Pharmacogenomics and Individualized Therapy: Current Issues in Oncology

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Relevant Disclosures

Grant/Research support:
- Myriad Genetics
- Merck Pharmaceuticals

Countless stash of pens, notepads, tote bags, coffee cups, blankets and stress balls from all types of drug manufacturers
Objectives

- Review examples of pharmacogenomic influence on therapy in the treatment of oncology patients
- Describe ongoing efforts to facilitate CYP2D6 genotyping into the selection of hormonal agents for the treatment of ER positive breast cancer
- Explain the importance of UGT1A1 and drug transporter polymorphisms as they relate to the efficacy and toxicity of irinotecan
- Discuss future implementation strategies for pharmacogenomics and individualized therapy
All patients with same diagnosis

Standard therapy
Responders and Patients Not Predisposed to Toxicity

Alternate therapy
non-responders and toxic responders
Individualizing Treatment in Oncology

Germline pharmacogenomics
- TPMT deficiency with thiopurines
- **CYP2D6 polymorphisms with tamoxifen**
- **UGT polymorphisms with irinotecan**
- CYP2C9 and VKORC1 variants with warfarin
- COMT and MDR-1 genotype with morphine

Tumor DNA
- Oncotype Dx and MammaPrint for Breast Cancer
- KRAS mutations in colorectal cancer

Therapeutic drug monitoring
- Busulfan in SCT
- **Fluorouracil in colorectal cancer**
The Tamoxifen Story…

Why do approximately 35% of patients with ER positive breast cancer NOT respond to tamoxifen?
Patient Case

- 40 yo premenopausal AA female
- PMH: depression x 3 years
- Current medications:
  - Paroxetine 20 mg PO daily

Problem:
- ER+, PR+, Her2- 1.2 cm infiltrating ductal carcinoma of the right breast, node negative
- Oncotype Dx Recurrence Score is 10 (low risk)

Treatment plan:
- Tamoxifen 20 mg PO daily x 5 years
Oncotype Dx: the Genes

**Proliferation**
- Ki-67
- STK15
- Survivin
- Cyclin B1
- MYBL2

**Estrogen**
- ER
- PR
- Bcl2
- SCUBE2

**Invasion**
- Stromelysin 3
- Cathepsin L2

**HER-2**
- GRB7
- HER-2

**GSTM1**

**BAG1**

**CD68**

**Reference**
- Beta-actin
- GAPDH
- RPLPO
- GUS
- TFRC

RS = + 0.47 × HER-2 group score
- 0.34 × ER group score
+ 1.04 × proliferation group
+ 0.10 × invasion group score
+ 0.05 × CD68
- 0.08 × GSTM1
- 0.07 × BAG1

<table>
<thead>
<tr>
<th>Category</th>
<th>RS (0 – 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>RS &lt; 18</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>RS ≥ 18 and &lt; 31</td>
</tr>
<tr>
<td>High risk</td>
<td>RS ≥ 31</td>
</tr>
</tbody>
</table>
Oncotype Dx: Chemotherapy Benefit

![Graph showing the relationship between recurrence score and 10-year distant disease recurrence rate for Tamoxifen (Tam) and Tamoxifen + chemotherapy (Tam + chemo). The graph indicates a lower recurrence rate for Tam + chemo compared to Tam across different recurrence scores.](image-url)
Patient Case

40 yo premenopausal AA female
PMH: depression x 3 years
Current medications:
  – Paroxetine 20 mg PO daily

Problem:
  – ER +, PR+, Her2 - 1.2 cm infiltrating ductal carcinoma of the right breast, node negative
  – Oncotype Dx Recurrence Score is 10 (low risk)

Treatment plan:
  – Tamoxifen 20 mg PO daily x 5 years
## Patient Case CYP2D6 Genotype

<table>
<thead>
<tr>
<th>Tests Ordered</th>
<th>RESULT</th>
<th>FLAG</th>
<th>UNITS</th>
<th>REFERENCE INTERVAL</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen 2D6 Genotyping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 Allele 1:</td>
<td>*17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 Allele 2:</td>
<td>*17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LabCorp Burlington**

1447 York Court
Burlington, NC 27215-3361

**Phone:** 800-735-4087

**Account Number:**
919-966-4408

**Address:**
Dept Of Molecular Genetics
UNC Chapel Hill Dr Weck
101 Manning Drive
CHAPEL HILL NC 27514
Tamoxifen Metabolism

J Natl Cancer Inst. 2003;95:1758
Endoxifen: Updated findings

Endoxifen…
- Decreases ERα protein levels via targeting it for proteosome degredation
- Blocks estrogen response element (ERE) activation thus blocking ERα transcriptional activity
- Inhibits estrogen-induced breast cancer cell proliferation in the presence of tamoxifen and metabolites

Effects are concentration dependent
- Greater benefit if 10-1000 nM
- EM’s produce 90 +/-40 nM, IM’s 40-60 nM
- PM’s < 30 nM

Cancer Res. 2009;69:1722-7
Approximately 10% of Caucasians have a loss of CYP2D6 activity
- Most important allele is CYP2D6*4
- Can classify patients:
  - Ultra-rapid metabolizer (UM)
  - Extensive metabolizers (EM)
  - Intermediate metabolizers (IM)
  - Poor metabolizers (PM)

Many other drugs affect CYP2D6
- Potent inhibitors: fluoxetine and paroxetine
- Moderate inhibitors: sertraline, cimetadine, amiodarone and haloperidol
Gene Polymorphisms: CYP2D6

- **No change in activity**
  - CYP2D6*1
  - CYP2D6*2
  - CYP2D6*33
  - CYP2D6*35

- **Reduced activity**
  - CYP2D6*9
  - CYP2D6*10
  - CYP2D6*17
  - CYP2D6*29
  - CYP2D6*36
  - CYP2D6*37
  - CYP2D6*41

- **No activity**
  - CYP2D6*3-*8
  - CYP2D6*11-*16
  - CYP2D6*18
  - CYP2D6*19
  - CYP2D6*20
  - CYP2D6*38
  - CYP2D6*40
  - CYP2D6*42
  - CYP2D6*44
## CYP 2D6 Polymorphisms

<table>
<thead>
<tr>
<th>Allele</th>
<th>Enzyme Activity</th>
<th>Caucasian</th>
<th>African American</th>
<th>Japanese</th>
</tr>
</thead>
<tbody>
<tr>
<td>*4</td>
<td>None</td>
<td>18-23%</td>
<td>7-9%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*5</td>
<td>None</td>
<td>2-4%</td>
<td>6-7%</td>
<td>5-6%</td>
</tr>
<tr>
<td>*6</td>
<td>None</td>
<td>1%</td>
<td>&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>*10</td>
<td>Reduced</td>
<td>4-8%</td>
<td>3-8%</td>
<td>39-41%</td>
</tr>
<tr>
<td>*17</td>
<td>Reduced</td>
<td>N/A</td>
<td>15-34%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Pharmacogenomics 2002; 3:229-243
CYP 2D6 and Endoxifen

CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

J Natl Cancer Inst. 2003;95:1758
Genotype and Drug Effects on CYP2D6

J Natl Cancer Inst. 2003;95:1758
Monogenic Example Affecting Drug Metabolism

- Identify the pathway of drug metabolism most likely to affect efficacy and/or toxicity
- Investigate relevant polymorphisms in genes controlling this pathway
- Correlate polymorphism with PK/PD

**Conduct a retrospective trial**
- Establish connection between genetic polymorphism and clinical endpoint

**Conduct a prospective trial**
- Determine optimal treatment for patients of varying genotypes
Association Between CYP2D6 and Outcomes

- Retrospective analysis of 1325 patients who received tamoxifen for early stage breast cancer

- Genotypes assessed (German and US population)
  - Reduced function: *10, *41
  - Absent function: *3, *4, *5
  - Classified as EM, heterozygous EM/IM, or PM

- Endpoints (median follow up 6.3 years)
  - Time to disease recurrence
  - Event-free survival
  - Disease-free survival
  - Overall survival

JAMA. 2009;302(13):1429-1436
Patients who are \textbf{PM} had \textbf{SHORTER} time to disease recurrence compared with patients with \textbf{EM} patients.

\textit{JAMA. 2009;302(13):1429-1436}
Adjuvant Tamoxifen and CYP2D6 Trials

CYP2D6 associated with recurrence
- Goetz et al. 2005, 2007 (USA)
- Schroth et al. 2007, 2009 (Germany)
- Kiyotani et al. 2008 (Japan)
- Newman et al. 2008 (UK)
- Xu et al. 2008 (China)
- Okishiro et al. 2009 (Japan)
- Ramon et al. 2009 (Spain)
- Bijl et al. 2009 (Netherlands)

CYP2D6 not associated with recurrence
- Wegman et al. 2005, 2007 (Sweden)
- Nowell et al. 2005 (USA)
Monogenic Example Affecting Drug Metabolism

- Identify the pathway of drug metabolism most likely to affect efficacy and/or toxicity
- Investigate relevant polymorphisms in genes controlling this pathway
- Correlate polymorphism with PK/PD
- Conduct a retrospective trial
  - Establish connection between genetic polymorphism and clinical endpoint
- **Conduct a prospective trial**
  - Determine optimal treatment for patients of varying genotypes
LCCC 0801:
Evaluating the Role of Genotype in Tamoxifen Therapy for Breast Cancer

Principle Investigator: Lisa Carey, MD

William Irvin, MD, E. Claire Dees, MD; Francis Collicchio, MD; James P. Evans MD, PhD; David Flockhart, MD, PhD (Indiana University); Howard McLeod, PharmD, Karen Weck, MD, Christine Walko, PharmD
LCCC 0801: Active community participation
Primary Objective

To evaluate the change in endoxifen levels following an increase in tamoxifen dose from 20 mg to 40 mg among patients with intermediate metabolizing CYP2D6 genotypes.

Alleles being assessed
- No change in activity: *2, *33, *35
Study Design

**Initial study visit:**
Menopause Symptom Scale and FACT-b
Blood for genotype and tamoxifen PK collected

**One Week Phone Call:**
Patient is told CYP2D6 status

**EM/EM:** remain on 20 mg PO daily of tamoxifen

**EM/PM, EM/IM, IM/IM, IM/PM, PM/PM:** increase to 40 mg PO daily of tamoxifen

**Four Month Follow-Up:**
Menopause Symptom Scale and FACT-b
Blood for tamoxifen PK
CYP2D6 Allele Frequency

<table>
<thead>
<tr>
<th>Allele Study</th>
<th>*1, *2 EM</th>
<th>*35 EM</th>
<th>*3-6 PM</th>
<th>*9 IM</th>
<th>*10 IM</th>
<th>*17 IM</th>
<th>*29 IM</th>
<th>*41 IM</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCCC 0801 (n=118)</td>
<td>0.48</td>
<td>0.02</td>
<td>0.25</td>
<td>0.02</td>
<td>0.03</td>
<td>0.04</td>
<td>0.02</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>LCCC 0801 AA (n=25)</td>
<td>0.32</td>
<td>0</td>
<td>0.22</td>
<td>0</td>
<td>0</td>
<td>0.18</td>
<td>0.08</td>
<td>0.14</td>
<td>0.06</td>
</tr>
<tr>
<td>LCCC 0801 non-AA (n=93)</td>
<td>0.53</td>
<td>0.02</td>
<td>0.25</td>
<td>0.02</td>
<td>0.03</td>
<td>0.01</td>
<td>0</td>
<td>0.13</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ASCO 2009, abstract #553
## Genotype and Endoxifen

<table>
<thead>
<tr>
<th>Genotype category</th>
<th>N</th>
<th>Median endoxifen baseline (ng/mL)</th>
<th>Median endoxifen 4 months later (ng/mL)</th>
<th>Median intrapatient change from baseline (Interquartile range) (ng/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM</td>
<td>29</td>
<td>34.33</td>
<td>29.23</td>
<td>-1.47 (-28 to 11.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>IM</td>
<td>51</td>
<td>18.45</td>
<td>21.84</td>
<td>7.64 (-0.6 to 23.9)</td>
<td>0.0008</td>
</tr>
<tr>
<td>PM</td>
<td>9</td>
<td>4.18</td>
<td>12.89</td>
<td>6.07 (2.6 to 12.5)</td>
<td>0.0195</td>
</tr>
</tbody>
</table>

4 month EM vs. IM: No statistical difference (p=0.84)

4 month EM vs. PM: Higher in EM (p=0.02)

4 month IM vs. PM: Higher in IM (p=0.02)

SABC 2009, abstract #410
Patient Case

40 yo premenopausal AA female
PMH: depression x 3 years
Current medications:
  – Paroxetine 20 mg PO daily

Problem:
  – ER +, PR+, Her2 - 1.2 cm infiltrating ductal carcinoma of the right breast, node negative
  – Oncotype Dx Recurrence Score is 10 (low risk)

Treatment plan:
  – Tamoxifen 20 mg PO daily x 5 years
How should tamoxifen be dosed in this patient?

1. Tamoxifen 20 mg PO daily
2. Tamoxifen 40 mg PO daily
3. Anastrozole 1 mg PO daily
4. Anastrozole 1 mg PO daily + ovarian ablation
UGT polymorphisms and Irinotecan

Why do some patients develop severe neutropenia and/or diarrhea after receiving irinotecan?
Irinotecan Metabolism

Weak Activity in vitro

**ACTIVE**

**Inactive**
Irinotecan Conclusions

Current Irinotecan package insert warns of increased neutropenia in 7/7 patients and recommends a (non-specified) lower initial dose in these patients

- FDA approved Invader UGT1A1 Molecular Assay to identify UGT1A1*28 patients using peripheral blood

UGT1A1 testing is valuable for predicting risk of hematologic toxicity in patients receiving higher doses of irinotecan (> 200 mg/m^2)

Genotyping may have less utility for patients receiving irinotecan 125 mg/m^2 weekly or 180 mg/m^2 every 2 weeks (FOLFIRI regimen)
Does dose matter?

Relationships between irinotecan dose and incidence of hematologic toxicity by genotype

JNCI. 2007;99:1290-5
Are we underdosing some patients?
Genotype Directed Phase I Trial of FOLFIRI

Standard dose of irinotecan in FOLFIRI
- **180 mg/m²** every 2 weeks
- Dose escalation began at 215 mg/m²

59 patients with metastatic colorectal cancer receiving FOLFIRI first line were enrolled and stratified by genotype
- UGT1A1 *1/*1
- UGT1A1 *1/*28
- Homozygous *28/*28 patients were excluded

Primary objective: Maximum tolerated dose (MTD)
- UGT1A1 *1/*1: **370 mg/m²**
- UGT1A1 *1/*28: **310 mg/m²**

*JCO.* 2010;28(5):866-71
UGT1A1: Meet the family

- 250 Caucasians with metastatic colorectal cancer

- **UGT1A7*3/*3**: associated with hematologic toxicity after cycle 1 (multivariate analysis)

- Haplotype 1 (34.2%) “protective”
  - Reference genes UGT1A1*1, *60, *93 and UGT1A7*3
  - PLUS sex (females have higher risk)
  - Predicted lower hematologic toxicity on all cycles

- Haplotype 2 (23.2%)
  - Variant genes UGT1A1*28, *60, *93 and UGT1A7*3
  - Associated with response rate

- **UGT1A1*60** was better predictor than UGT1A1*28 at predicting SN38 gluronidation
Irinotecan PK: An updated roster

50% variability in ANC nadir explained by:
- UGT1A1*93
- ABCC1 IVS11 -48C>T
- SLCO1B1*1b
- ANC baseline levels
- Sex

30% variability in SN38 AUC explained by:
- ABCC1 1684 T>C
- ABCB1 IVS9 -44A>G
- UGT1A1*93

40% variability in irinotecan AUC explained by:
- ABCC2 -24C>T
- SLCO1B1*5
- HNF1A 79 A>C
- Age
- Irinotecan dose

Will we need an irinotecan “SNP Chip”?

*J Clin Oncol* 2009;27:2604-14
Genotyping for the UGT1A1*28 allele would be most helpful for predicting neutropenia in which of the following irinotecan regimens?

1. Irinotecan 125 mg/m\(^2\) every week
2. Irinotecan 180 mg/m\(^2\) every 2 weeks as part of the FOLFIRI regimen
3. Irinotecan 350 mg/m\(^2\) every 3 weeks
4. None of the above, I’m going with FOLFOX!
5-Fluorouracil PK-directed therapy

When genotyping isn’t clear, we always have phenotype!
5-Fluorouracil

Remains the cornerstone of colorectal cancer therapy after more than 40 years

First line therapy for Stage IV colorectal cancer
- FOLFOX +/- bevacizumab
- FOLFIRI +/- bevacizumab

Adjuvant therapy for Stage III and high risk patients with Stage II disease
- FOLFOX
Individualized vs. Conventional FU

**N = 208**
Patients with Stage IV colorectal cancer receiving FU over 8 hours weekly

- Concentrations were measured after 3 and 7 hours
- Arm B doses were adjusted weekly based on levels from the previous week until the range of 20-25 mg*h/L

**FU 1500 mg/m2 given over 8 hours + LV**

**PK-guided FU to achieve an AUC of 20-25 mg*h/L over 8 hours + LV**

*J Clin Oncol.* 2008;26:2099-2105
**PK-guided Dose Adjustment**

### In the Absence of Toxicity

<table>
<thead>
<tr>
<th>FU Plasma Concentration (μg/L)</th>
<th>AUC (mg·h·L⁻¹)</th>
<th>FU Dose Adjustment (± % of previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500</td>
<td>&lt; 4</td>
<td>+70</td>
</tr>
<tr>
<td>500-1,000</td>
<td>4 to &lt; 8</td>
<td>+50</td>
</tr>
<tr>
<td>1,000-1,200</td>
<td>8 to &lt; 10</td>
<td>+40</td>
</tr>
<tr>
<td>1,200-1,500</td>
<td>10 to &lt; 12</td>
<td>+3</td>
</tr>
<tr>
<td>1,500-1,800</td>
<td>12 to &lt; 15</td>
<td>+20</td>
</tr>
<tr>
<td>1,800-2,200</td>
<td>15 to &lt; 18</td>
<td>+10</td>
</tr>
<tr>
<td>2,200-2,500</td>
<td>18 to &lt; 20</td>
<td>+5</td>
</tr>
<tr>
<td>2,500-3,000</td>
<td>20 to &lt; 24</td>
<td>Unchanged</td>
</tr>
<tr>
<td>3,000-3,500</td>
<td>24 to &lt; 28</td>
<td>−5</td>
</tr>
<tr>
<td>3,500-3,700</td>
<td>28 to &lt; 31</td>
<td>−10</td>
</tr>
<tr>
<td>&gt; 3,700</td>
<td>&gt; 31</td>
<td>−15</td>
</tr>
</tbody>
</table>

- Grade II toxicity: dose decreased by 200 mg
- Grade III toxicity: 1 week break, then dose decreased by 300 mg

*J Clin Oncol.* 2008;26:2099-2105
Dosage Required to Reach Target FU AUC

![Graph showing dosage required to reach target FU AUC comparison between Arm A and Arm B.](image)

*J Clin Oncol.* 2008;26:2099-2105
## Individualized vs. Conventional FU: Results

<table>
<thead>
<tr>
<th></th>
<th>Arm A: Conventional Dosing</th>
<th>Arm B: Individualized Dosing</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Dose</strong></td>
<td>1500 mg/m²</td>
<td>1790 mg/m² (765-3300)</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>18.3%</td>
<td>33.7%</td>
<td>0.004</td>
</tr>
<tr>
<td>OS</td>
<td>16 months</td>
<td>22 months</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Toxicity (First 3 months, WHO Grade III/IV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Hand-Foot</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

*J Clin Oncol. 2008;26:2099-2105*
Individualized vs. Conventional FU: Summary

PK-directed FU therapy improved:
- Response rates
- Overall survival
- Toxicity (specifically, diarrhea)

In arm A, 4 of 49 patients were in the desired range
In arm B, desired range was reached:
- 94% of patients
- Mean of 4 cycles (range 1-10)

Used a non-conventional FU dosing regimen

*J Clin Oncol.* 2008;26:2099-2105
Cohort study:
Patients with Stage IV colorectal cancer receiving first line FOLFOX4 every 2 wks

- Target concentration similar to range of 20-25 mg*h/L
- Similar dosing nomogram used as in previous study

Standard FOLFOX based on BSA

FOLFOX with PK-directed FU to achieve a target conc of 600 ug/L

- Target concentration similar to range of 20-25 mg*h/L
- Similar dosing nomogram used as in previous study

ASCO GI Cancer Symp. 2009;Abstr #356
FOLFOX4 with or without PK-directed FU

<table>
<thead>
<tr>
<th></th>
<th>Arm A: Conventional Dosing</th>
<th>Arm B: Individualized Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of theoretical dose at 3 months</td>
<td>85 +/- 10</td>
<td>110 +/- 22</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR+PR</td>
<td>46 %</td>
<td>69.5 %</td>
</tr>
<tr>
<td>Med OS</td>
<td>22 months</td>
<td>28 months</td>
</tr>
<tr>
<td><strong>Toxicity (WHO Grade III/IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 %</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Mucositis</td>
<td>15 %</td>
<td>0.8 %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25 %</td>
<td>18 %</td>
</tr>
</tbody>
</table>

ASCO GI Cancer Symp. 2009; Abstr #356
OnDose™ Collection Process

- Patient receives FU infusion in clinic
  - Blood draw between 2 - 45 hours after the start of the continuous FU infusion
  - Peripheral blood into a 6mL EDTA collection tube
  - Add (provided) stabilizing agent immediately

- Blood is centrifuged within 30 minutes
  - Plasma is pipetted into a separate 3 mL cyrovial
  - Label tube with provided bar code label

- Complete Test Request Form (TRF)
  - Exact infusion start time, draw time, infusion duration

- Prepaid FedEx envelope included with sampling kit

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OnDose™ Product Information
OnDose™ Results

Results will be returned usually within 7 days
## OnDose™ Dosing Recommendations

### Adapted 5-FU Dose Adjustment Chart

<table>
<thead>
<tr>
<th>AUC (mg•h/L)</th>
<th>Adjustment (± % of previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>+70%</td>
</tr>
<tr>
<td>4 to &lt;8</td>
<td>+50%</td>
</tr>
<tr>
<td>8 to &lt;10</td>
<td>+40%</td>
</tr>
<tr>
<td>10 to &lt;12</td>
<td>+30%*</td>
</tr>
<tr>
<td>12 to &lt;15</td>
<td>+20%</td>
</tr>
<tr>
<td>15 to &lt;18</td>
<td>+10%</td>
</tr>
<tr>
<td>18 to &lt;20</td>
<td>+5%</td>
</tr>
<tr>
<td>20 to &lt;24</td>
<td>Unchanged</td>
</tr>
<tr>
<td>24 to &lt;28</td>
<td>-5%</td>
</tr>
<tr>
<td>28 to &lt;31</td>
<td>-10%</td>
</tr>
<tr>
<td>&gt;31</td>
<td>-15%</td>
</tr>
</tbody>
</table>
Patient receiving FOLFOX obtains a 5FU AUC of 16 ng*hr/L. How should the next cycle of 5FU be dosed?

1. Increase dose by 50%
2. Increase dose by 10%
3. Do not change dose
4. Decrease dose by 15%
5FU AUC Results from OnDose™

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Target Range</th>
<th>Infusion Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnDose (5-FU AUC)</td>
<td>16 mg·h/L</td>
<td>20-24 mg·h/L</td>
<td>48 hrs 0 mins</td>
</tr>
</tbody>
</table>

The assay consists of biochemical analysis that measures the concentration of 5-FU using a two-reagent immunoagglutination technique. The Area Under the Curve (AUC) is calculated from the measured concentration of 5-FU multiplied by the infusion duration. The infusion duration and dose are provided by the health care provider. This result assumes the patient was at steady state when the sample was drawn, the sample was drawn peripherally (i.e. not drawn from a portacath) and that the sample was handled according to laboratory instructions. The basis for the quantitative target range in colorectal cancer, as noted on this report, is found in the following studies: Gamelin F et al. J Clin Onc 2008; 26: 1099-106. Yehou M et al. Cancer Chemother Pharmacol 2003; 52: 252 - 256. Gamelin F et al. J Clin Onc 1998; 16: 1470-1476, Gamelin E et al, Cancer. 1998; 77:441-51.

**AUC = 7 ng·hr/L**

**AUC = 16 ng·hr/L**

<table>
<thead>
<tr>
<th>Date</th>
<th>AUC (mg·h/L)</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>03-JUL-2010</td>
<td>7</td>
<td>2,400</td>
</tr>
<tr>
<td>23-JUL-2010</td>
<td>16</td>
<td>3,600</td>
</tr>
</tbody>
</table>
Future Directions

Tamoxifen and CYP2D6
- Dosing recommendations for IM patients
- How should we define an “IM”?
- Treatment recommendations for PM patients

Irinotecan and UGT1A1 + transporters
- Prospective dose determination studies
- Development of an irinotecan SNP chip?

PK-directed FU dosing
- Prospective study results with FOLFOX/FOLFIRI based regimens
- Prospective studies focusing on utility in community settings
In Memory: Merrill J. Egorin, MD

“Two things he believed most strongly -- doing all the right things for patients ... and he was really dedicated to training young people, looking after the newest members in the field and helping them advance”