Pharmacology as a tool to dose individualize cancer therapy

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University of Chicago

1st International Workshop on Dose Optimization Strategies for Targeted Drugs – Focus on Oncolytics
Zaandam, Netherlands
March 23, 2015
Patient Name: Lou Kemia

Height: 72 Inches
Weight: 180 Pounds

Drug dosage/ M²: 100

Calculate Body Surface Area  Reset

Results

BSA = 2.04 M²
Dose = 204.00
Select Units
EDITORIAL

Body-Surface Area as a Basis for Dosing of Anticancer Agents: Science, Myth, or Habit?
Phase I and Pharmacologic Study of Intermittent Twice-Daily Oral Therapy With Capecitabine in Patients With Advanced and/or Metastatic Cancer


J Clin Oncol, 1998

Table 2. Duration of Treatment

<table>
<thead>
<tr>
<th>Dose Level, mg/m²/d</th>
<th>No. of Cycles Administered (one cycle = 21 days)</th>
<th>No. of Patients</th>
<th>No. of Cycles Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>502</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1,004</td>
<td>13</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>1,657</td>
<td>24</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>2,510</td>
<td>40</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>3,000</td>
<td>42</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>3,514</td>
<td>36</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Dose optimization

1. What is the optimal starting (labeled) dose for the indicated population?

2. What is the optimal starting dose for the individual, as determined by that patient’s pretreatment characteristics?

3. What is the optimal dose for the individual, as based on pharmacologic response to the previous doses?
Dose optimization

1. What is the optimal starting (labeled) dose for the indicated population?
   - Historically, the optimal starting dose was the maximal safe dose, usually as determined in phase 1 studies
     • <1/3 of patients with DLT
Overall survival by treatment arm.

![Graph showing overall survival by treatment arm with key information:
- T 175: N=158, Events=148, Median=0.94, Cox Regression
- T 210: N=156, Events=147, Median=0.99, P Value=.30
- T 250: N=155, Events=138, Median=1.15

Time to tumor progression for renal cell carcinoma patients in the 25-, 75-, and 250-mg CCI-779 dose groups. mos, months.

<table>
<thead>
<tr>
<th>CCI-779 mg</th>
<th>n</th>
<th>Median mos</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>36</td>
<td>6.3</td>
<td>3.6, 7.8</td>
</tr>
<tr>
<td>75</td>
<td>38</td>
<td>6.7</td>
<td>3.5, 8.5</td>
</tr>
<tr>
<td>250</td>
<td>37</td>
<td>5.2</td>
<td>3.7, 7.4</td>
</tr>
</tbody>
</table>

Log-Rank Test $P = .933$
Take home message: The optimal dose cannot be ascertained in phase 1, and the objective should be to define a range of phase 2 doses.
The example of cabozantinib

1.1.1. Is the proposed dosing regimen supported by the exposure-response (ER) relationship for efficacy?

No, the proposed dosing regimen is not supported by the E-R relationship of efficacy and the analysis suggests that a lower dose may provide similar benefit in terms of the primary endpoint, progression-free survival (PFS). E-R relationship between PFS and dose intensity or AUC\textsubscript{Dose}.

A trial to determine if a lower dose of cabozantinib results in a better toxicity profile and tolerability with non-inferior efficacy to the dose of 140 mg daily. The primary objectives would be to show less toxicity, based on comparison of the overall incidence of common adverse reactions and of serious/severe adverse reactions, with the lower dose to the 140 mg dose with demonstration of non-inferior activity (progression-free survival and overall response rate).
2. What is the optimal starting dose for the individual, as determined by that patient’s pretreatment characteristics?

- Body size
- Genotype
- Organ function
- Other drugs
Capecitabine label implies precise dosing is necessary

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Total Daily Dose* (mg)</th>
<th>Number of Tablets to be Taken at Each Dose (Morning and Evening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.25</td>
<td>3000</td>
<td>0</td>
</tr>
<tr>
<td>1.26-1.37</td>
<td>3300</td>
<td>1</td>
</tr>
<tr>
<td>1.38-1.51</td>
<td>3600</td>
<td>2</td>
</tr>
<tr>
<td>1.52-1.65</td>
<td>4000</td>
<td>0</td>
</tr>
<tr>
<td>1.66-1.77</td>
<td>4300</td>
<td>1</td>
</tr>
<tr>
<td>1.78-1.91</td>
<td>4600</td>
<td>2</td>
</tr>
<tr>
<td>1.92-2.05</td>
<td>5000</td>
<td>0</td>
</tr>
<tr>
<td>2.06-2.17</td>
<td>5300</td>
<td>1</td>
</tr>
<tr>
<td>≥ 2.18</td>
<td>5600</td>
<td>2</td>
</tr>
</tbody>
</table>

*Total Daily Dose divided by 2 to allow equal morning and evening doses
1.1.1 Is body surface area-based dosing appropriate for omacetaxine?
No. The reviewer’s analysis found that clearance of omacetaxine was not correlated with

**AUC vs. BSA by Gender**

- Blue dots: Male
- Red dots: Female

**AUC vs. BSA by Dose**

- Blue dots: 1 mg
- Green dots: 2 mg
- Orange dots: 3 mg
Defining the optimal dose for an individual

• One can readily identify covariates associated with pharmacokinetic variability

• But dose optimization requires an understanding of the relationship of exposure to safety and efficacy
Metabolism of Irinotecan (CPT-11)

CPT-11 → CE → SN-38 → UGT1A1 → SN-38G

CYP3A4 → APC
Variation (Indel) at the **UGT1A1** Promoter

- Bosma, NEJM, 1995
- Monaghan, Lancet, 1996
Neutropenia (q3 wk schedule) is Correlated with $UGT1A1$ Genotype (*28) (Innocenti et al, JCO, 2004)

Bar represents median values.
Nonparametric trend analysis among 6/6, 6/7, 7/7, p<0.01
population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

**Patients with Reduced UGT1A1 Activity**

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.
Carl has metastatic colorectal cancer. Now Genzyme can help you determine his risk of serious adverse effects before he starts therapy.

Genzyme now offers the Invader® UGT1A1 Molecular Assay, an FDA-cleared innovative screening test designed to help you identify patients who are at increased risk for severe toxicity when treated with irinotecan. This simple blood test will assist you in making adjustments in your patient’s therapy before adverse effects occur.

For more information about Genzyme’s cancer testing services, including our menu of innovative tests that can help physicians understand a patient’s response to cancer therapy, visit www.genzymegenetics.com or call (800) 447-5816.

Experience Tomorrow’s Cancer Testing Laboratory Today.
UGT1A1
遺伝子多型検査って何だろう？

監修：安藤 雄一
名古屋大学医学部附属病院
化学療法部 准教授
Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the *UGT1A1* Genotype of Patients With Cancer


### Table 2. Dose Escalations and DLTs by Dose Level and *UGT1A1* Genotype

<table>
<thead>
<tr>
<th>Irinotecan Dose, mg</th>
<th>Total No. of Patients</th>
<th>No. of DLTs</th>
<th>Type of DLT</th>
<th>No. of Patients</th>
<th>Type of DLT</th>
<th>No. of Patients</th>
<th>Type of DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700</td>
<td>31</td>
<td>1</td>
<td>G4 neutropenia &gt; 4 days and G3 diarrhea</td>
<td>9</td>
<td></td>
<td>5</td>
<td>G4 neutropenia (n = 2), G3 (n = 2) or G4 (n = 1) fabrile neutropenia</td>
</tr>
<tr>
<td>850</td>
<td>22</td>
<td>4</td>
<td>G3 fabrile neutropenia (n = 2), G4 fabrile neutropenia and G4 diarrhea, G4 neutropenia &gt; 4 days</td>
<td>16</td>
<td></td>
<td>4</td>
<td>G3 nausea, G3 nausea and vomiting, G5 neutropenia, G4 neutropenia &gt; 4 days and thrombocytopenia</td>
</tr>
<tr>
<td>1,000$</td>
<td>6</td>
<td>2</td>
<td>G3 diarrhea and fabrile neutropenia, G3 diarrhea and G4 neutropenia &gt; 4 days</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Optimal dosing of irinotecan

• *UGT1A1* genotype identifies patients at increased risk of neutropenia at standard doses.
• The relationship of irinotecan and/or SN-38 exposure to efficacy is uncertain.
• Therefore, genotyping does not allow identification of an optimal dose.
Dose optimization

3. What is the optimal dose for the individual, as based on pharmacologic response to the previous doses?
   – Plasma concentrations
   – Toxicity biomarkers
   – Efficacy biomarkers
Could TDM be beneficial for modern oncology drugs?

- Requires knowledge of concentration-response relationship
  - Efficacy
  - Toxicity
- Requires interpatient variability >> intrapatient variability
  - Requires pharmacokinetic studies over duration of anticipated use
Intraindividual variability of antiretrovirals (Nettles, Clin Inf Dis, 2006)

- Lopinavir/ritonavir 24-92%
- Nelfinavir/M8 metabolite 30-54%
- Ritonavir 34-43%
- Saquinavir 52-55%
Phase II Trial of Dasatinib in Patients with Metastatic Breast Cancer Using Real-Time Pharmacodynamic Tissue Biomarkers of Src Inhibition to Escalate Dosing

Christina I. Herold¹, Vijaya Chadaram², Bercedis L. Peterson², P. Kelly Marcom², Judith Hopkins³, Gretchen G. Kimmick², Justin Favaro⁴, Erika Hamilton⁵, Renee A. Welch², Sarah Bacus⁶, and Kimberly L. Blackwell²
32% of patients had serial liver biopsies!!


**Cycle 1**
- Starting dose
  - (Dasatinib 50 or 70 mg PO BID)
- Continue 4 weeks

**Cycle 2**
- Optimal Src inhibition\(^a\)
  - Hold dose constant
  - Dasatinib 50 mg PO BID
- Suboptimal Src inhibition\(^b\)
  - and tolerating drug
  - Escalate dose
  - Dasatinib 70 or 100 mg PO BID

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\(^a\) Optimal Src inhibition defined as 80% or more inhibition of phosphorylation of both FAK and pax compared with baseline phosphorylation levels.

\(^b\) Suboptimal Src inhibition defined as less than 80% inhibition of phosphorylation of either FAK or pax compared with baseline phosphorylation levels.
But the dasatinib plasma concentration was never measured!
A Novel Noncanonical Signaling Pathway for the μ-Opioid Receptor

Lei Zhang, Horace H. Loh, and Ping-Yee Law

Department of Pharmacology, University of Minnesota Medical School, Minneapolis, Minnesota

Received July 3, 2013; accepted September 23, 2013
Morphine-Induced Epidermal Growth Factor Pathway Activation in Non-Small Cell Lung Cancer

Naomi Fujioka, MD,* Julia Nguyen, BS,* Chunsheng Chen, MD,* Yunfang Li, MD,* Teena Pasrija, PhD,* Gloria Niewans, MD,† Katherine N. Johnson, MS,* Vinita Gupta, PhD,‡ Robert A. Kratzke, MD,* and Kalpana Gupta, PhD*

December 2011 • Volume 113 • Number 6
Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development

Y Wang¹, C Sung¹, ², C Dartois¹, R Ramchandani², BP Booth², E Rock³ and J Gobburu¹

On the Use of Change in Tumor Size to Predict Survival in Clinical Oncology Studies: Toward a New Paradigm to Design and Evaluate Phase II Studies

R Bruno¹ and L Claret¹
Conclusions

• There are many opportunities for dose optimization in oncology, both at the population and individual patient levels.

• Oncology drug development needs to shift away from conventional paradigms (e.g., single dose phase 2 studies) and incorporate modern pharmacometric approaches.