Drug Interactions in Stem Cell Transplantation

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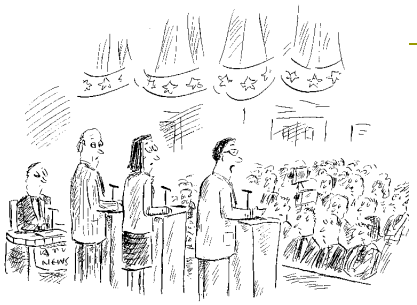


"Let me be vague."

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 HCT recipients important?

- Drug interaction leads to an undesired outcome, whether it be ↓ efficacy or ↑ toxicity
- Type of interactions
  - Pharmaceutical
  - Pharmacokinetic
  - Pharmacodynamic

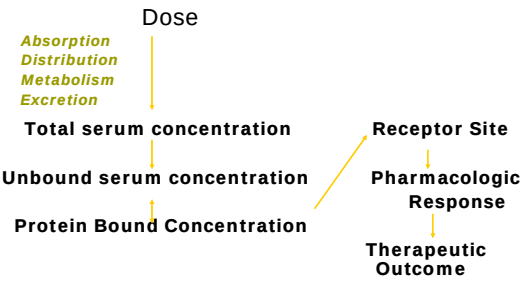
The challenges unique to HCT patients are …..

- 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



Rational Use of Drugs in Patients

- What the body does to the drug – pharmacokinetics
- What the drug does to the body – pharmacodynamics
  - Safety and efficacy

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.
- Distribution
  - Process of reversible transfer of a drug to and from the site of measurement.
  - Modifying factors:
    - blood flow
    - plasma protein binding
    - diffusion
    - solubility

Volume of Distribution

- A measure of the apparent space in the body available to contain the drug.
- Relates the amount of drug in the body to the concentration of drug in the blood.

$$Vd = \frac{\text{Amt of drug in body}}{\text{Conc. of drug in blood}} = \frac{\text{Dose}}{\text{Concentration}}$$

Elimination Processes

- Metabolism
  - predominately liver
  - Other sites: kidney, lung, GI, plasma
- Excretion
  - Kidneys and GI
  - Other sites: milk, sweat, saliva, tears

Biotransformation (Metabolism)

- Theory:
  - Drug inactivation
  - Increased elimination from the body
- However:
  - Metabolites may have biological activity; similar or different than parent
  - May contribute to toxic and/or beneficial effects

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 metabolites
    - CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4

The Cytochrome P450 (CYP) Enzyme System

- Phase I enzymes
  - Liver
    - several different isozymes located in endoplasmic reticulum
    - e.g., CYP1A2, CYP2A6, CYP2B6, CYP2C, CYP3A
  - Extrahepatic: intestine (CYP3A4/5), kidney (CYP3A5), brain (CYP2B6), lungs, breast
- Large source of drug interactions
  - Differences in enzyme regulation between animals – humans
  - Variety of in-vitro methods
    - Inhibition: cDNA expressed or human microsomes
    - Induction: human hepatocytes or some constructed cell lines
  - In-vivo methods
    - healthy volunteer studies with 'cocktails' largely used but effects of cytokines (e.g., IL6) upon PXR function which contributes to regulation of CYP3A/CYP2B6/pgp induction

Examples of important CYP in HCT

Drug	Substrate for	Reaction
Cyclophos-phamide (CY)[1]	2C9, 2C19	Activation to 4hydroxyCY (HCY)
	2B6, 3A4/5*	
	3A4/5	Detoxification to dechloroCY
Imatinib[2]	3A4/5	Elimination
Prednisone	3A4/5	"
Dexamethasone	3A4/5	"
Cyclosporine	3A4/5	"
Tacrolimus	3A4/5	"
Sirolimus	3A4/5	"

[1]Ren Cancer Research 1997; Huang Biochem Pharmacol 2000; Qiu Clin Pharm Ther 2004. [2]Package insert.

Effect upon CYP

Drug	Effect	Model*	Reference
CY	↑CYP3A4, CYP2B6	I	Lindley Drug Metab Disp
	↓ CYP3A4	I	Moore Clin Pharmacol Ther
Imatinib	↓ CYP2C9, CYP2D6	I	Package insert
	CYP3A4/5	I, HV	", Obrien Br J Cancer 2003
Prednisone	? ↑ CYP3A4/5		
DEX	↑ CYP3A4/5	I, HV	McCune Clin Pharm Ther

*Models. I:in vitro; HV:PK study in healthy volunteers; C:PK study in cancer patients

CY: cyclophosphamide; DEX: dexamethasone ↑: induces ↓ inhibition

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: Conjugation reactions

- Acetylation (Procainamide, sulfonamides)
- 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
- Sulfation

ATP-binding cassette (ABC) superfamily

Transporter	Substrate
ABCB1 (MDR1)*	calcineurin inhibitors, sirolimus
ABCC1 (MRP1)	etoposide, glutathione conjugates of corticosteroids
ABCC2 (MRP2)	CEPM (CY metabolite), Mycophenolic acid
ABC C3, C4, C5	Methotrexate
ABCG2 (BCRP)	

*codes for pglycoprotein (pgp)

Pauli-Magnus Pharmacogenetics 2003; 13: 189; Sekine Annals of Oncology 2001; 12: 1515; Qiu J Pharmacol Exper Ther 2004; Oleschuk Am J Physiol Gastrointest Liver Physiol 2003 Feb;284(2):G280;

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)

Pauli-Magnus Pharmacogenetics 2003; 13: 189; Sekine Annals of Oncology 2001; 12: 1515; Slattery AAPS 2002; Oleschuk Am J Physiol Gastrointest Liver Physiol 2003 Feb;284(2):G280;

Excretion

- Drugs are eliminated from the body unchanged or as metabolites
- Polar >>>>>>Lipid soluble drugs
- Involves
  - Glomerular filtration
  - Active tubular transport
  - Passive tubular absorption

Clearance

- A measure of the body's ability to eliminate drugs.
- May be regarded as the volume from which all the drug would appear to be removed per unit time
- Clearance is the PK parameter most useful for evaluation of an elimination mechanism
- Described in terms of eliminating organ
  - hepatic clearance
  - renal clearance
  - pulmonary clearance

Elimination Half-Life

- The time is take 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
Cl = total body clearance

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

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

Learning Objectives

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GVHD Medications

Cyclosporine, Tacrolimus, Mycophenolate mofetil, Methotrexate, Sirolimus, Prednisone

Less commonly used GVHD medications

- Immunomodulating modalities: mTOR-inhibitors, thalidomide, hydroxychloroquine, vitamin A analogs, clofazimine, rituximab, alemtuzumab, etanercept
- Cytostatic agents: mycophenolate mofetil, methotrexate, 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

AED	Effect
Grapefruit juice	↓ intestinal CYP3A, ↔ pgp
Phytoestrogens/flavonoids	competitively ↓ABCG21
St. John's wort	↑ CYP3A4, pgp
Garlic	↑ CYP3A4

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

Calcineurin Inhibitors

- Pharmacodynamic relationships
  - ↓CyA/TAC ↑risk of aGVHD
  - ↑CyA/TAC ↑nephrotoxicity
    - occurs even with targeting trough CyA or TAC trough concentrations
- Substrates for CYP3A4/CYP3A5 and p-glycoprotein

Yee; N Engl J Med 1988; 319: 65; Ghalie Annals Pharmacother 1994; 28: 379; Wingard BBMT 1998

Calcineurin Inhibitors

- Personalized through trough concentrations of cyclosporine or tacrolimus, but considerable interpatient variability in efficacy and toxicity remain
  - Cyclosporine concentrations poorly correlate with calcineurin activity in HCT and kidney transplant recipients[1]
  - Calcineurin activity higher in kidney transplant patients receiving tacrolimus vs. cyclosporine[2]
- Calcineurin activity
  - Methods available for over 15 years, with some recent methodologic advances
  - But, calcineurin activity, assessed using the newer methods, have yet to be associated with clinical outcomes in solid organ transplant recipients[3]
  - Within HCT recipients, two studies have conflicting findings regarding the association between CN activity and acute GVHD[1]

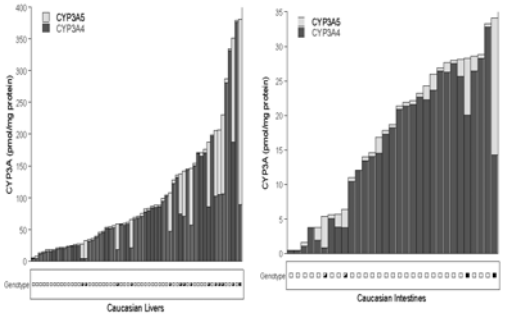
[1]Sanquer S et al. Transplantation 2004;77(6):854-8. Pai SY et al, Blood 1994;84(11):3974-9
[2]Koefoed-Nielsen et al. Transplant International 2006;19: 821-7. [3]Jorgensen KA et al. Scandinavian journal of immunology 2003;57(2):93-8. Barten MJ et al. Cell proliferation 2007;40(1):50-63.

Pharmacogenomics of renal dysfunction in HCT patients receiving calcineurin inhibitors

- Various pharmacogenomic associations found in solid organ transplant patients
- ABCB1 and CYP3A5 responsible for the renal disposition of calcineurin inhibitors
- Investigated pharmacogenomic associations in the multidrug resistance (*ABCB1*) and cytochrome P450 3A5 (*CYP3A5*) genes and acute kidney injury (AKI) and chronic kidney disease (CKD) in 121 CY/TBI conditioned patients
- No pharmacogenomic associations found
  - Patients genotyped for *CYP3A5*1>*3* and *ABCB1* single nucleotide polymorphisms (SNPs, 1199G>A, 1236C>T, 2677G>T/A, and 3435C>T).
  - AKI occurred in 48 of 121 patients (39.7%) and CKD in 16 of 66 patients (24.2%)
- Haplotype estimation and univariate association analyses performed because of strong ABCB1 linkage disequilibrium

Woodahl EL...McCune JS. Pharmacogenomics J. 2008 Aug;8(4):248-55. Epub 2007 Aug 14.

Variability in CYP3A content



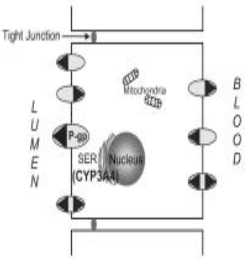
Lin et al. Mol Pharmacol 2002;62:162-72

P-glycoprotein

- ATP-dependent drug transporter (ABCB1)
- Transports a large number of structurally diverse agents primarily cationic or neutral hydrophobic drugs
- Limits oral drug bioavailability
- Transports drugs out of renal tubular epithelial cells and mesangial cells on the glomerulus

P-glycoprotein

- P-gp mRNA High
  - Kidney, Adrenal
- P-gp mRNA Intermediate
  - Liver, Lung
  - Jejunum, Colon, Rectum
  - Lymphoid bone marrow & T-cells
- P-gp mRNA Low
  - Brain, Spleen
  - Prostate, Ovary
  - Muscle, Skin
  - Stomach, Esophagus



Paine et al. Ther Drug Monitor 2004; 26: 463.

Medication that increase CyA or TAC plasma concentrations

Agent	Effect CYP3A	Effect pgp
Amiodarone		↓
Clarithromycin, Erythromycin	↓	↓
Diltiazem, Nicardipine, Verapamil	↓	↓
Fluconazole, Itraconazole, Ketoconazole, Voriconazole	↓	↓
Grapefruit Juice	↓	
Chloramphenicol	?	?
Theophylline	?	?
Imatinib	↓?	

- Management: Monitor concentrations, ↓ dose of CNI PRN

Hebert. Metabolic Drug Interactions 2000 Ch 37; Shimada Transplant International 2003.

Medication that decrease CyA or TAC plasma concentrations

Agent	CYP3A Effect	P-gp Effect
Carbamazepine	↑	
Phenobarbital	↑	↑
Phenytoin	↑	↑
Rifampin	↑	↑↓
St. John's Wort	↑	↑
CY/cytarabine	↑ (?)	?

- Management: Monitor concentrations, ↑ dose of CNI PRN

Interactions

- Drug-drug interactions
  - Cyclophosphamide
    - Activated by cytochrome P450, thus inhibitors would decrease HCY. Itraconazole ↑ exposure to metabolites associated with hepatotoxicity
  - Cyclosporine increases mycophenolic acid clearance
- Drug-food Interactions:
  - Grapefruit juice inhibits CYP3A4 and thus ↑ sirolimus absorption
  - Not always predictable. Expect grapefruit juice to ↑ absorption of etoposide, a CYP3A4/pglycoprotein substrate, but it actually decreased the absorption in cancer patients.

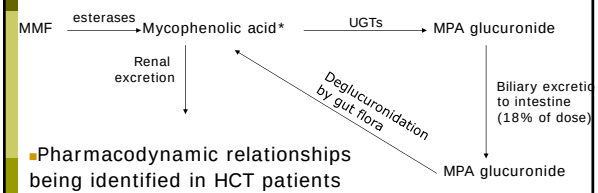
Hassan. Ca Chemo Pharm 1993; 33: 181, Buggia Anticancer Res 1996; 16: 2083. Marr Blood. 2004;103:1557 Reif Eur J Clin Pharmacol. 2002;58:491.

Methotrexate

- Pharmacodynamics
- Interactions
  - Avoid salicylates, NSAIDs and probenecid
    - ↑ nephrotoxicity, bone marrow suppression, mucositis
  - TMP/SMX, penicillins

McDonnell (Hansten & Horn; Dorr)

Mycophenolate Mofetil (MMF)



- Pharmacodynamic relationships being identified in HCT patients
- Cholestyramine
  - ↓ MPA AUC 40% (10-61%)
  - Avoid this combination
- Norfloxacin/metronidazole
  - ↓ enterohepatic recirculation ↓ MPA AUC by 30%

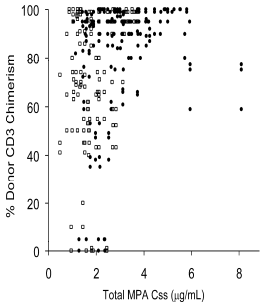
Pharmacodynamics After MMF Administration to HCT Patients

- Evaluated in heterogenous populations, differing by recipient age, conditioning regimen, graft sources
- Acute GVHD associated with low total MPA trough concentrations[1] or low free MPA AUC (but not trough)[2]
- Graft rejection associated low total MPA trough concentrations[2] or total MPA Css (but not trough)[3]
- Low T cell chimerism associated with low total MPA Css[3]

[1]Osunkwo I, et al. Biol Blood Marrow Transplant. 2004;10:246-58. [2]Jacobson P, et al. Clin Pharmacol Ther. 2005;78:486-500; [3]Giaccone L, et al. Blood. 2005;106:4381-8.

MPA Pharmacodynamics in Nonmyeloablative, Unrelated Donor HCT

- 85 patients, hematologic malignancies, FLU/TBI, HLA-matched unrelated-donor, cyclosporine/MMF post-grafting
- 16 patients with a total MPA Css <3 µg/mL had low (<50%) donor T-cell chimerism (P = .03)
  - Only modifiable risk factor for donor chimerism
- 6 patients with MPA Css <2.5 µg/mL had graft rejection
- Elevated unbound Css was associated with CMV reactivation (20 vs 31 ng/mL, P = .03)
- No significant associations with acute GVHD or relapse



Giaccone L, et al. Blood. 2005;106:4381-8.

Mycophenolate Mofetil Drug Interactions

- Antacids (Magnesium and Aluminum Hydroxides)[1]
  - ↓ MPA Cmax by 33% & ↓ 24 hour AUC 17%
- Ferrous Sulfate
  - ↓ MPA AUC 90% in one cross-over study,[2] but another study in renal transplant patients suggests no interaction[3]
- Calcium Polycarbophil (e.g. Fibercon)
  - ↓ MPA AUC 25-50%
- No effect on TMP/SMX, acyclovir, ganciclovir, oral contraceptives[1]

[1]Bullingham Clin Pharmacokinetics 1998; 34: 429; Br J Clin Pharmacol 1996;41:513-6 [2]Clin Pharmacol Ther 2000;68:613-6; [3]Mudge Transplantation 2004; 77: 206; CellCept Package Insert J Clin Pharmacol 2002;42:1275-80;

Mycophenolate Mofetil Drug Interactions

- CyA
  - ↓ AUC of MPA and ↑ AUC of MPA glucuronide
  - Disrupts enterohepatic recirculation by affecting transport
- TAC
  - May inhibit UGT
- Management: If switch from CyA to TAC, ↓ MMF dose

Brown Ther Drug Monitor 2002, 24: 598. Shipkova Ther Drug Monitor 2001; 23: 717; Shaw

Sirolimus

- Substrate for CYP3A4/5 & p-glycoprotein
  - Similar drug interactions as tacrolimus and cyclosporine
- Effect of other immunosuppressants upon sirolimus dose-normalized Ctrough
  - not affected by methylprednisolone pulses (500-3000 mg)
  - higher in patients on cyclosporine vs. tacrolimus

Stepkowski Am J Transplantation 2004; 4: 1345; Backman Brit J Clin Transplant 2003; 54: 65

Sirolimus-Neoral

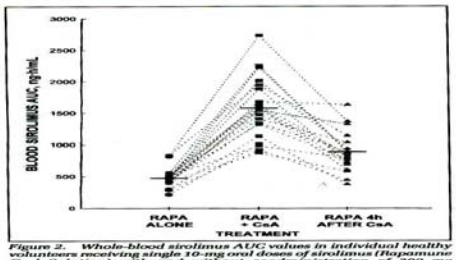


Figure 2. Whole-blood sirolimus AUC values in individual healthy volunteers receiving single 10-mg oral doses of sirolimus (Rapamune Oral Solution) with and without coadministration of 300 mg cyclosporine (Neoral Soft Gelatin Capsules). Bars indicate mean values.

Zimmerman. J Clin Pharmacol 2003; 43: 1168

Sirolimus

- Substrate for CYP3A4/5 & p-glycoprotein
- Factors important in drug interactions similar to those important for tacrolimus and cyclosporine
- Dose-normalized Ctrough higher in patients on cyclosporine vs. tacrolimus

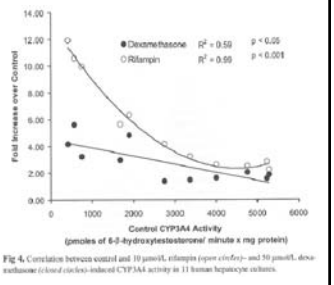
Cattaneo. Am J Transplantation 2004; 4: 1345.

Corticosteroids

- In general, steroid metabolism involves sequential hydroxylation followed by conjugation to water-soluble metabolites
- Urinary elimination of the 6 β-hydroxy metabolites makes up 8-10% of the dose for prednisone
- 6 β-hydroxylation occurs via CYP3A4 and CYP3A5 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



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

Effects of dexamethasone upon CYP3A/pgp

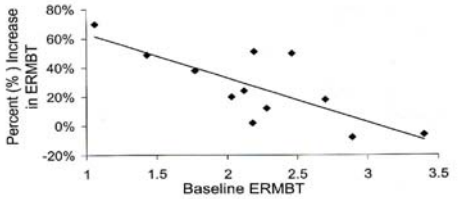


Fig 1. Correlation between baseline erythromycin breath test result and increase in erythromycin breath test result that occurs with dexamethasone administration ($r^2 = 0.58$, $P = .004$).

McCune Clin Pharmacol Ther 2000.

We haven't the money, so we have to think

Ernest Rutherford

Haploidentical Donors

- Virtually all have one haplotype-mismatched donor
  - Can select from best of any relatives based on age, infectious disease status, and natural killer (NK) reactivity
  - Immediate access to donor-derived cellular therapies
- In 1980s, mortality risk was too high
- Recent interest due to improved patient selection (by disease and genetics), supportive care, and GVHD prophylaxis

Dey BR. *Br J Haematol*. 2006;135:423-37; Aversa F. *Bone Marrow Transplant*. 2008;41:473-81.

Umbilical Cord Blood

- Use in adults limited by small cell dose, resulting in delayed engraftment
- Double cord blood leads to rapid neutrophil recovery with one single cord ultimately "winning"
  - Have increased incidence of acute GVHD, long-term thrombocytopenia in subset of patients
- Many unanswered questions about HLA matching, RIC, minimum cell dose, immune reconstitution, ex vivo expansion

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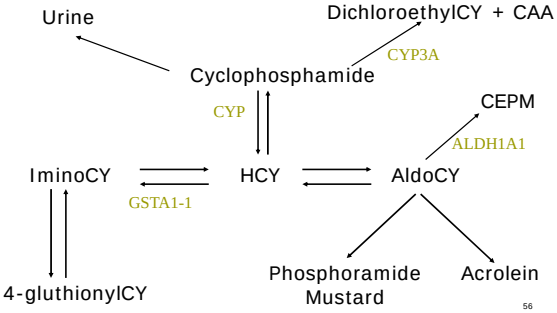
Wagner J, et al. *Biol Blood Marrow Transplant*. 2006;12:1206-17.

Cyclophosphamide



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McDonald GB, et al. *Blood*. 2003;101:2043-8.

CY Pharmacodynamics Differ With Conditioning Regimens

- With TBU/CY, there were no statistically significant associations between the AUC of CY or its metabolites and liver toxicity, non-relapse mortality, relapse, or survival (all P > .15)
  - Oral busulfan doses targeted to Css 800-900 ng/mL
  - Personalization of CY doses based on its pharmacokinetics in TBu/CY unlikely to be beneficial
- CY, like busulfan, pharmacodynamics differ between conditioning regimens
- Lower toxicity by using bu/fludarabine regimen?

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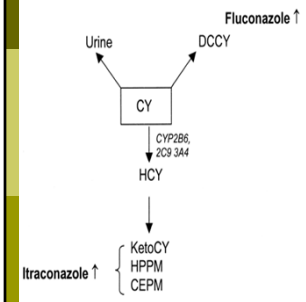
McCune JS, et al. *Biol Blood Marrow Transplant*. 2007;13:853-62.

Reported interactions with CY

- CY autoinduces clearance
- Significance unknown
  - Thiotepa ↓ CYP2B6
  - CY half-life[1]
    - ↑ by allopurinol, ↓ by barbiturates, corticosteroids
  - ↓ alkylating activity: barbiturates, AED[1]
  - Ondansetron: ↓ CY AUC in CPB regimen[2]
  - Aprepitant: moderate CYP3A4 inhibitor, mild CYP2C9 and CYP2C19 inhibitor…no effects on CY to HCY formation
- In-vitro: DEX, phenobarb, rifampin ↑ HCY formation

[1]Stolbach JAMA 1982; Jao 1972, Faber 1974; [2]Gilbert Ca Chemo Pharm 1998; 42: 497. Cagnoni 1999; Van Meerten 1995; 12 (3): 168.

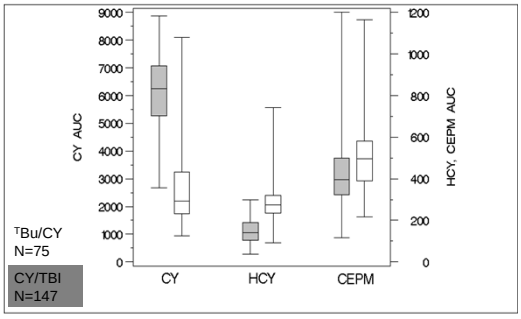
CY-itraconazole interaction



- Itraconazole (200 mg IV QD, or oral solution 2.5 mg/kg TID)
- fluconazole (400 mg IV/PO QD)
- Patients who received itraconazole developed higher serum bilirubin and creatinine values in the first 20 days after SCT
  - highest values in patients who received itraconazole concurrent with CY

Marr Blood 2004; 103 (4): 1557.

CY Pharmacokinetics Depend on Conditioning Regimen



McCune JS, et al. Biol Blood Marrow Transplant. 2007;13:853-62.

Conclusions

- Drug interactions are frequent in HCT patients
- Changes in CYP cause many pharmacokinetic drug interactions, but other types of interactions are also relevant
- Within GVHD prophylaxis, the routine use of monitoring for calcineurin inhibitors can guide management.
- Further pharmacodynamic data needed to know impact of interactions with mycophenolate mofetil, corticosteroids and sirolimus