Developmental Pharmacology of Anti-Cancer Drugs in Infants and Young Children with Brain Tumors: It’s Not Easy Being Little

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Overview of talk

- Cancer in infants and young children with brain tumors
- Dosing anti-cancer drugs in this population
- Pharmacokinetic studies of drugs in SJYC07
  - Cyclophosphamide
  - Methotrexate
Cancer in infants and young children

- Diagnostic and management challenges
- Heightened vulnerability
  - Acute complications and toxicities
  - Long-term sequelae

(Gurney, *NCI Monograph*, 1999)
Percent distribution of the major types of cancer in children, newborns, and infants

<table>
<thead>
<tr>
<th>Histology</th>
<th>Children &lt; 15 yr (%)</th>
<th>Newborns &lt; 30d (%)</th>
<th>Infants &lt; 1yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>31</td>
<td>13</td>
<td><strong>14</strong></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>18</td>
<td>3</td>
<td><strong>15</strong></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>8</td>
<td>54</td>
<td><strong>27</strong></td>
</tr>
<tr>
<td>Renal</td>
<td>6</td>
<td>13</td>
<td><strong>11</strong></td>
</tr>
</tbody>
</table>

*US SEER 17, 2000-2006
Therapeutic approaches to treat infants and young children with brain tumors

- **Surgery**
- **Radiation**
  - Limited (e.g., avoid CNS radiation in children < 3 yr)
- **Anti-cancer drugs**
  - Limited by ineffective drugs, poorly defined dosing practices, and changes in drug disposition due to development
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Developmental pharmacology in infants & young children

- **Absorption**
  - Gastric/duodenal pH
  - Gastric emptying/intestinal motility

- **Distribution**
  - Body water
  - Body fat
  - Plasma proteins

Drug disposition in infants & young children

• Metabolism
  – Enzyme ontogeny (Hines)
    • Class I – fetal but low/absent within 1-2 yr (e.g., CYP3A7, FM01)
    • Class II – fetal increased postnatally (e.g., CYP2A6, 3A5)
    • Class III – onset 3rd trimester, but largest incr. 1-2 yrs after birth (e.g., CYP2C9, UGTs)

• Excretion
  – Renal function
  – Transporter ontogeny

Methods of dosing anticancer drugs in infants is highly variable

- Flat dosing (mg)
- Weight-based dosing (mg/kg)
- BSA-based dosing (mg/m^2) dosing
- The “rule of 30”
  - Most pediatricians recognize this rule
  - Variably applied either based upon age (< 12, < 6, < 3 mos) or weight (< 10, < 20, < 30 kg)
  - No data to support any of these age or weight cut-offs
Dosing anti-cancer drugs in infants and young children is highly variable: vincristine

<table>
<thead>
<tr>
<th></th>
<th>P9934 MB</th>
<th>AALL01P1 Infant ALL</th>
<th>P9645 Hepato</th>
<th>NWTS 5</th>
<th>Rhabdomyosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12 months</td>
<td>0.065 mg/kg</td>
<td>1.5 mg/m²</td>
<td></td>
<td>0.05 mg/kg</td>
<td>0.05 mg/mg</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>0.065 mg/kg</td>
<td>0.05 mg/kg (50% &lt; 1 mo)</td>
<td>0.025 mg/kg</td>
<td>0.025 mg/kg</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 kg</td>
<td>0.065 mg/kg</td>
<td>1.5 mg/m²</td>
<td>1.5 mg/m² @&gt; 30 kg</td>
<td>1.5 mg/m² @ &gt; 30 kg</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 kg</td>
<td>0.065 mg/kg</td>
<td>0.05 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Variability in dosing based upon the differences in dosing approaches: vincristine

Child at the 50th percentile for weight and height

![Graph showing vincristine dose (mg) vs. age (months) for different types of tumors: Wilms tumor, Rhabdomyosarcoma, Hepatoblastoma, and Medulloblastoma. The graph indicates the dosing variability based on age and tumor type.](image-url)
# Anti-cancer drug doses modified for clinical reasons

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason for Modification</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine/vinblastine</td>
<td>Decreased biliary excretion</td>
<td>Decrease by 50%; further decrease in the presence of jaundice</td>
</tr>
<tr>
<td>Actinomycin</td>
<td>Decreased biliary excretion</td>
<td>-</td>
</tr>
<tr>
<td>Adriamycin/daunomycin</td>
<td>Decreased biliary excretion</td>
<td>Consider full dose daunomycin after 3-6 mo age in ALL</td>
</tr>
<tr>
<td>Cyclophosphamide/ifosfamide</td>
<td>Hepatic activation decreased at birth</td>
<td>-</td>
</tr>
<tr>
<td>Methotrexate (i.v.)</td>
<td>Renal excretion decreased until 6-8 mos</td>
<td>Decrease proportionately to decrease in GFR</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Decreased biliary excretion (and protein binding)</td>
<td>Decrease by 50%; decrease further if jaundice present</td>
</tr>
</tbody>
</table>
Overview of talk

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  - Methotrexate
SJYC07 protocol

- Total anticipated enrollment: 365 patients
- Enrolled at SJCRH: 292 patients
- Expected to consent to PK studies: 262 pts
Cyclophosphamide metabolism is very complex

- Induction therapy
- Consolidation therapy
- Low-dose oral maintenance therapy

(Stearns, Nature Rev Cancer, 2006)
Hypothesis: 4-OH CTX systemic exposure will change with age

CTX → 4OH-CTX

CYP2C19 → CYP3A

ALDH1A1

GST → GFR

CEPM
Pharmacokinetic study design

• **Induction**
  – 1.5 g/m² over 1 h infusion
  – Serial sampling: Pre, EOI, 3, 6, 24 h

• **Consolidation**
  – Low risk: 1.5 g/m² over 1 h infusion
  – High risk: 600 mg/m² over 1 h infusion x 2 days
  – Serial sampling: Pre, EOI, 3, 6, 24 h

• **Maintenance**
  – 30 mg/m² orally once daily
  – Serial sampling: Pre, 0.5, 1.75, 3, 6 h + troughs
Bioanalysis of CTX and metabolites

- CTX & CEPM
  - Quantitated simultaneously in plasma with LC-MS/MS method

- 4OH-CTX
  - Phenylhydrazine added to whole blood to derivatize 4OH-CTX
  - Quantitated with LC-MS/MS method

Pharmacokinetic modeling

Modeling performed with NONMEM VI software

\[ k_{\text{ENZ}} \times \left( 1 + \frac{E_{\text{max}} \times C_{\text{CTX}}}{EC_{50} + C_{\text{CTX}}} \right) \]

\[ k_{\text{ENZ}} \]

\[ \text{Enzyme} \]

\[ k_{23} \]

\[ \text{CEPM} \]

\[ k_{\text{4OH-CTX}} \]

\[ k_{\text{4OH-CTX}} \]

\[ k_{\text{CEPM}} \]

\[ \text{4OH-CTX} \]

\[ \text{CL\text{\textsubscript{IND}}} \]

\[ \text{CTX} \]

\[ \text{CL\text{\textsubscript{NON}}} \]

\[ \text{CL\text{\textsubscript{NON}}} \]

\[ \text{McCune, J Clin Pharmacol, 2008} \]
Patient accrual

- Total anticipated enrollment: 365 patients
- Enrolled at SJCRH: 292 patients
- Expected to consent: 262 patients
- Currently (5/24/11) enrolled/consented at SJCRH: 82/78 pts
- Induction (C1D9) CTX samples analyzed: ~39 pts
Plasma concentration-time data for CTX and metabolites

n = 39 patients

~10-fold variability among patients noted
Diagnostic plots show lack of bias in model fit
Systemic exposure (AUC) to CTX and metabolites decreases with age.
• Youngest patient (25 days old) clearance 4-fold > than other patients.
• Using published data on the ontogeny and *in vitro* CTX hydroxylation activities of CYP3A4, 3A7, 2A6, 2B6, and 2C9, we simulated age-dependent contributions of different CYP isoforms to CTX hydroxylation.
• Simulation (right) showed a similar pattern to *in vivo* clearance.
4-OH CTX inactivation through CEPM constant with age
4-OH CTX inactivation through non-CEPM pathways increased with age

Preliminary findings

• Activation and elimination of 4OH-CTX
  – Mediated by several pathways that change with age

• Wide interpatient variability (10-fold) and in very young infant CTX clearance to 4-OH very high

• Will examine association between exposure and toxicity

• Data will provide part of the information necessary to determine optimal dosing
Pharmacogenetics of CTX

Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide
Corine Ekhart, Valerie D. Doedeman, Sjoerd Rodenhuis, Paul H.M. Smits, Jos H. Beijnen and Alwin D.R. Huitema

(Pharmacogenet Genom, 2008)

Genetic polymorphisms of CYP2B6 affect the pharmacokinetics/pharmacodynamics of cyclophosphamide in Japanese cancer patients
Miki Nakajima, Sayaka Komagata, Yuto Fujiki, Yoshihiro Kanada, Hiromichi Ebi, Kuniaki Itoh, Hirofumi Mukai, Tsuyoshi Yokoi and Hironobu Minami

(Pharmacogenet Genom, 2007)

Cytochrome P450 Pharmacogenetics as a Predictor of Toxicity and Clinical Response to Pulse Cyclophosphamide in Lupus Nephritis
Kazuki Takada, Million Arefayene, Zeresenay Desta, Cheryl H. Yarboro, Dimitrios T. Boumpas, James E. Balow, David A. Flockhart and Gabor G. Illei

(Arthritis Rheumatism, 2004)
Why study pharmacogenetics in infants and young children?

• Polymorphisms which affect PK in adults will not affect PK in children if gene is not yet expressed ("age trumps genetics")

Developmental Pharmacogenetics: A General Paradigm for Application to Neonatal Pharmacology and Toxicology

JS Leeder

Table 1 Systematic approach for initial evaluation of the relative contributions of ontogeny and genetic variation with respect to issues related to variability in drug disposition and toxicity in newborns

1. What gene products are quantitatively important in the disposition (absorption, distribution, metabolism, and excretion) of the drug(s) in question?

2. For each gene product, what is the developmental trajectory for the acquisition of functional activity?

3. Is allelic variation in the gene(s) of interest associated with any functional consequences in vivo?

4. Is there any evidence that allelic variation affects the developmental trajectory of the drug disposition phenotype?

5. What is the developmental context in which the gene(s) of interest is/are operating?

(Leeder, Clin Pharmacol Ther, 2009)
DMET chip

- 1,936 polymorphisms
- 225 drug metabolizing enzymes and transporters (DMET) genes
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MTX pharmacokinetics

- Renal elimination
  - Glomerular filtration
  - Transporters

(Rhodin, Pediatr Nephrol, 2009)
MTX pharmacokinetics

Methotrexate pharmacokinetics in infants with acute lymphoblastic leukemia

Patrick A. Thompson · Daryl J. Murry · Gary L. Rosner · Simon Lunagomez · Susan M. Blaney · Stacey L. Berg · Bruce M. Camitta · ZoAnn E. Dreyer · Lisa R. Bomgaars

(Cancer Chemother Pharmacol, 2007)

Pharmacokinetics of High-Dose Methotrexate in Infants Treated for Acute Lymphoblastic Leukemia

Gudmar Lönnroth, MD, PhD,1* Maria Grazia Valsecchi, PhD,2 Paola De Lorenzo, PhD,2 Martin Schrappe, MD, PhD,3 Liisa Hovi, MD,4 Myriam Campbell, MD,5 Georg Mann, MD,6 Gritta Janka-Schaub, MD, PhD,7 Chi-Kong Li, MD,8 Jan Stary, MD,9 Ian Hann, FRCPCH,10 and Rob Pieters, MD, PhD11 for the Interfant-99 study group

(Pediatr Blood Cancer, 2009)
MTX given over 4 courses
Dosing & methods

- MTX (5 g/m²) given i.v. over 24 h
  - 10% of dose given in first hour as loading dose
- Empiric dose reduction for infants < 1 month of age at start of therapy
  - 2.5 g/m²
- Sampling: 6, 23, 42, 66 h
  - Additional samples collected until < 0.1 µM
- Pharmacokinetic modeling
  - Two-compartment model with 1ˢᵗ order elimination
  - ADAPTII (v. 5) software
Patient enrollment

- Because samples are part of clinical monitoring, they are required for all patients
- Including patients from all study sites ~365 patients
- Largest study of methotrexate PK in patients < 3 years of age with brain tumors
Simulated serum MTX concentrations
MTX systemic clearance increases with age and exposure (AUC) decreases with age, and no change in clearance with course.

**Preliminary Observations:**
- Wide variability in MTX clearance
- Part of this variability is explained by age
- Clearance does not change with subsequent courses
- Pharmacogenetics will be examined
• Developmental processes in infants and young children affect the PK of anti-cancer drugs

• SJYC07 gives us the opportunity to develop pharmacokinetic models describing the PK of drugs in children with brain tumors
Future directions

• Continue to collect PK samples
• Perform genotyping with DMET chip
• Assess relationship between age, drug exposure and toxicity

• Use results to design optimal dosing regimens for infants and young children with brain tumors
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- Dr. Mike Tagen
- Dr. Feng Bai
- Dr. Amar Gajjar
- Dr. Carl Panetta
- Stewart Lab
- ALSAC
- St. Jude clinicians
- Patients and families
Questions?