Therapeutic Drug Monitoring in Oncology Improves Patient Outcomes

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Member, Fred Hutchinson Cancer Research Center
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Therapeutic drug monitoring (TDM) or target-concentration intervention (TCI)

• Definition: involves adjustment of drug doses on the basis of concentrations measured in individual patients, is a dosing alternative for many narrow-therapeutic-index drugs

• Prerequisites: narrow therapeutic index, wide inter-patient variability, well-defined concentration – effect relationship, reliable and clinically feasible assays

TDM in Oncology

• Although the limitations of body surface area (BSA) dosing are well recognized in the clinical pharmacology community, many medical oncologists are still believers\(^1\)

• Any dose personalization method – TDM, germline pharmacogenomics, new -omics tool – must improve efficacy or avoid lethal toxicity. Reducing manageable toxicity not enough\(^2\)

• Even new genetic tools predicting cancer risk (BRCA1/2 in young women with breast cancer) or relapse risk in breast cancer patients (Oncotype Dx\(^\text{®}\) to guide adjuvant chemotherapy) aren’t quickly adopted\(^3\)

TDM in Oncology Improves Patient Outcomes?

• Build and validate more population pharmacokinetic models. Use limited sampling schedules to better understand concentration-effect relationship.¹

• Therapeutic target ranges should be prospectively validated through ‘phase II’ case series (randomized clinical trials are highly unlikely to be funded in the US)

• Technological advances towards point-of-care TDM (but slow uptake of these technologies²)

Allogeneic hematopoietic cell transplant (alloHCT)

• Procedure used predominantly in patients with inherited disorders or refractory cancers
• Goal: Cure patient with no regimen-related toxicity or graft versus host disease (GVHD)

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<th>Conditioning regimen</th>
<th>Day of rest</th>
<th>Allogeneic Graft infusion</th>
<th>Post grafting immunosuppression</th>
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<td>Day: -8 to -2</td>
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“You have to deal with the time you live in”
– Dottie Thomas

accessed 29 Feb 16
Reduced NIH Funding from 2002 to 2014 (& elimination of Pharmacology study section)
AlloHCT

- Initially based on premise of high dose radiation and chemotherapy to myeloablate the recipient’s own hematopoietic system
- High doses of older (off-label) chemotherapy with substantive (historically fatal) toxicity

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Seattle Approach: Does TDM Improve Outcomes in AlloHCT?

- Almost all (very old) drug use is off label
- Develop (usually novel) analytical method
- Characterize the pharmacokinetic variability
- Conduct pharmacodynamic study to determine the association of clinical outcomes with plasma area under the curve (AUC) or trough concentration in a (relatively) homogeneous population
- If association found, then conduct ‘phase II’ (Phase III not feasible) study evaluating the benefit of TDM
- Personalize doses with TDM
## RCT of Conventional vs. TDM Dosing: Too Few AlloHCT Patients

<table>
<thead>
<tr>
<th>First author</th>
<th>Patient population</th>
<th>TDM (regimen)</th>
<th>TDM dosing cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans¹</td>
<td>182 pediatric acute lymphoblastic leukemia</td>
<td>Methotrexate, teniposide, cytarabine (120 week regimen)</td>
<td>B-cell ALL patients had ↑ 5 year continuous complete remission</td>
</tr>
<tr>
<td>Fety²</td>
<td>122 adults locally advanced head and neck cancer</td>
<td>5-fluorouracil only (5-fluorouracil and cisplatin)</td>
<td>↔ Relapse free survival ↓ toxicity</td>
</tr>
<tr>
<td>Gamelin³</td>
<td>208 adults stage IV colorectal cancer</td>
<td>5-fluorouracil (5-fluorouracil and leucovorin)</td>
<td>↑ objective response rate Trend towards ↑ survival ↓ toxicity</td>
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# Does TDM of AlloHCT Conditioning Regimen Improve Outcomes?

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<td></td>
<td></td>
<td>N/A</td>
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<td>Clinical use of TDM?</td>
<td>Yes</td>
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**Notes:**
- CA182963 is an active metabolite for Busulfan.
- PK Variability ranges from 2.8 fold to 16-fold.
- Conditioning regimens include CY/TBI, TBU/CY, CY/TBU, FLU/TBU, ATG, FLU/TBI.
- AUC association with clinical outcomes is mostly Yes.
- Phase II study of TDM benefit is primarily Yes.
- Clinical use of TDM is generally Yes.
Alkylating Agent Busulfan (BU)
AlloHCT Conditioning

1953: Activity in chronic myeloid leukemia

1968: First preclinical study of busulfan and cyclophosphamide (BU/CY) as HCT conditioning
   Blood. 1968 Oct;32(4):629-37 (Santos & Tutschka at Hopkins)

1978: First publication of BU/CY in humans
   Blood. 1978 Sep;52(3):627-36

1980: First report of hepatotoxicity
   Am J Pathol. 1980 May;99(2):369-86

1989: First pharmacokinetic/dynamic report of AUC with hepatotoxicity (then lethal) in adults
(Targeted) Busulfan TDM

- First dose based on body surface area (BSA) or body weight
- Get multiple blood samples to estimate AUC
- Clearance = dose divided by AUC
- Know target AUC
- Adjust dose based on patient’s clearance to achieve target AUC
- Must be quick – busulfan only administered over four days
# Busulfan TDM Improves Outcomes

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<tr>
<th>Outcome</th>
<th>PD Association</th>
<th>TDM Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>Yes (N=24 – 41)</td>
<td>↑ engraftment rates from 74% to 96% (N=32)</td>
</tr>
<tr>
<td>Hepato-toxicity</td>
<td>Yes (N=35-51)</td>
<td>↓ hepatotoxicity rates from 75% to 18% (N=27)</td>
</tr>
<tr>
<td>Relapse in CML</td>
<td>Yes (N=45)</td>
<td>↓ relapse rate from 15% to 8% (N=131)</td>
</tr>
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Busulfan’s Hill Equation In Bu/CY

Too much: Hepatotoxicity in adults

‘Goldilocks’
Just ‘right’ exposure

Not enough:
Rejection
Relapse in select diseases

Pharmacokinetics and Pharmacodynamics Volume 2, 1988
In 2008, more than 60% of patients reported to the CIBMTR who received oral busulfan and 50% of those receiving IV busulfan had pharmacokinetic data.

Improving Busulfan TDM

- Only 23% of adults and 24% of children achieve their target exposure with weight based dosing of IV busulfan
  

- Personalizing either IV or oral busulfan dosing cannot be simplified on the basis of *GSTA1* or *GSTM1* genotype
  

- Population pharmacokinetic models:
  - Use shorter sampling schedules to allow for outpatient TDM of daily IV busulfan using post-Bayesian estimates of individual patient data after model validation and clinical decision support construction
    
  
  - Initial dosing and TDM in children (N=1,492) and adults (N=128)
    
    *Clin Cancer Res. 2014 Feb 1;20(3):754-6*
Dashboards


MTX Dashboard

Select new patient: 

Doe, John

Demographic and clinical data
- MRN: 123456789
- Weight: 12.1 kg
- DOB: 12/12/2013
- Height: 71 cm
- AGE: 11 months
- BSA: 43 m²
- SEX: Male
- eGFR: 95 ml/min/1.73 m²

Laboratory data

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Conc (μM)</th>
<th>SCr (mg/dL)</th>
<th>Bili (mg/dL)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>24</td>
<td>140</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>48</td>
<td>1.7</td>
<td>0.2</td>
<td>0.5</td>
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<tr>
<td>72</td>
<td>N/A</td>
<td>0.2</td>
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MTX dosing data
- Dose: 960 mg
- Nominal Dose: 2233 mg/m²
- Protocol Number: COG-P9407

Goal: Improve overall survival by identifying metabolomics-based biomarkers associated with IV BU PK

SA1. Predose endogenous biomarkers
   - Retrospective cohort (Training) N=119
   - Prospective cohort (Validation) N=150
   - Global metabolomics
   - Targeted metabolomics – glutathione pathway

SA2. Postdose metabolism of IV BU
   - Prospective cohort N=150
   - 13 samples around morning doses on days 1-4 of IV BU
   - Targeted analysis of metabolites

SA3. Covariates of IV BU PK
   - Retrospective cohort
   - popPK model building N=1,610
   - Validation of popPK model and limited sampling schedule N=2,435
Key Points

- Any dose personalization method **must improve efficacy** or avoid (the rare) lethal toxicity
- Essential to understand the concentration – effect relationship
- Population pharmacokinetic (popPK)-based tools should be more rapidly accepted for TDM, but substantial barriers exist
- Future directions could include combining TDM, ideally using popPK models, with –omics based biomarkers
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Prodrug Cyclophosphamide (CY)
Pharmacokinetics (partial schema)

CY → Urine → DechloroCY

IminoCY ↔ 4HCY ↔ AldoCY

GlutathionylCY → Blood

Bile → Acrolein + Phosphoramide Mustard

Carboxyethyl phosphoramide mustard (CEPM)
Efforts to improve CY in HCT

- Considerable interpatient variability in the exposure of CY and its metabolites
  \[Blood.\ 2003\ Mar\ 1;101(5):2043-8\]

- In CY/TBI, personalizing CY doses to metabolite exposure using a population pharmacokinetic model decreased liver and renal toxicity
  \[Clin\ Pharmacol\ Ther.\ 2009\ Jun;85(6):615-22\]

- In TBU/CY, clinical outcomes were not associated with CY or its metabolite exposure
  \[BBMT.\ 2007\ Jul;13(7):853-62\]

- Outcomes may be improved by switching order of administration (CY/TBU). Pharmacodynamic associations with overall survival
  \[BBMT.\ 2013\ Jul;19(7):1033-9\]
Higher CEPM AUC Associated With Hepatotoxicity and Worse Overall Survival

McDonald Blood. 2003;101:2043-8
Population PK-based Dosing of CY to Target AUC of HCY and CEPM

\[
K_{\text{ENZ,CY}}^* \left( 1 + \frac{E_{\text{max}} C_{\text{CY}}}{E_{50} + C_{\text{CY}}} \right)
\]

Salinger Clin Cancer Res. 2006;12:4888-98
Nonrelapse mortality

Relapse

Overall survival

Replace CY with FLU for Lymphotoxicity

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Fludarabine Intracellular Disposition

Plasma F-ara-A Exposure

- Created population pharmacokinetic model and limited sampling schedule (LSS) for F-ara-A
- LSS increased outpatient compliance with PK sampling from 75% to 98%
- No associations observed between F-ara-A AUC and clinical outcomes (N=102)

## PopPK Tools Essential for TDM

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INTERDISCIPLINARITY
Why scientists must work together to save the world. PAGE 305
Acknowledgements

• UW/Fred Hutch PK lab
  – Danny Shen, PhD
  – Linda Risler, Brian Phillips, Tom Kalhorn, Laura Shireman
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• Fred Hutch study coordinators for various clinical trials which have busulfan TDM, PK studies of CY, MMF or fludarabine
• Statisticians: Barry Storer, David Blough, Tim Randolph

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  – Paolo Vicini
  – David Salinger
• University of Buffalo
  – Donald Mager, PharmD, PhD
  – Hong Li, PhD
• Funding
  – CA19028 (Appelbaum)
  – HL36444 (Storb)
  – CA078902 (Storb)
  – HL91744 (McCune)
  – HL91744S1 (McCune)
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TDM in Oncology: Oral Targeted Therapy

• Use TDM if no therapeutic response, adherence concerns, severe or unexpected toxicities\(^1\)

• Interaction with drugs or natural products (NP)
  – Concomitant chemotherapy – NP interactions can be a controversial issue with believers and non-believers regarding the risk of such interactions\(^2\)
  – 27% at risk of an adverse interaction\(^2\)
  – Only 30-55% of patients stated they’d discontinue their NP if an adverse interaction found\(^2\)
  – Best practices will be established for evaluating NP – drug interactions (AT008909)

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| Erlotinib – NSCLC | No association between AUC and progression free survival, overall survival and response rate in 308 patients |
| Pazopanib – mRCC | ↑ $C_{\text{trough}}$ >20.6 mcg/ml  
| | ↑ progression free survival, ↑ response rate and ↑ tumor shrinkage |
| Sunitinib – mRCC | ↑ AUC (>800 ng-h/ml)  
| | ↑ time to progression, ↑ overall survival, ↑ objective response rate |
| Sunitinib – GIST | ↑ AUC (>600 ng-h/ml)  
| | ↑ time to progression, ↑ overall survival |
| Vemurafenib – melanoma | ↑ AUC tertile  
| | ↓ tumor growth |
| Imatinib – GIST | ↑ $C_{\text{trough}}$ >1110 ng/ml  
| | ↑ time to progression |

mRCC: metastatic renal cell carcinoma; NSCLC: non-small cell lung cancer; GIST: gastrointestinal stromal tumor;

de Wit Drug Discov Today 2015 20(1): 18-36; Petit-Jean Ther Drug Monit 2015;37:2–21
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de Wit Drug Discov Today 2015 20(1): 18-36; Petit-Jean Ther Drug Monit 2015;37:2–21
Proposed $C_{\text{trough}} > 1100$ ng/ml

**Diagnosis of advanced GIST**

- **Unfavorable genotype**
  - Exon 9 KIT mutation
    - Imatinib, 800 mg daily
  - Wild-type or resistant genotype
    - Consider sunitinib or experimental agent

- **Mutation analysis shows imatinib-sensitive genotype, e.g., exon 11 KIT**
  - Imatinib, 400 mg daily, take blood for trough level at start of treatment, i.e., day 14
  - Response assessment at 3 months or sooner using Choi criteria

  + Repeat PK study at 3 months

- **Poor response or progression**
  - Adequate blood level—change to sunitinib
  - Low trough level—increase imatinib dosage

- **Good response**
  - Adequate blood level—continue at 400 mg
  - Low trough level—increase imatinib dosage

---

Imatinib

- BCR-ABL TKI imatinib revolutionized initial treatment of gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML)
- Variable response rates
- Problematic adherence rates in CML: One-third of patients are non-adherent\(^1\); adherence lowers with higher copayments\(^2\)
- 10+ trials have shown an association between imatinib trough – cytogenetic response in CML

\(^1\)Blood. 2009 May 28;113(22):5401-11 & Anticancer Res. 2011 Apr;31(4):1407-9;
\(^2\)J Clin Oncol. 2014 Feb 1;32(4):306-11;
TDM with Imatinib $C_{\text{trough}}$ in CML

• Established centralized imatinib TDM service at the Bordeaux University Hospital in France.\(^1\) Eventually open to all of Europe, in collaboration with European Treatment and Outcome Study (EUTOS) for CML\(^1\)

• Two prospective studies evaluating if TDM can improve long-term response in CML
  – I-COME (N=55), no benefit\(^2\) of routine TDM vs. rescue TDM
  – OPTIM (N=139), higher major molecular response at 12 months with TDM of $C_{\text{trough}} > 1000$ ng/ml vs. standard management (63% vs. 37%\(^3\))

MoABs TDM in *Clin Pharmacol Ther*

- April 2016 Mould DR Commentary: Why TDM in needed for monoclonal antibodies and how do we implement this?
- June 2016: Stroh & Lum Commentary: Should TDM for monoclonal antibodies remain the exception or become the norm?
Key Points

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• Essential to understand the concentration – effect relationship
• PopPK-based tools should be more rapidly accepted for TDM, but substantial barriers exist
• Future directions could include combining TDM, ideally using popPK models, with –omics based biomarkers
Q&A slides
Tests for Molecularly Targeted Therapies from the National Academies of Sciences, Engineering and Medicine’s report “Key to Unlocking Precision Medicine”

- Establish common evidentiary standards of clinical utility – using evidence generated both within and outside the context of clinical trials – across all stakeholders.
- Establish a more coordinated and transparent federal process for regulatory and reimbursement decisions.
- Enhance communication to patients and providers about the performance characteristics and evidence for use of specific tests.
- Update and strengthen oversight and accreditation of laboratories providing these tests.
- Ensure ongoing assessment of the clinical utility of the tests.
- Ensure development and use of electronic health records (EHRs) and related biomedical informatics tools and assessment that support the effective clinical use of biomarker tests for molecularly targeted therapies.
- Develop and maintain a sustainable national database for these tests through biomedical informatics technology to promote rapid learning for the improvement of patient care.
- Promote equity in access to these tests and the expertise for effective use of test results in clinical decision making.
- Enhance specimen handling and documentation to ensure patient safety and the accuracy of biomarker test results.
- Improve the processes for developing and updating clinical practice guidelines for the effective use of these tests.

Where do pharmacokinetics /pharmacodynamics (PK/PD) fit in the translational spectrum?

T1: Discovery: translation to humans PK/PD found here most often
Testing basic science discoveries for translation to humans

T2: Development: translation to patients PK/PD sometimes here
Testing new interventions in human subjects

T3: Delivery: translation to practice PK/PD sometimes here
Research on the application of new interventions in general practice

T4: Outcomes: translation to populations
Investigating factors/interventions that influence the health of populations

http://ncats.nih.gov/translation/spectrum
PK substantively improved on T1: Attrition of new drugs 1991-2000

PK/PD in T2 and T3: Focus on Precision Medicine

Patients receiving the same dose:

- No Benefit + Toxicity
- + Benefit + Toxicity
- + Benefit No Toxicity
- No Benefit No Toxicity
PK/PD in T2 and T3

- Almost exclusively conducted in academic medical centers in underserved populations
- Goal is to make FDA approved drugs work better.
Comprehensive review of medical literature for the cost-effectiveness of TDM

<table>
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</tr>
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<tbody>
<tr>
<td>A1</td>
<td>Systematic review containing several studies of A2 level and with consistent outcomes</td>
</tr>
<tr>
<td>A2</td>
<td>Prospective randomized clinical trials of good quality</td>
</tr>
<tr>
<td>B</td>
<td>Randomized clinical trials of moderate quality (e.g., too few patients) or other comparative trials (e.g., not randomized, cohort studies, case-control studies)</td>
</tr>
<tr>
<td>C</td>
<td>Noncomparative trials</td>
</tr>
<tr>
<td>D</td>
<td>Experts’ opinions (e.g., according to the authors)</td>
</tr>
</tbody>
</table>

Touw DJ et al. Ther Drug Monit. 2005 Feb;27(1):10-7
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Conclusion &amp; Recommendation for TDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (A2-B)</td>
<td>• Lowers mortality, toxicity, and cost-effective. Recommend, but studies conducted before extended interval dosing</td>
</tr>
<tr>
<td>Vancomycin (A2-B)</td>
<td>• Lowers renal toxicity and is cost-effective in select patient populations (intensive care units, oncology, concomitant nephrotoxic drugs). Recommended for those patients.</td>
</tr>
<tr>
<td>Antiepileptics (B-D)</td>
<td>• Improved efficacy, less toxicity, and cost-effective with classic antiepileptics (i.e., phenobarbital, phenytoin, carbamazepine, primidone, valproic acid). Recommend.</td>
</tr>
<tr>
<td></td>
<td>• Not useful with newer antiepileptics</td>
</tr>
<tr>
<td>Immuno-suppressants (D)</td>
<td>• Must be performed because of a shortage in donor organs, the wide pharmacokinetic variability, and the risk of drug-drug interactions. Recommend.</td>
</tr>
<tr>
<td>Drug Class (Evidence rating)</td>
<td>Conclusion &amp; Recommendation for TDM</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Theophylline (B-D)</td>
<td>• Optimizes treatment and can be cost-effective. Recommend that it can be helpful</td>
</tr>
<tr>
<td>Digoxin (B-D)</td>
<td>• Optimizes treatment in patients with cardiac failure or with atrial fibrillation (no cost-effectiveness data). Recommend that it may be useful in those patients.</td>
</tr>
<tr>
<td>Psychiatric Drugs (A1-D)</td>
<td>• Useful for lithium, nortriptyline, desipramine, imipramine, haloperidol, and clozapine (no cost-effectiveness data). Recommend that is should be used</td>
</tr>
<tr>
<td></td>
<td>• For other psychiatric drugs, can help in questions of adherence and drug-drug interactions</td>
</tr>
<tr>
<td>Protease inhibitors (A2-C)</td>
<td>• Must be used for nelfinavir</td>
</tr>
<tr>
<td></td>
<td>• Could be useful for other protease inhibitors and nonnucleoside reverse transcriptase inhibitors.</td>
</tr>
</tbody>
</table>

Touw DJ et al. Ther Drug Monit. 2005 Feb;27(1):10-7
Efforts to improve CY in HCT

- Considerable interpatient variability in the exposure of CY and its metabolites
  
  *Blood. 2003 Mar 1;101(5):2043-8*

- In CY/TBI, personalizing CY doses to metabolite exposure using a population pharmacokinetic model decreased liver and renal toxicity
  
  *Clin Pharmacol Ther. 2009 Jun;85(6):615-22*

- In TBU/CY, clinical outcomes were not associated with CY or its metabolite exposure
  
  *BBMT. 2007 Jul;13(7):853-62*

- Outcomes may be improved by switching order of administration (CY/TBU). Pharmacodynamic associations with overall survival
  
  *BBMT. 2013 Jul;19(7):1033-9*
Can Personalized Dosing Improve CY/TBI?

• Pharmacodynamic relationships
  – High plasma AUC of carboxyethylphosphoramide mustard (CEPM) associated with higher risk of liver toxicity, nonrelapse mortality, and lower overall survival
  – Presumably plasma CEPM concentrations reflective of hepatic CEPM concentrations, which result from metabolism of hydroxycyclophosphamide (HCY)
  – HCY toxic to murine sinus endothelial cells

• Feasible to personalize CY doses based on the AUC of CEPM and AUC of HCY
  – Lower CEPM AUC to lower risk of liver toxicity
  – Maintain AUC of HCY to lowest AUC in prior study to maintain engraftment
  – Rapid population pharmacokinetic modeling needed in future studies to more accurately personalize CY dose to achieve metabolite AUCs

Impact of Personalized CY Dosing upon Outcomes in CY/TBI Patients

- Fifty patients received personalized CY dosing
- The use of population TDM – a blend of population and individual information – led to more precise CY dose recommendations
  - Mean second CY dose was 66 (0-100) mg/kg, and the mean total CY dose was 111 (45-145) mg/kg
- Compared to 100 controls receiving CY 120 mg/kg in patients receiving 12 Gy total body irradiation (TBI)
Fludarabine Intracellular Disposition
<table>
<thead>
<tr>
<th></th>
<th>FLU/TBU&lt;sup&gt;1&lt;/sup&gt;</th>
<th>FLU/TBU/THY</th>
<th>FLU/TBU/THY&lt;sup&gt;2&lt;/sup&gt;</th>
<th>TBU/FLU</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC protocol #</td>
<td>1519</td>
<td>1913</td>
<td>2041</td>
<td>2270</td>
</tr>
<tr>
<td>Total N</td>
<td>27</td>
<td>22</td>
<td>15</td>
<td>90</td>
</tr>
<tr>
<td><strong>Busulfan (Css target 800-1000 ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting dose</td>
<td>1 mg/kg PO Q6hr</td>
<td>3.2 mg/kg IV Q24h</td>
<td>4 mg/kg IV Q24h</td>
<td>130 mg/m² IV Q24h</td>
</tr>
<tr>
<td>Days</td>
<td>-5 to -2</td>
<td>-5 to -2</td>
<td>-5 to -2</td>
<td>-5 to -2</td>
</tr>
<tr>
<td><strong>Fludarabine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, in mg/m² (total)</td>
<td>30 (120)</td>
<td>30 (120)</td>
<td>50 (250)</td>
<td>40 (160)</td>
</tr>
<tr>
<td>Days</td>
<td>-9 to -6</td>
<td>-9 to -6</td>
<td>-9 to -6</td>
<td>-5 to -2</td>
</tr>
<tr>
<td>F-ara-A PK</td>
<td>Yes/no association</td>
<td>No</td>
<td>Yes/highest HR for NRM</td>
<td>No</td>
</tr>
<tr>
<td>Thymoglobulin</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Post-grafting immunosuppression</td>
<td>CsA/MTX</td>
<td>TAC/MTX</td>
<td>TAC/MTX</td>
<td>CY/TAC/MMF</td>
</tr>
<tr>
<td>Reason for closure</td>
<td>Accrual goal met</td>
<td>Low donor chimerism</td>
<td>high NRM</td>
<td>Accrual goal met</td>
</tr>
</tbody>
</table>

Cancer Chemother Pharmacol 2012 Jan;69(1):263-72
Efforts to improve fludarabine in FLU/TBU HCT conditioning

• Pharmacodynamics of F-ara-A are influenced by the conditioning regimen, same as busulfan and CY
  *Cancer Chemother Pharmacol 2012 Jan;69(1):263-72*

• F-araA AUC can be characterized using a population pharmacokinetic model and limited sampling schedule
  *Clin Cancer Res. 2009 Aug 15;15(16):5280*

• Ex vivo F-ara-ATP accumulation rate in CD4+ and CD8+ cells can be characterized
  *Cancer Chemother Pharmacol, SEP 2008 62 (4): 735-739*

• Suppression of absolute lymphocyte count after fludarabine administration can be characterized using a population pharmacokinetic – pharmacodynamic model
  *Cancer Chemother Pharmacol. 2015 Jan;75(1):67-75*

• Proposed evaluating F-ara-A AUC prior to gene therapy
Efforts to improve fludarabine in nonmyeloablative HCT

Increasing Need for GVT Effect → Intensity → Toxicity

- Total body irradiation (TBI)
- Fludarabine + Busulfan (BU, 3.2-16 mg/kg)
- BU + Melphalan
- BU + Cyclophosphamide (BU/CY) or CY/BU
- CY/TBI
- TBI + Fludarabine (90-250 mg/m²)

Protocol 1980: PK/PD in Nonmyeloablative PBSC Recipients

Calcineurin inhibitor, kinetics based targeting

Fludarabine 30mg/m²/day IV

In vitro FTP formation

2 Gy TBI + HLA matched G-PBMC

MMF 15 mg/kg Q8 hour (URD) or Q12 hour (related) to day 28, then taper

<table>
<thead>
<tr>
<th>Day</th>
<th>-14 to -5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>2</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancillary Study PK</td>
<td>In vitro FTP formation</td>
<td>F-ara-A AUC</td>
<td>F-ara-A AUC</td>
<td>F-ara-A AUC</td>
<td>MPA AUC</td>
<td>MPA AUC</td>
<td>MPA AUC</td>
<td>MPA AUC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancillary Study PD</td>
<td>CD4⁺ CD8⁺</td>
<td>IMPDH</td>
<td>CD4⁺ CD8⁺</td>
<td>IMPDH</td>
<td>IMPDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Study PD</td>
<td>rejection, acute graft versus host disease (GVHD), chronic GVHD, non-relapse mortality (NRM), infections, relapse/progression, survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aRectangles represent the HCT procedure and the endpoints obtained during clinical care or FHCRC treatment protocol (Section 8). Ovals designate ancillary study PK and PD which are highlighted by relevant Aim. Aim 1 highlighted blue, Aim 2 yellow and Aim 3 green using the candidate PK and PD biomarkers from Aims 1 and 2; bCalcineurin inhibitor used will be cyclosporine or tacrolimus, which will be dose adjusted to achieve target trough concentrations, based on FHCRC treatment protocol; cMMF dose not adjusted based on AUC or trough MPA concentration. MMF taper started at day 28 and specified per FHCRC treatment protocol; dDay 28 T cell chimerism is the primary endpoint of Aim 3. Endpoints will be assessed beyond day 28 based on clinical need or FHCRC treatment protocol.
Plasma F-ara-A Exposure

- Retrospective analysis of 41 patients receiving fludarabine 30 or 50 mg/m2/day
- First population pharmacokinetic model for F-ara-A
  - Best fit with a two compartment model
  - Interpatient variability 37%
- BSA was the only covariate that was associated with pharmacokinetic variability
- Limited sampling schedule (LSS) by simulation, seeking to minimize precision and bias
- Led to successfully estimating F-ara-A AUC in outpatient population
Fludarabine biomarkers in nonmyeloblastic HCT

• Biomarkers for fludarabine evaluated
  – Before conditioning started, F-ara-ATP accumulation rate quantified in enriched CD4⁺ and CD8⁺ cells isolated from 34 and 36 patients, respectively.
  – After the first fludarabine dose, F-ara-A UAC in 102 patients
  – After the last fludarabine dose, the ratio of circulating CD4⁺ and CD8⁺ cells (CD4⁺/CD8⁺ ratio) in 102 patients

• Interpatient variability in the pharmacologic biomarkers was high, ranging from 3.7-fold (F-ara-A UAC) to 39-fold (F-ara-ATP in CD8⁺ cells).

• Poor correlation between the F-ara-A UAC and the F-ara-ATP accumulation rate in CD4⁺ (R² = 0.01) and CD8⁺ cells (R² = 0.00).
Fludarabine biomarkers in nonmyeloablative HCT

• Circulating CD8\(^+\) cells were more sensitive to fludarabine administration, with an average (range) decline of 82% (-20 – 100%) compared to 68% (range: -47 – 100%) for circulating CD4\(^+\) cells.

• No associations were seen between the four biomarkers and clinical outcomes (day +28 donor T-cell chimerism, acute graft-versus-host disease (GVHD), neutrophil nadirs, cytomegalovirus reactivation, chronic GVHD, relapse, non-relapse mortality, or overall mortality).
F-ara-A - Lymphocyte Population Pharmacodynamic Model

\[ \frac{\text{Leukocyte}_{\text{baseline}}}{\text{Leukocyte}_{\text{circulating}}} \]


\[ \begin{align*}
    k_{\text{in}} & \rightarrow X_1 \rightarrow k_t \rightarrow X_2 \rightarrow k_t \rightarrow X_3 \rightarrow k_t \\
    k_k & \ast [F-ara-A] \\
    \text{Lo} & = \text{baseline absolute lymphocyte count} \\
    k_{\text{in}} & = \text{Lo} \ast k_t \\
    k_t & = 1/\tau
    \end{align*} \]
Lymphodepletion Can Be Characterized by F-ara-A Concentrations

Protocol 1519

Protocol 2041

Unpublished data
Plasma F-ara-A Population Pharmacodynamic Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Designation</th>
<th>Parameter Estimate (SE)</th>
<th>BSV (as % CV, on diagonal) and correlation (as Pearson r), off diagonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ALC</td>
<td>Lo</td>
<td>0.954/μL (10.8%)</td>
<td>Lo</td>
</tr>
<tr>
<td>Rate constant - transit between cell compartments</td>
<td>k_t</td>
<td>0.0441/hr (15 hr) (7.39%)</td>
<td>59%</td>
</tr>
<tr>
<td>Rate constant - cell kill</td>
<td>k_K</td>
<td>30.2/hr (1.4 min) (41.7%)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

- BSV of pharmacokinetic parameters ranged from 35.1 to 46.2%
Protocol 1980: PK/PD in Nonmyeloablative PBSC Recipients

Calcineurin inhibitor, kinetics based targeting

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</tr>
</thead>
<tbody>
<tr>
<td>Ancillary Study PK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Ancillary Study PD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Parent Study PD</td>
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TDM of Imatinib Trough Concentrations

Picard et al:
- 68 CML chronic or accelerated phase patients receiving daily imatinib doses of 400 mg or 600 mg, respectively, for at least 12 months
- Higher trough imatinib concentrations associated with higher rates of complete cytogenetic response and major molecular response
- Daily imatinib dose not associated with major molecular response

IRIS trial: 5 year followup
- Significant correlation between a complete cytogenetic response (CCyR) and higher imatinib plasma concentration
- Average imatinib trough concentrations
  - CCyR: 1009 + 544 ng/ml
  - No CCyR: 812 + 409 ng/mL
  - P = 0.01
- Similar correlation with major molecular response (MMR) (P=0.02)
- Conclusion: maintaining imatinib plasma trough levels above 1000 ng/mL is an independent prognostic factor that may be important for achieving CCyR and MMR

IRIS Results
Careful Attention Needed for Busulfan Pharmacokinetic Sampling

- Ensure the exact time of blood draw, using the same clock, is written
- Ensure troughs are drawn prior to starting infusion of next dose

McCune JS, hypothetical data for teaching purposes.
Careful Attention Needed for Busulfan Pharmacokinetic Sampling

- At end of infusion, make sure administration and flush is completed. If not, concentrations may be high.

- Example:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Conc (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>1372</td>
</tr>
<tr>
<td>150</td>
<td>750</td>
</tr>
<tr>
<td>245</td>
<td>391</td>
</tr>
<tr>
<td>365</td>
<td>198</td>
</tr>
</tbody>
</table>

1 half-life = 25 min?
2 half-lives = 215 min

McCune JS, hypothetical data for teaching purposes.