rate
- Minimize adverse event

Y = f (X)

Optimal responders  Suboptimal responders  Non-responders

Genetic information (X)

Adapted from W. Tong 2007

Individualized Drug Therapy

- Select the Right dose of the Right drug to the Right patient at the Right time

Goal:
- Increase efficacy
- Decrease ADRs

Challenges:
- Extrinsic factors – environmental (smoking, diet, alcohol); drug interactions
- Intrinsic factors – demographic, disease, genes and genetic makeup
Genomic Applications in Disease Management

Etiology – Pathophysiology
Occurrence – Risk assessment
Subtypes – Diagnosis
Natural history - prognosis

Response - Pharmacogenomics

Pharmacokinetics
- absorption
- distribution
- metabolism
- elimination

Pharmacodynamics
- drug targets
- therapeutic effects

GENETIC POLYMORPHISMS

Pharmacokinetic
- Transporters
- Metabolism

Pharmacodynamic
- Receptors
- Ion channels
- Enzymes
- Immune molecules

Pharmacokinetics is the study of what the body does to a drug
Pharmacodynamics is the study of what a drug does to the body

Impact of Pharmacogenomics in Drug Therapy

- Drug metabolism
  - Phase I metabolism
  - Phase II metabolism
- Drug transport
  - Drug absorption
  - Drug distribution
  - Drug elimination
- Drug targets
  - Pharmacologic action of the drug in the body driven by receptors, enzymes, etc.
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Pharmacokinetics is the study of what the body does to a drug.

Drug metabolism in liver cells

Phase I
- UPTAKE
- OXIDATION
- CONJUGATION
- EXPORT

Phase II
- Substance
- Oxidized substance
- Conjugate
- Export

Impact of Pharmacogenomics
Phase I Drug Metabolism

- Key enzymes = CYP450 2D6, 2C19, 2C9
- Genetic basis: mutation of CYP subtype alleles
- Phenotypic classification into poor, intermediate, extensive or ultrarapid metabolizers resulting in different drug clearance & optimal dose for efficacy
- Examples:
  - 2D6 – Tamoxifen, TCA, antipsychotics, β-blockers, opioid analgesics
  - 2C19 – proton pump inhibitors (e.g. omeprazole)
  - 2C9 – warfarin, phenytoin, NSAIDs, oral hypoglycemics
CYP2D6 and Tamoxifen

- Tamoxifen is a “pro-drug” requiring metabolic activation for pharmacologic activity
- CYP2D6 is a rate-limiting enzyme catalyzing the conversion of tamoxifen into active metabolites with significantly greater affinity for the estrogen receptor ⇒ cell inhibition

Impact of Pharmacogenomics

Phase II Drug Metabolism

- Key enzymes = UDP-glucuronyl transferase (UGT1A1), N-acetyltransferase (NAT-2)
  - Facilitate for export or elimination
- Genetic basis: homozygous or heterozygous genotype expression
- Phenotypic classification into slow & rapid inactivators resulting in different drug clearance & optimal dose for efficacy
- Examples:
  - UGT1A1 – irinotecan
  - NAT-2 – isoniazid

UGT1A1 and Irinotecan

Dervieux T et al. Mutation Res. 573:160, 2005
UGT1A1*28:
The most common variant

Phenotype:
- Reduced gene expression
- Reduced glucuronidation and SN38 detoxification

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<th>Allele</th>
<th>Caucasian</th>
<th>Asian</th>
<th>African</th>
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<tr>
<td>UGT1A1*28 (TA)</td>
<td>61.2%</td>
<td>84%</td>
<td>47%</td>
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<tr>
<td>UGT1A1*28 (TA)</td>
<td>30.7%</td>
<td>16%</td>
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</tbody>
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Clinical Outcomes of UGT1A1 Expression


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Transporters’ Function on Pharmacokinetics and Tissue Drug Levels

Impact of Pharmacogenomics Drug Transport

- Facilitated by drug transporters
- Efflux and influx transporters
  - e.g. P-gp, OCT1
- Affect pharmacokinetics of drug molecules
  - Absorption – intestinal epithelial membrane
  - Distribution – blood brain barrier
  - Metabolism – sinusoidal membrane to move drugs in and out of hepatocytes
  - Elimination – renal tubules

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Pharmacodynamics is the study of what a drug does to the body.
Impact of Pharmacogenomics

Drug Targets
- Drug targets = any protein involved in the pharmacological action of the drug, such as receptors, enzymes, signal transduction proteins, etc.
  - Her-2 predicts response to trastuzumab
- Genetic polymorphisms in drug targets contributes to variable drug response
  - EGFR mutation predicts response to erlotinib
  - VKORC1 (vitamin K epoxide reductase complex 1) variants result in lower therapeutic warfarin dose

Impact of Pharmacogenomics on Drug Therapy

Examples
- Cardiovascular
  - Anticoagulant
  - Antihypertensives
  - Heart failure
  - Statins
- HIV
- CNS
- Transplantation
- Oncology

Impact of Pharmacogenomics in Oncology

- Efficacy pharmacogenomics
  - Prediction of drug efficacy based on patient’s or tumor’s genetic profile with routinely applicable genetic tests and easily accessible test samples
- Safety pharmacogenomics
  - Prediction of drug toxicity based on a patient’s genetic profile
Efficacy Pharmacogenomics in Oncology
- Early identification of responders to potential increase treatment success
- Decrease risk of toxicity and drug resistance in non-responders
- Select most appropriate treatment
- Examples:
  - Trastuzumab (Herceptin) – Her-2
  - Erlotinib (Tarceva) – EGFR mutation
  - Platinum compounds – ERCC-1

Safety Pharmacogenomics in Oncology
- Identification of at risk individuals
  - Decrease drug toxicity and related complications, morbidity and mortality
  - More appropriate dosing, potentially increase dose intensity by lessen chance for dose delay and/or dose reduction
  - Decrease direct and indirect treatment costs
- Examples:
  - Irinotecan – UGT1A1
  - 5-fluorouracil – dihydropyrimidine dehydrogenase (DPD)

Impact of Pharmacogenomics on Breast Cancer Management
- Biomarkers at Diagnosis
  - Prognosis
  - Treatment
  - Follow-ups
### Impact of Pharmacogenomics on Breast Cancer Treatment

**Biomarkers**
- ER/PR, Her-2
- Treatment selection and prognosis prediction

**Gene-expression Assays in early stage breast cancer**
- TAILORx trial – OncotypeDX 21-gene assay  
  - Stage I ER+ and stage II ER+, Node neg
- MINDACT trial – MammaPrint 70-gene assay  
  - Stage I & II, age less than 61 yrs, ER+ or -

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### Impact of Pharmacogenomics on Breast Cancer Treatment

**Her-2 and Topoisomerase II**
- HER-2 overexpression effect on anthracycline sensitivity and dose-response remains inconclusive
- Topoisomerase II alpha protein overexpression is associated with increased anthracycline sensitivity
- Amplification of TOP2A gene is associated with sensitivity of metastatic breast cancer to anthracycline
- Her-2 and TOP2A are not amplified together 50% of the time
- Her2/TOPO2A coamplified tumors may be the best predictors?

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**MD Anderson Experience**
- N = 74 stage I – III breast cancer
- 30-gene expression pharmacogenomic test was used at diagnosis to calculate pharmacogenomic score
- Post-neoadjuvant chemo (T/FAC), a residual cancer burden (RCB) score was calculated based on residual tumor & LN features
- The classification of the RCB scores were labeled using the classification of pCR (pathologic clinical response) & RD (residual disease) to predict response to chemo
- Four RCB classes: RCB-0 (pCR), RCB-I (near-pCR), RCB-II (mod RD), & RCB-III (ext RD)
- Results: Pharmacogenomic test correctly predicted RD in 75% of RCB-0/I & 92% of RCB-III subjects

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What lies in front of us in the pipeline?

- Microtubule-associated protein tau predicts sensitivity to taxane
- CDK10 protein maintains sensitivity to hormonal therapy
- Genetic polymorphisms of CYP2B6 affecting the pro-drug cyclophosphamide activation
- DNA repair enzyme XRCC1 to predict treatment outcome of anthracycline and CMF-based chemotherapy in invasive breast cancer
- ?????

Summary

- Pharmacogenomics will continue to play a significant role in the treatment of cancer.
- Personalized medicine will alter/improve the treatment of cancer in many ways.
- It is pertinent that we keep abreast with the development of pharmacogenomics to optimize the care of oncology patients.