Drug Interactions in Stem Cell Transplantation

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Awareness of drug interactions increasing in patients with cancer

- Prevalence in HSCT patients unknown
- 4.5-58% in cancer patients
- Numerous electronic databases exist with variable reliability
- Electronic systems and alerts are promising, but have challenges
  - alert fatigue


Learning objectives

- Explain the common metabolic pathways in the liver
- Identify approaches to overcome drug interactions seen in HSCT
- Identify those drug interactions of importance
- Understand how to preemptively prevent drug interactions from occurring

When is a drug interaction in HSCT recipients important?

- Many potential drug interactions
- Type of interactions
  - Pharmaceutical
  - Incompatibilities at administration site
  - Pharmacokinetic
  - What the body does to the drug
  - Pharmacodynamic
  - What the drug does to the body
  - HSCT interaction example: live vaccines
- Important if leads to an undesired outcome, whether it be ↓ efficacy or ↑ toxicity

The challenges unique to HSCT patients are …..

- The concentration-effect (i.e., pharmacodynamic) relationships are rarely defined
- Degree of an interaction (and thus its significance) rarely described
- Cytokines influence regulation
- Interpatient variability in the interaction
- When an adverse drug interaction occurs, we often lack the pharmacokinetic data to explain it

Quick review of pharmacokinetic-based drug interaction basics

- Drug metabolizing enzymes
- Drug transporters
Relationship between pharmacokinetics and pharmacodynamics

Dose
Absorption
Distribution
Metabolism
Excretion
Total serum concentration
Receptor Site
Unbound serum concentration
Pharmacologic Response
Protein Bound Concentration
Therapeutic Outcome

Pharmacology is multifactorial
- Can affect both the pharmacokinetics and pharmacodynamics
- Factors include...
  - Age
  - Sex
  - Ethnicity
  - Weight
  - Condition being treated
  - Pharmacogenetics
  - Idiosyncrasy
  - Drug interaction

Pharmacokinetic parameters
- Absorption
  - The rate at which a drug leaves the site of administration and the extent to which it occurs
  - HSCT interaction example: proton pump inhibitors with mycophenolate mofetil
- Distribution
  - Process of reversible transfer of a drug to and from the site of measurement
  - HSCT interaction example: non-steroidal anti-inflammatory drugs (NSAIDs) with methotrexate (also interacts at kidney)

Pharmacokinetic parameters: elimination
- Metabolism
  - Predominately liver
  - Other sites: kidney, lung, gastrointestinal tract (GI), plasma
  - HSCT interaction example: many
- Excretion
  - Kidneys and hepatic/GI tract
  - Other sites: milk, sweat, saliva, tears
  - HSCT interaction example: cyclosporine with mycophenolic acid

Biotransformation (Metabolism)
- Theory
  - Drug inactivation
  - Increased elimination from the body
- Reality
  - Metabolites may have biological activity; similar or different than parent
  - May contribute to toxic and/or beneficial effects
  - Example: Cyclophosphamide metabolized by cytochrome P450 (CYP) to 4-hydroxycyclophosphamide

Phase I metabolism
- Oxidation, reduction, hydrolysis
- Cytochrome P450 family of enzymes
  - 7 primary enzymes responsible for majority of drug metabolism
  - Can predict drug interactions based on knowledge of metabolizing enzymes
    - Various family, subfamily, individual genes
      - CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5
- Inhibition \( \downarrow \) CYP, \( \uparrow \) concentration, \( \downarrow \) dose
- Induction \( \uparrow \) CYP, \( \downarrow \) concentration, \( \uparrow \) dose
Cytochrome P450 (CYP) enzyme system

- Large (but not only) source of drug interactions
- Many in vitro methods to identify which CYP metabolizes a drug, and potential drug interactions
- However, magnitude of drug interaction difficult to predict
  - 'Cocktail' studies in healthy volunteers
  - Cytokines (e.g., IL6) affect CYP

Examples of important CYP in HSCT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Substrate</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>3A4/5</td>
<td>Elimination</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>3A4/5</td>
<td>&quot;</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>3A4/5</td>
<td>&quot;</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3A4/5</td>
<td>&quot;</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>3A4/5</td>
<td>&quot;</td>
</tr>
<tr>
<td>Cyclophosphamide (CY)</td>
<td>2C9, 2C19</td>
<td>Activation to 4hydroxyCY (HCY)</td>
</tr>
<tr>
<td></td>
<td>3A4/5*</td>
<td>Detoxification to dechloroCY</td>
</tr>
</tbody>
</table>

Phase II metabolism

- Term coined to represent metabolism occurring after oxidation, reduction or hydrolysis associated with bioactivation
- Many drugs don't require Phase I metabolism
- Functional group created conjugated to less toxic or inactive compound

Phase II: Relevant conjugation reactions

- Glutathione S-transferase
  - Mediate conjugation of electrophilic compounds to glutathione
  - Important detoxifying pathway for alkylation agents
- Glucuronidation
  - Most common conjugation reaction for drugs
  - UGT (UDP-glucuronosyl transferase)
  - Conjugation of endogenous substances, bilirubin, mycophenolic acid, morphine

Drug transporters

- Of the 400 transporters in the human genome, 30 are relevant to pharmacokinetics
- ATP-binding cassette (ABC) superfamily
- Relevant to systemic pharmacokinetics and intracellular transport

ABC transporters relevant to HSCT patients

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1 (MDR1)*</td>
<td>calcineurin inhibitors, sirolimus corticosteroids</td>
</tr>
<tr>
<td>ABCC1 (MRP1)</td>
<td>methotrexate</td>
</tr>
<tr>
<td>ABCC2 (MRP2)</td>
<td>cyclophosphamide metabolite mycophenolic acid</td>
</tr>
<tr>
<td>ABCC3</td>
<td>methotrexate</td>
</tr>
<tr>
<td>ABCG2 (BCRP)</td>
<td>etoposide, topotecan</td>
</tr>
</tbody>
</table>

* codes for pglycoprotein (ppp)

### Additional transporters
- **Organic anion transporting polypeptide (OATP)**
  - methotrexate, opioids, corticosteroid metabolites
- **Organic anion transporters (OAT)**
  - beta-lactams, metabolites of corticosteroids, NSAIDs
- **Equilibrative nucleoside transporter 1 (ENT)**
  - fludarabine
- **Concentrative pyrimidine-preferring nucleoside transporter 1 (CNT)**
  - fludarabine

### Excretion
- Drugs are eliminated from the body unchanged or as metabolites
- Complex, for example renal excretion involves
  - Glomerular filtration
  - Active tubular transport
  - Passive tubular absorption
- HSCT interaction example: NSAIDs inhibit renal tubular secretion of methotrexate and/or reduce renal blood flow by inhibiting prostaglandin synthesis

### Pharmacokinetic parameters
- Clearance measures body’s ability to eliminate drugs
- Elimination half-life is time it takes for the amount of drug in the body to be reduced by 50%
  \[ T_{1/2} = \frac{0.693 \times V_d}{Cl} \]
  - where Vd = volume of distribution and Cl = total body clearance
- Impact of CYP interactions on clearance
  - Inhibition: ↓ CYP, ↓ clearance, ↑ concentration, ↑ dose
  - Induction: ↑ CYP, ↑ clearance, ↓ concentration, ↓ dose

### Elimination half-life
**Example: Plasma Concentrations Drug with T_{1/2} = 12 hrs**

<table>
<thead>
<tr>
<th>Dose</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_0</td>
<td>20 µg/ml</td>
<td>40 µg/ml</td>
</tr>
<tr>
<td>C_{12hr}</td>
<td>10 µg/ml</td>
<td>20 µg/ml</td>
</tr>
<tr>
<td>C_{24hr}</td>
<td>5 µg/ml</td>
<td>10 µg/ml</td>
</tr>
<tr>
<td>C_{36hr}</td>
<td>2.5 µg/ml</td>
<td>5 µg/ml</td>
</tr>
<tr>
<td>C_{48hr}</td>
<td>1.2 µg/ml</td>
<td>2.5 µg/ml</td>
</tr>
<tr>
<td>C_{60hr}&lt; 1 µg/ml</td>
<td>1.2 µg/ml</td>
<td></td>
</tr>
<tr>
<td>C_{72hr}&lt; 1 µg/ml</td>
<td>&lt; 1 µg/ml</td>
<td></td>
</tr>
</tbody>
</table>

### Steady state
- Css = the concentration at which the rate of drug input is equal to the rate of drug elimination
  - Can be defined as area under the curve/dosing interval (busulfan)
  - Takes approximately 5 T_{1/2} to reach steady state
  - Takes approximately 5 T_{1/2} to completely eliminate a drug after discontinuation
  -Css is dependent on dosage and clearance

### Approximate half-lives of relevant immunosuppressants
- Calcineurin inhibitors: 11-35 hours (hr)
- Sirolimus: 62 hr
- Mycophenolic acid: 0.6-11.9 hr
- Methylprednisolone, prednisone: 1.7 to 4.1 hr
**Learning objectives**

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**GVHD Medications**

Cyclosporine, Tacrolimus, Sirolimus, Methotrexate, Mycophenolate mofetil, Corticosteroids

**Less commonly used GVHD medications**

- Immunomodulating modalities: mTOR-inhibitors, thalidomide, hydroxychloroquine, vitamin A analogs, rituximab, alemtuzumab, etanercept
- Cytostatic agents: cyclophosphamide, pentostatin

**The interactions discussed**

- Pharmacokinetic interactions relevant to GVHD prophylaxis and treatment
  - Will discuss herbal preparations, but recall they are unique because of potential pill to pill variability in content, for fungal contamination, immunologic properties....
  - Omitting others not because they are less important but they may be
    - more easily identified (e.g., the opioids because of close concentration – effect relationship)
    - more broad therapeutic index of the medication (e.g., most antibiotics)

**Effect of food/herbs**

<table>
<thead>
<tr>
<th>Food/herb</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grapefruit juice</td>
<td>↓ intestinal CYP3A, ↔ pgp</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>↑ CYP3A4, pgp</td>
</tr>
<tr>
<td>Garlic</td>
<td>↑ CYP3A4</td>
</tr>
</tbody>
</table>

- Difficult to know magnitude of problem
- Difficult to predict
  - Expect grapefruit juice to ↑ absorption of etoposide, a CYP3A4/glycoprotein substrate, but it actually ↓ absorption in cancer patients
- Pharmacodynamic (e.g., antioxidant) concerns reviewed well in Nutrition chapter of Thomas 4th edition

**Calcineurin inhibitors (CNI)**

- Cyclosporine (CyA) and tacrolimus (TAC)
  - Considerable pharmacokinetic variability in CNI concentrations obtained in patients receiving same dose
  - CNI concentrations related to clinical outcomes (pharmacodynamics)
    - ↓ CyA/TAC ↑ risk of acute GVHD
    - ↑ CyA/TAC ↑ nephrotoxicity

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Personalized dosing of CNIs

- Using pharmacokinetics, CNI doses personalized to achieve target trough concentrations
- But...considerable interpatient variability in efficacy and toxicity remain
  - Better biomarkers (e.g., calcineurin activity\(^1\), pharmacogenomics\(^2\)) still needed
- Drug interactions can be identified, and doses adjusted as needed
- Important because CNIs are substrates (metabolized by) CYP3A and p-glycoprotein

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P-glycoprotein

- Additional names
  - Multidrug resistance protein (MRP1)
  - ATP-dependent drug transporter (ABCB1)
- Drug interaction potential
  - Limits oral drug bioavailability
  - Transports drugs out of renal tubular epithelial cells and mesangial cells on the glomerulus
  - Blood brain barrier
  - Intracellular accumulation

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Variability in CYP3A content


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Medications that increase CyA or TAC plasma concentrations

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>CYP3A</th>
<th>P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoles – vary within class</td>
<td>↓</td>
<td>+</td>
</tr>
<tr>
<td>(Fluconazole, Itraconazole, Ketoconazole, Voriconazole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oltizam, Verapamil</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>Clarithromycin, Erythromycin</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>Imatinib</td>
<td>↑</td>
<td>?</td>
</tr>
</tbody>
</table>

Management: Monitor concentrations, ↓ dose of CNI PRN

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Medications that decrease CyA or TAC plasma concentrations

<table>
<thead>
<tr>
<th>Inducers</th>
<th>CYP3A</th>
<th>P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme inducing antiepileptics (EIAED)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Management: Monitor concentrations, ↑ dose of CNI PRN

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Importance of transporters: Cyclosporine causing interactions

- Interaction with statins
  - Unexpected interaction of CyA with two statins (rosuvastatin and pravastatin)
  - Numerous mechanisms: CyA inhibits OATP1B1 (organic anion-transporting polypeptide 1B1), OATP1B3, and BCRP (breast cancer resistance protein)
- Interaction with mycophenolate mofetil
  - CyA inhibits ABC2, which reduces the enterohepatic recirculation of mycophenolic acid (MPA), and increases MPA clearance

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Sirolimus

- Substrate for CYP3A & p-glycoprotein
- Similar drug interactions as CyA and TAC
- Long half-life (average: 62 hours)
- Will take 5–7 days for steady state sirolimus concentrations if drug interaction occurs

Potential sirolimus interactions

<table>
<thead>
<tr>
<th>Effect on sirolimus concentrations</th>
<th>INCREASE</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)</td>
<td>EIAED (carbamazepine, phenytoin, phenobarbital)</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>St. John’s wort</td>
<td></td>
</tr>
<tr>
<td>Diltiazem, Verapamil</td>
<td>Nevirapine</td>
<td></td>
</tr>
<tr>
<td>CyA</td>
<td>Rifabutin</td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin, Erythromycin</td>
<td>Grapefruit Juice</td>
<td></td>
</tr>
</tbody>
</table>

Management: Monitor concentrations, adjust sirolimus dose PRN


Mycophenolate mofetil (MMF)

- Similar amount of pharmacokinetic variability as CNIs
- Pharmacodynamic relationships being identified in HSCT patients

Potential MMF interactions

- Increase MPA levels
  - Rosiglitazone (?)
- Decrease MPA levels
  - Select antibiotics (gut decontamination, norfloxacin & metronidazole, Augmentin)
  - Some proton pump inhibitors
  - Rifampin (?)
  - Calcium polycarbophil
  - Cholestyramine
  - Telmisartan
  - Sevelamer

Corticosteroids

- In general, steroid metabolism involves sequential hydroxylation followed by conjugation to water-soluble metabolites
- 6 β-hydroxylation occurs via CYP3A4/5 but is a relatively minor pathway
- P-glycoprotein appears to be involved in the transport of some steroids (cortisol, dexamethasone, methylprednisolone)

Corticosteroid drug interactions

- Increase levels
  - Ketoconazole
  - Oral Contraceptives
- Decrease levels
  - Phenytoin
  - Phenobarbital
  - Carbamazepine
  - Rifampin
Conclusions

- Drug interactions are frequent in HSCT patients
- Changes in CYP cause many pharmacokinetic drug interactions, but other types of interactions are also relevant
- Considerable interpatient variability in magnitude of a drug interaction
- Management of drug interactions much easier when pharmacokinetic monitoring is available
- Further data needed to know impact of drug interactions with sirolimus, mycophenolate mofetil, corticosteroids and post-HSCT cyclophosphamide