Drug Interactions in Stem Cell Transplantation

Jeannine McCune, PharmD, BCOP
University of Washington
Fred Hutchinson Cancer Research Center

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

Lemachatti et al. Anticancer Res. 2009 Nov;29(11):4741-4 ; van Leeuwen Ann Oncol. 2011 Oct;22(10):2334-41. Epub 2011 Feb 22. Scott et al. J Am Med Inform Assoc. 2011 Nov-Dec;18(6):789-98

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

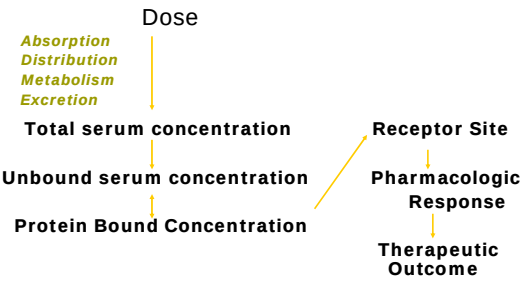
The challenges unique to HSCT patients are …..

- 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



Slide courtesy of Gail Anderson, PhD

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 4hydroxycyclophosphamide

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 ↓ CYP, ↑ concentration, ↓ dose
- Induction ↑ CYP, ↓ concentration, ↑ 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

Drug	Substrate	Reaction
Cyclosporine	3A4/5	Elimination
Tacrolimus	3A4/5	"
Sirolimus	3A4/5	"
Prednisone	3A4/5	"
Dexamethasone	3A4/5	"
Cyclophos-phamide (CY)[2]	2C9, 2C19	Activation to 4hydroxyCY (HCY)
	2B6, 3A4/5*	
	3A4/5	Detoxification to dechloroCY

Hebert. Metabolic Drug Interactions 2000; Shimada Transplant International 2003. Ren Cancer Research 1997; Huang Biochem Pharmacol 2000; Qiu Clin Pharm Ther 2004

Phase II metabolism

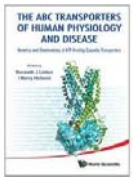
- Term coined to represent metabolism occurring after oxidation, reduction or hydrolysis associated with bioactivation
  - Many drugs don't require Phase I metabolism
- Functional group created conjugated to less toxic or inactive compound

Phase II: Relevant conjugation reactions

- Glutathione *S*-transferase
  - Mediate conjugation of electrophilic compounds to glutathione
  - Important detoxifying pathway for alkylating 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

Transporter	Substrate
ABCB1 (MDR1)*	calcineurin inhibitors, sirolimus
	corticosteroids
ABCC1 (MRP1)	methotrexate
ABCC2 (MRP2)	cyclophosphamide metabolite
	mycophenolic acid
ABCC3	methotrexate
ABCG2 (BCRP)	etoposide, topotecan

*codes for pglycoprotein (pgp)

Endres et al. Eur J Pharm Sci. 2006 Apr;27(5):501-17

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

Zhang et . Clin Pharmacol Ther. 2011 Apr;89(4):481-4; Pauli-Magnus Pharmacogenetics 2003; 13: 189; Sekine Annals of Oncology 2001; 12: 1515; Oleschuk Am J Physiol Gastrointest Liver Physiol 2003 Feb;284(2):G280;

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%
- $T_{1/2} = \frac{0.693 \cdot Vd}{Cl}$
  - 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

Dose	100 mg	200 mg
C_0	20 μg/ml	40 μg/ml
C_{12hr}	10 μg/ml	20 μg/ml
C_{24hr}	5 μg/ml	10 μg/ml
C_{36hr}	2.5 μg/ml	5 μg/ml
C_{48hr}	1.2 μg/ml	2.5 μg/ml
C_{60hr}	< 1 μg/ml	1.2 μg/ml
C_{72hr}	< 1 μg/ml	< 1 μg/ml

Slide courtesy of Gail Anderson, PhD

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
- Take 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

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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

Pidala BBMT 2011, 17(10):1528; [2]Ferrara Lancet 2009, 373: 9674; Holler Best Pract Res Clin Haematol. 2007 Jun;20(2):281-94, Wolff BBMT 2011;17(1):1-17

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

	Effect
Grapefruit juice	↓ intestinal CYP3A, ↔ pgp
St. John's wort	↑ CYP3A4, pgp
Garlic	↑ CYP3A4

- Difficult to know magnitude of problem
- Difficult to predict
  - Expect grapefruit juice to ↑ absorption of etoposide, a CYP3A/pglycoprotein substrate, but it actually ↓ absorption in cancer patients
- Pharmacodynamic (e.g., antioxidant) concerns reviewed well in Nutrition chapter of Thomas 4th edition

Cancer Research 2004; 64: 4346; Leather BMT 2004; 33:137.

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

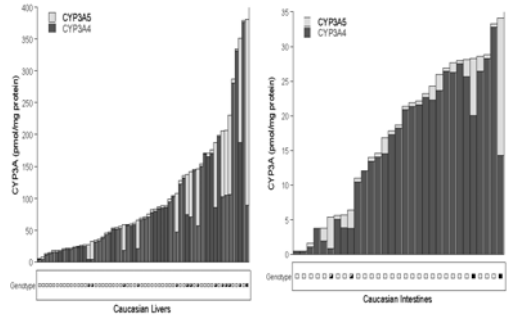
Yee; N Engl J Med 1988; 319: 65; Ram et al. Biol Blood Marrow Transplant. 2011 Aug 26

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

[1]Sanquer S et al. Transplantation 2004;77(6):854-8. Pai SY et al, Blood 1994;84(11):3974-9; Koefoed-Nielsen et al. Transplant International 2006;19: 821-7. [2]Woodahl EL et al, Pharmacogenomics J. 2008 Aug;8(4):248-55.

Variability in CYP3A content



Lin et al. Mol Pharmacol 2002;62:162-72

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

Medications that increase CyA or TAC plasma concentrations

	Effect	
Inhibitors	CYP3A	P-gp
Azoles – vary within class (Fluconazole, Itraconazole, Ketoconazole, Voriconazole)	↓	↓
Diltiazem, Verapamil	↓	↓
Chloramphenicol	?	?
Norfloxacin	↓	?
Clarithromycin, Erythromycin	↓	↓
Grapefruit Juice	↓	
Imatinib	↓?	

Management: Monitor concentrations, ↓ dose of CNI PRN

Hebert. Metabolic Drug Interactions 2000 Ch 37; Leather HL. Bone Marrow Transplant. 2004 Jan;33(2):137-52

Medications that decrease CyA or TAC plasma concentrations

	Effect	
Inducers	CYP3A	P-gp
Enzyme inducing antiepileptics (EIAED)		
Carbamazepine	↑	
Phenobarbital	↑	↑
Phenytoin	↑	↑
Rifampin	↑	↑↓
St. John's Wort	↑	↑

Management: Monitor concentrations, ↑ dose of CNI PRN

Hebert. Metabolic Drug Interactions 2000 Ch 37; Leather HL. Bone Marrow Transplant. 2004 Jan;33(2):137-52

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 ABCC2, which reduces the enterohepatic recirculation of mycophenolic acid (MPA), and increases MPA clearance

Zhang et . Clin Pharmacol Ther. 2011 Apr;89(4):481-4; Endres et al. Eur J Pharm Sci. 2006 Apr;27(5):501-17

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

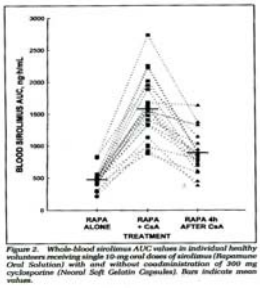


Figure 2. Whole-blood sirolimus AUC values in individual healthy volunteers receiving single 10-mg oral doses of sirolimus (Rapamune Oral Solution) with and without coadministration of 300 mg cyclosporine (Neoral Soft Gelatin Capsules). Bars indicate mean values.

Stenton et al. Clin Pharmacokinet. 2005;44(8):769-86; Zimmerman. J Clin Pharmacol 2003; 43: 1168

Potential sirolimus interactions

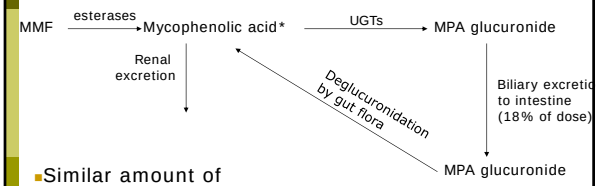
Effect on sirolimus concentrations

INCREASE	Decrease
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	EIAED (carbamazepine, phenytoin, phenobarbital)
Amiodarone	St. John's wort
Diltiazem, Verapamil	Nevirapine
CyA	Rifabutin
Amprenavir	Rifampin
Clarithromycin, Erythromycin	
Grapefruit Juice	

Management: Monitor concentrations, adjust sirolimus dose PRN

Micromedex

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

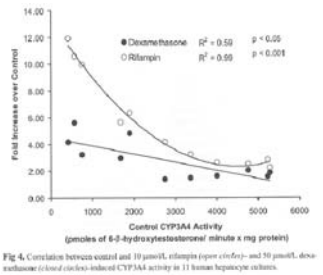


Fig 4. Correlation between control and 10 μmol/L rifampin (open circles)- and 50 μmol/L dexamethasone (closed circles)-induced CYP3A4 activity in 11 human hepatocyte cultures.

Hebert Metabolic Drug Interactions Chapter 37; McCune Clin Pharmacol Ther 2000.

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