Significant Drug Interactions in Hematopoietic Stem Cell Transplantation

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Learning Objectives

- Identify common drug interactions in HCT
- Describe the mechanism(s) of these interactions
- Describe the adverse effects that result from polypharmacy in HCT
- Recommend appropriate management of common drug combinations

Prevalence of Drug Interactions in HCT

- Guastaldi and colleagues performed a cross-sectional study in 70 SCT patients over 7 months
  - 46 patients (65.7%) allo-transplant
  - 24 patients (34.8%) auto-transplant
  - Median of 8 medications (range, 4-16)
  - 60%: ≥ 1 potential drug interaction
  - 21.4%: ≥ 1 potential major drug interaction
  - 31 types of drug interactions (of 128 total)
  - Cyclosporine (CSA) most common agent identified in a potential drug interaction (28.1%)

Guastaldi RB, et al. *Int J Clin Pharm*. 2011;33:1002-1009

Types of Drug Interactions

- Pharmacokinetic (PK) interaction
  - Change in drug and/or metabolite concentration due to changes in absorption, distribution, metabolism or elimination
    - Most common site: hepatocytes in the liver and intestinal enterocytes during CYP450-mediated metabolism
- Pharmacodynamic (PD) interaction
  - Change in the physiologic activity of a drug
    - e.g., increased/decreased therapeutic effect, increase adverse effect

CYP450 Superfamily

- Group of enzymes in the liver, intestines and kidney
- Decrease/alter pharmacologic activity of drugs and assist in elimination
- >50 genes identified
- 8 genes responsible for majority of drug interactions
  - CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4
  - CYP3A4: ~50% of all CYP450 enzymes and involved in >50% of all drug metabolism

CYP450 Superfamily

- Polymorphisms
  - Mutations in CYP450 enzyme altering normal function
    - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5
  - Mutations: slow metabolizers and extensive metabolizers
  - Poor metabolizers
    - Inactive CYP2C19 enzyme: 25% of Asian population, 3-6% of Caucasian

CYP-mediated drug interactions

- Interactions between medications can expand the variability of metabolism by 400-fold

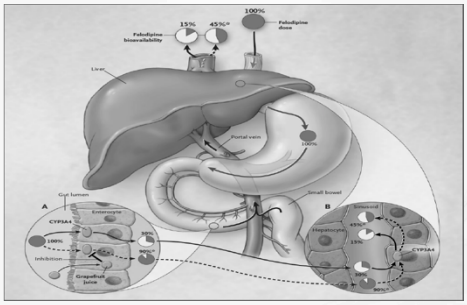
Inhibition	Induction
Mechanism: 1. Direct inactivation of enzyme 2. Competition between substrates	Mechanism: 1. ↓ synthesis of enzyme 2. ↑ breakdown of enzyme
Result: 1. ↑ [drug] and ↑ elimination t1/2 2. ↑ potential for toxic side effects	Result: 1. ↓ [drug] and ↓ elimination t1/2 2. ↑ potential for therapeutic failure
Onset: ~1-3 days (depends on t1/2)	Maximum effect: 1-2 weeks (depends drug t1/2 and protein synthesis)
Deinhibition: typically 1-3 days (depends on drug t1/2)	Deinduction: weeks (depends on t1/2 and degradation of enzyme)

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006
Wilinson GR. *N Engl J Med*. 2005;352:2211-2221.

CYP-mediated drug interactions

- First-pass metabolism after oral administration can be majorly affected by a drug interaction
  - CYP enzymes in the intestine more exposed to interacting drugs versus hepatic CYP enzymes
  - The bioavailability can ↑ or ↓ dramatically in the presence of an inhibitor or inducer
  - The elimination of the drug can also ↑ or ↓

CYP-mediated drug interactions; First-Pass Metabolism



Wilinson GR. *N Engl J Med*. 2005;352:2211-2221.

P-glycoprotein

- What is P-glycoprotein (P-gp)?
  - Membrane transporter produced by the multidrug resistance gene (MDR1)
- Where is P-gp located?
  - Enterocytes of small intestine
  - Hepatocytes
  - Proximal tubular cells of kidneys
  - Endothelial cells of blood-brain barrier
- What is P-gp's role in drug elimination?
  - Acts as an efflux pump by removing intracellular drug thereby ↓ absorption and ↑ elimination

P-gp-mediated drug interactions

- Drug-induced inhibition of P-gp activity results in:
  - ↑ drug absorption by enterocytes in the intestines
  - ↓ drug elimination by biliary/renal excretion
- Interaction with P-gp is not a class effect
  - e.g., CCB: diltiazem and verapamil are P-gp substrates, yet nifedipine is not
- Substrate overlap between P-gp and CYP3A but is not absolute

Kim RB. *Drug Metab Rev*. 2002;34:47-54
Kim RB et al. *Pharm. Res.* 1999;16:408-414

P-gp-mediated drug interactions

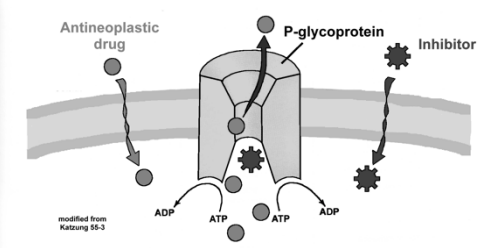


Image used with permission from Dr. Janet Fitzakerley
University of Minnesota Medical School Duluth

Audience Response Question

- Sirolimus is metabolized by CYP3A4 and P-gp. It also undergoes extensive first-pass metabolism. Ketoconazole is a known inhibitor of CYP3A4 and P-gp. What will most likely happen if these two drugs are administered together?

a. The bioavailability of ketoconazole with decrease
b. The bioavailability of sirolimus will increase
c. The serum concentration of sirolimus will decrease
d. The serum concentration of ketoconazole will increase

Drug interactions by class: Chemotherapy

Drug interactions with busulfan

Mechanisms for drug interactions with busulfan (Bu)

1. Competition for glutathione
   - Bu is metabolized by conjugation with glutathione via glutathione S-transferase (GST) catalysis
2. Inhibition/Induction of CYP3A4
   - Bu undergoes oxidative metabolism and not proven that CYP450 plays a role
   - Irregardless, some CYP3A4 inhibitors/inducers alter Bu metabolism

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006
Busulfex [package insert]. Edison, NJ: ESP Pharma Inc; 2011.

Drug interactions with busulfan

Table 1. Busulfan Drug–Drug Interactions

Drug	Mechanism	Effect	Recommendation	Data Type
Acetaminophen	Competition for glutathione	Increased busulfan serum level	Do not use 72 hours before or 72 hours after busulfan administration.	Theoretical based on metabolism of agents [13]
Itraconazole, voriconazole[a]	Reduced busulfan clearance	Increased busulfan serum level	Use with caution; monitor for adverse effects of busulfan; consider fluconazole as an alternative.	PK, HSCT [11]
Metronidazole	Inhibition of CYP3A4, competition for glutathione	Increased busulfan trough level	Do not use 72 hours before or 72 hours after busulfan administration.	PK, prospective HSCT [12]
Phenytoin	Induction of GST and CYP3A4	Decreased busulfan plasma level ≥ 15%	Consider using another anticonvulsant; if using phenytoin, monitor AUC of busulfan to guide levels.	CR, PK [7]

PK indicates pharmacokinetic studies; CR, case reports.
[a]Voriconazole interaction is theoretical based on the metabolism of the agent by the CYP450 3A4 system [14].

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006
Busulfex [package insert]. Edison, NJ: ESP Pharma Inc; 2011.
Nilsson C et al. *Bone Marrow Transplant*. 2003;31:429-435

Drug interactions with busulfan

- Nilsson and colleagues evaluated concomitant Bu and metronidazole in 24 allogeneic HCT patients
  - Group A: Bu + metronidazole x 4 days
  - Group B: Bu alone x 2 days, Bu + metronidazole x 2 days
  - Group C: Bu alone x 4 days

Mean trough levels (ng/ml)		
Group	*Mean +/- s.d.*	*P-value (vs. Group C)*
A	948 +/- 280	<0.001
$B_{(0\text{-}54h)}$	452 +/- 68	n.s.
$B_{(60\text{-}90h)}$	807 +/- 90	<0.001 (<0.0001 vs. $B_{0\text{-}54h}$)
C	507 +/- 75	N/A

Nilsson C et al. *Bone Marrow Transplant*. 2003;31:429-435.

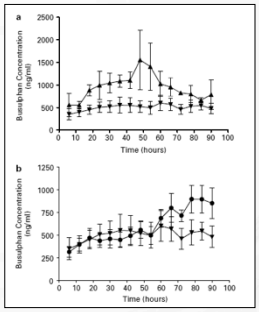
Drug interactions with busulfan

Nilsson study cont…

△ Group A: Bu + metronidazole

○ Group B: Bu x2 days, then Bu + metronidazole x2 days

▽ Group C: Bu alone



Nilsson C et al. *Bone Marrow Transplant*. 2003;31:429-435.

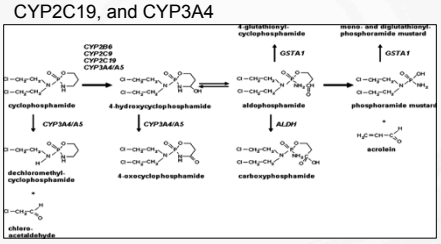
Drug interactions with busulfan

- Nilsson study cont.
  - Regimen-related toxicity (RRT)
    - Group A: 5/5 ↑ liver function tests (LFTs); 3/5 with sinusoidal obstruction syndrome (SOS)
    - Group B: 5/9 ↑ bilirubin; 1/9 ↑ LFTs; no SOS diagnoses
    - Group C: 3/10 ↑ AST; no SOS diagnoses
  - Authors' conclusions
    - ↑ [Bu] may be due to ↓ glutathione content secondary to metronidazole reactive metabolites using glutathione as a scavenger
    - ↑ risk for SOS may be due to high [Bu] *and* increased metronidazole reactive metabolites

Nilsson C et al. *Bone Marrow Transplant*. 2003;31:429-435.

Drug interactions with cyclophosphamide

- Cyclophosphamide (CY) CYP450 metabolism
  - Substrate of CYP2A6, **CYP2B6**, CYP2C8, CYP2C9, CYP2C19, and CYP3A4



Timm R et al. *Pharmacogenomics J*. 2005;5:365-373.

Drug interactions with cyclophosphamide

- CY is a MAJOR substrate for CYP2B6
- Consider alternative therapy if CYP2B6 inducers or inhibitors are given concurrently with CY
  - Strong CYP2B6 Inducers:
    - carbamazepine, fosphenytoin, nevirapine, phenobarbital, phenytoin, primidone, rifampin
  - Strong CYP2B6 Inhibitors
    - thiotepa

Lexicomp Online, Lexi-Drug Online, Hudson, Ohio: Lexi-Comp, Inc; 2013; December 14, 2013

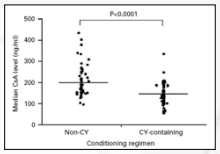
Drug interactions with cyclophosphamide

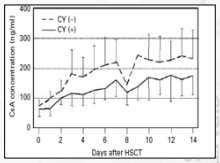
- de Jonge and colleagues published a case report about a patient who was on CY and phenytoin concurrently
  - Pharmacokinetic analysis
    - 133% ↑ rate of 4-hydroxycyclophosphamide (4- OHCP) formation
    - 51% ↑ AUC of 4-OHCP
    - 67% ↓ AUC of CY(parent compound)
  - Subsequent doses decreased by 47%
  - No specific toxicities observed
  - Authors' conclusion: avoid coadministration of phenytoin and CY due to significant induction of CY metabolism by phenytoin

de Jonge et al. *Cancer Chemother Pharmacol*. 2005;55:507-510.

Drug interactions with cyclophosphamide

- Nagamura et al. retrospectively evaluated cyclosporine (CSA) levels in patients that had CY-containing conditioning regimens vs. non-CY regimens
  - 103 patients
  - CY dosing: 60mg/kg/day x 2 days
  - CSA levels evaluated were on intravenous dosing





Nagamura et al. *Bone Marrow Transplant*. 2003;32:1051-1058.

Drug interactions with cyclophosphamide

- Nagamara cont.
  - CY/no-CY, age, donor and use of antibiotic were evaluated in multivariate regression analysis
    - Only CY found to have significant influence on CSA levels
  - Authors' hypotheses/conclusions
    - Autoinduction of hepatic enzymes by CY, including CYP3A4, may result in ↓ CSA levels
      - Enzyme induction can last for several weeks
    - CY may activate renal elimination of CSA
      - No published reports support this

Nagamura et al. *Bone Marrow Transplant*. 2003;32:1051-1058.

Drug interactions with cyclophosphamide

- Hassan and colleagues studied the PK interaction between Bu and CY in 36 patients
  - 3 groups
    1. CY/TBI (no BU)
    2. Bu/CY where 1st dose of CY <24 hours after last dose of Bu
    3. Bu/CY where 1st dose of CY >24 hours after last dose of Bu
  - Results: In Group 2 vs. Groups 1,3
    - Clearance of CY significantly lower
    - Half-life of CY significantly longer
    - SOS significantly higher and mucositis more frequent
  - Significant positive correlation between [Bu] and $AUC_{4\text{-}OHCP}$

Hassan et al. *Bone Marrow Transplant*. 2000;25:915-924.

Drug interactions with cyclophosphamide

- Hassan cont.
  - Authors' hypotheses/conclusions
    - Administering Bu prior to CY puts patients at risk for CY toxicity
      - Bu's main metabolic pathway is mediated by glutathione,
      - CY active metabolites, including 4-OHCP, eventually undergo "enzymatic detoxification" by glutathione
      - <24 hours after Bu administration, hepatocytes are depleted of glutathione and CY active metabolites are not detoxified
    - Consider altering preparative regimens in terms of time schedules and dose intensity

Hassan et al. *Bone Marrow Transplant*. 2000;25:915-924.

Drug interactions with etoposide

- Etoposide
  - Major CYP3A4 substrate
  - Consider alternative therapy if CYP3A4 inducers or inhibitors are given concurrently with etoposide
    - Strong CYP3A4 Inducers:
      - carbamazepine, dexamethasone (systemic),enzalutamide, fosphenytoin, nafcillin, nevirapine, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine
    - Strong CYP3A4 inhibitors:
      - atazanavir, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, darunavir, delavirdine, fosamprenavir, indinavir, itraconazole, ketoconazole (systemic),lopinavir, nefazodone, nelfinavir, nicardipine, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Lexicomp Online, Lexi-Drug Online, Hudson, Ohio: Lexi-Comp, Inc; 2013; December 14, 2013

Drug interactions with other chemotherapy

- Thiotepa
  - Strong CYP2B6 Inhibitor
  - Consider alternative therapy if CYP2B6 substrates are given concurrently with thiotepa
    - CYP2B6 substrates
      - Bupropion, cyclophosphamide, efavirenz, irinotecan, ketamine, methadone, promethazine, propofol, selegiline
- Melphalan, Fludarabine, Carboplatin
  - No significant PK drug interactions

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Audience Response Question

- Which of the following may result if rifampin is administered with cyclophosphamide?

a. Increase in AUC of active metabolite, 4-OHCP
b. Increase in AUC of cyclophosphamide (parent compound)
c. Decrease in AUC of rifampin
d. No significant change in AUC for either drug

Drug interactions by class: Immunosuppressive Agents

Drug interactions with calcineurin inhibitors

- CSA and tacrolimus
  - Extensively metabolized by CYP3A4 in liver and small intestine
    - Strong CYP3A4 Inducers:
      - carbamazepine, dexamethasone (systemic),enzalutamide, fosphenytoin, nafcillin, nevirapine, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine
    - Strong CYP3A4 inhibitors:
      - atazanavir, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, darunavir, delavirdine, fosamprenavir, indinavir, itraconazole, ketoconazole (systemic),lopinavir, nefazodone, nelfinavir, nicardipine, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

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Drug interactions with calcineurin inhibitors

- CSA and tacrolimus
  - P-gp substrates
    - P-gp inducers
      - carbamazepine, dexamethasone (systemic), doxorubicin, nefazodone, phenobarbital, phenytoin, prazosin, rifampin, St Johns Wort, tenofovir, tipranavir, vinblastine
    - P-gp inhibitors
      - abiraterone acetate, amiodarone, atorvastatin, carvedilol, clarithromycin, cobicistat, crizotinib, cyclosporine (systemic), darunavir, dipyridamole, dronedarone, erythromycin (systemic), grapefruit juice, itraconazole, ivacaftor, ketoconazole (systemic), lapatinib, lomitapide, lopinavir, mefloquine, nelfinavir, nicardipine, nilotinib, progesterone, propranolol, quinidine, quinine, ranolazine, reserpine, ritonavir, saquinavir, sunitinib;, tacrolimus (systemic), tamoxifen, telaprevir, ulipristal, vandetanib, vemurafenib, verapamil, voriconazole
- *Please refer to Appendix 1 in your handout*

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Table 3 Clinically relevant pharmacokinetic drug interactions with cyclosporine (CyA)

Drug	*Data type*	*Proposed mechanism of interaction by drug*	*Clinical effect (potential or actual)*	*Recommended action*
Azole antifungals				
Fluconazole[56–62]	Case reports; PK studies	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity	Monitor levels. ↓ CyA dose
Itraconazole[51,63,64]			See Table 4	Monitor levels. ↓ CyA dose
Voriconazole[65]			See Table 5	Monitor levels. ↓ CyA dose
Calcium channel blocker[a] (diltiazem, verapamil)[66]	PK studies; case reports	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity	Monitor levels. ↓ CyA dose
			↓ CyA CL 50–70%	
Carbamazepine[67]	Case report	CYP3A4 induction	↓ CyA [ ] → GVHD	Monitor CyA levels. ↑ CyA dose
				Change to nonenzyme-inducing antiepileptic
Chloramphenicol[68]	Case report	Unknown	↑ CyA C_{min} → ↑ toxicity	Monitor CyA levels. ↓ CyA dose
Etoposide[69]		↓ Clearance of etoposide via P-glycoprotein mechanism	↑ Etoposide AUC 59%	CYA has been used to overcome P-glycoprotein resistance. No action to be taken, interaction intentional
			↓ Etoposide CL 35%	
			↑ Etoposide $t_{1/2}$ → > toxicity	
Fluoroquinolones (norfloxacin)[b, 70]	Case report	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity	Monitor CyA levels. ↓ CyA dose (~43%)
Imatinib mesylate	Hypothesis	CYP3A4 inhibition	Unknown, anticipate ↑ [ ] CyA	Monitor CyA levels
Macrolide antibiotics				
Clarithromycin[52,54]	Case reports	CYP3A4 inhibition	↑ CyA C_{min} 26–33%	Monitor CyA levels. ↓ CyA dose
Erythromycin[70]	Case reports	CYP3A4 inhibition	↑ CyA C_{min} 4.7-fold → toxicity	Monitor CyA levels. ↓ CyA dose by 50%
Mycophenolate mofetil (MMF)[70]	PK studies	Attenuates enterohepatic recirculation of MPAG/MPA	↓ AUC of MPA	Monitor patient for side effects of MMF
			↑ MMF C_{min} two-fold when CyA discontinued	
Phenytoin[67,70]	PK studies; case reports	CYP3A4 induction	↓ CyA C_{min}	Monitor CyA levels. ↑ CyA dose
			↓ CyA AUC 50% → ↑ GVHD	
Quinupristin/dalfopristin (QND)[c]	Case report	Unknown[c]	↑ CyA C_{min} three-fold → ↑ toxicity	Monitor CyA levels. ↓ CyA dose
Rifampin[67, 71]	Healthy volunteers	CYP3A4 induction	↓ CyA AUC$_{0-4}$ 26%	Avoid if possible
			↓ CyA AUC$_{0-\infty}$ 73%	↑ CyA doses according to levels
			↓ F CyA 63%	
Sirolimus[66] (oral liquid)	Healthy volunteers	CYP3A4 inhibition of sirolimus; inhibition P-glycoprotein transport	↑ Sirolimus C_{max} 116%[d]	Administer sirolimus 4h after administration of CyA
			↑ Sirolimus AUC 230%[d]	Monitor CyA levels if necessary
			↑ Sirolimus C_{max} 57%[e]	
			↑ Sirolimus AUC 80%[e] → Toxicity	
Sirolimus[66] (tablets)	Healthy volunteers	CYP3A4 inhibition of Sirolimus	↑ Sirolimus C_{max} 512%[d]	Administer sirolimus 4h after administration of CyA
			↑ Sirolimus AUC 1440%[d]	Monitor CyA levels if necessary
			↑ Sirolimus C_{max} 33%[e]	
			↑ Sirolimus AUC 35%[e] → ↑ Toxicity	

Leather HL. *Bone Marrow Transplant*. 2004;33:137-152.

Table 3 (Continued)

Drug	Data type	Proposed mechanism of interaction by drug	Clinical effect (potential or actual)	Recommended action
Sildenafil[89]	PK study	CYP3A4 inhibition	↑ Sildenafil C_{max} 44% ↑ Sildenafil AUC 90%	Start sildenafil at 25 mg May need to adjust antihypertensives if coprescribed
St John's wort[90–92]	Case reports	CYP3A4 induction	↑ $t_{1/2}$ (elimination) → profound hypotension ↓ CyA C_{min} → GVHD	Avoid

[ ]=concentration; ↑=increased; →=leads to; ↓=decreased; AUC=area under the curve; C_{min}=trough concentration; CL=clearance; F=bioavailability; GVHD=graft-versus-host disease; PK=pharmacokinetic; CYP3A4=cytochrome *P450 3A4* isoenzyme.
[a]Nifedipine does not increase CyA levels and can be used safely.
[b]Ciprofloxacin [100] and levofloxacin [101] have been studied and no clinically significant interaction exits.
[c]PK of QND not known, thought to be due to CYP3A4 inhibition.
[d]Pharmacokinetic changes to sirolimus when administered *simultaneously with* cyclosporine dose.
[e]Pharmacokinetic changes to sirolimus when administered *4 h after* cyclosporine dose. MPA=mycophenolic acid.

Table 2 Clinically relevant pharmacokinetic drug interactions with tacrolimus

Drug	Data type	Proposed mechanism of interaction by drug	Clinical effect (potential or actual)	Recommended action
Azole antifungals				
Fluconazole[8,10]	Case reports; PK studies	CYP3A4 inhibition	↑ Tacrolimus C_{min} → ↑ toxicity[a]	Monitor levels. ↓ Tacrolimus dose[a]
Itraconazole[8–10]			See Table 4	Monitor levels. ↓ Tacrolimus dose
Voriconazole[11]			See Table 5	Monitor levels. ↓ Tacrolimus dose
Calcium channel blockers	*In vitro*	CYP3A4 inhibition	↑ Tacrolimus AUC 26–177%	Monitor levels. ↓ Tacrolimus dose.
Diltiazem[96,104]	Case report		↑ C_{min} [ ] tacrolimus → ↑ toxicity	
Verapamil	*In vitro*	CYP3A4 inhibition	↑ Exposure→toxicity	Monitor levels. ↓ Tacrolimus dose
Chloramphenicol[96]	Case report	CYP3A4 inhibition	↑ Tacrolimus AUC 7.5-fold→toxicity	Monitor levels. ↓ Tacrolimus dose
Imatinib mesylate[105]	Abstract	CYP3A4 inhibition	Unknown, anticipate ↑ [ ] tacrolimus	Monitor levels.
Macrolide antibiotics				
Clarithromycin[10,23]	Case reports	CYP3A4 inhibition	↑ Tacrolimus C_{min} two-fold→Toxicity	Monitor levels. ↓ Tacrolimus dose
Erythromycin[24–26]	*In vitro*; case reports		↑ Tacrolimus C_{min} six-fold→↑ toxicity	Monitor levels. ↓ Tacrolimus dose
Phenobarbital[27]	*In vitro*; case reports	CYP3A4 induction	↓ Tacrolimus [ ]→GVHD	Monitor levels. ↑ Tacrolimus dose
Phenytoin[28]	Case report	CYP3A4 induction	↓ Tacrolimus [ ]→GVHD	Monitor levels. ↑ Tacrolimus dose
Rifampin[29–31]	Healthy volunteers	CYP3A4 induction	↓ Tacrolimus AUC_{0-t} 68% ↓ Tacrolimus AUC_{∞} 35% ↓ F_{bio} 51%	Monitor levels. ↑ Tacrolimus dose
St John's wort[32]	Case report	CYP3A4 induction, ? ↑ P-glycoprotein transporter expression	↓ Tacrolimus [ ]→GVHD	Monitor levels. ↑ Tacrolimus dose
Theophylline[33]	Case report	CYP3A4 inhibition	↑ Exposure→toxicity	Monitor levels. ↓ Tacrolimus dose

[ ]=Concentration; ↑=increased; →=leads to; ↓=decreased; AUC=area under the curve; C_{min}=trough concentration; F=bioavailability; GVHD=graft-versus-host disease; PK=pharmacokinetic; CYP3A4=cytochrome *P450 3A4* isoenzyme.
[a]Drug interaction occurs when both agents administered orally and where fluconazole dose is >200 mg/day.

Leather HL. *Bone Marrow Transplant*. 2004;33:137-152.

Table 2. Tacrolimus (T) and Cyclosporine (C) Pharmacokinetic Drug-Drug Interactions

Drug	Mechanism	Data Type	Effect	Recommendation
CYP inhibitors				
Amiodarone	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels at 3 days to 4 weeks	If used concurrently, monitor T/C levels and adjust dosage; need to monitor levels 1–4 weeks after adding amiodarone [53].
Azoles	CYP3A4 and P-gp inhibition	PK, CR, HSCT; renal	Increased T/C levels	Adjust dosage according to Table 5.
Estrogens	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels	If used concurrently, monitor T/C levels and adjust dosage [57].
Macrolides (not azithromycin)	CYP3A4 inhibition	CR; acute renal failure	Increased T/C levels	Avoid concurrent use; if used concurrently, monitor T/C levels [59].
Metronidazole	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels	If used concurrently, monitor T/C levels and adjust dosage [36].
Non-dihydropiridine CCBs	CYP3A4 inhibition	PK, CR; neurotoxicity	Increased T/C levels	Consider a 20% T/C dosage reduction on starting CCB; monitor T/C levels [56].
Proton pump inhibitors	CYP3A4/5 and CYP2C19 inhibition	PK, renal/liver; CR, no clinical effect	Increased T exposure	If used concurrently, monitor T level and adjust dosage [38].
InvivoTKIs	CYP3A4 inhibition (nilotinib-P-gp inhibition)	Animal studies	Increased T/C levels	Monitor T/C levels [43].
Aprepitant	CYP3A4 inhibition	HSCT; no clinical effect	Increased T/C levels	Monitor T/C levels [45].
Statins	CYP3A4 inhibition; OATP1B1 metabolism	Randomized, renal, healthy; CR; rhabdomyolysis with C	Increased statin AUC three- to 20-fold (depending on statin used); less interaction with T [47]	If used concurrently, consider lower initial and maintenance dose of statins; monitor for rhabdomyolysis especially with C use (stop statin immediately if it occurs) [53].
CYP inducers				
Phenytoin	CYP3A4 induction	CR; no clinical effect	Decreased T/C levels	If used concurrently, monitor T/C level and adjust dosage [58].
Competition at CYP3A				
Corticosteroids	CYP3A4/Pgp induction	CR/PK studies	Decreased T/C levels	If used concurrently, monitor T/C level during and after steroid use [46].
	CYP3A4 substrate	CR; possibly increased neurotoxicity	Increased T/C steroid levels	If used concurrently, monitor T/C level; monitor for steroid toxicity [61].
Dihydropyridine CCBs	CYP3A4 substrate; P-gp inhibitor	PK, CR; no clinical effect	Increased T/C levels (nifedipine only T)	If used concurrently, monitor T/C level [66].
Tacrolimus and cyclosporine	Competition at CYP3A4	Based on metabolism and additive toxicity	Decreased C metabolism [48]	Discontinue T/C 24 hours before initiation of the other [42].
Sirolimus	CYP3A4 competition	PK; renal, volunteers	Decreased T/C levels; increased sirolimus AUC with C	If used concurrently, monitor T level and adjust dosage; sirolimus should be administered 4 hours after oral C [51,60].
Nafcillin	CYP3A4 competition	CR; acute renal failure	Decreased C level	Avoid concurrent use (possible interference with assay) [63].
Other interactions				
MMF	Inhibition of enterohepatic recirculation	PK; liver/renal	Decreased MMF level	Use caution if administering together; MMF dosage may need adjustment [49,62].
Caspofungin	Unknown	PK; healthy, transplantation, increased liver function test values w/C	Increased T level; Increased AUC of caspofungin with C	T is favored over C for coadministration with caspofungin; routine monitoring of T level is suggested [52,64].
Octreotide	Decreased C absorption	CR; no clinical effect	Decreased C effectiveness	If used together, monitor C level; a C dosage increase of 50% at the start of octreotide is suggested [67].

PK indicates pharmacokinetic studies; CR, case reports; CCBs, calcium channel blockers.

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006

Drug interactions with sirolimus

- Extensively metabolized by CYP3A4 in liver and small intestine
  - Strong CYP3A4 Inducers:
    - carbamazepine, dexamethasone (systemic),enzalutamide, fosphenytoin, nafcillin, nevirapine, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine
  - Strong CYP3A4 inhibitors:
    - atazanavir, boceprevir, chloramphenicol, clarithromycin, cobicistat, conivaptan, darunavir, delavirdine, fosamprenavir, indinavir, itraconazole, ketoconazole (systemic),lopinavir, nefazodone, nelfinavir, nicardipine, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
- Very long t1/2 (62+/-16 hours) so drug interactions can be delayed

Lexicomp Online, Lexi-Drug Online, Hudson, Ohio: Lexi-Comp, Inc; 2013; December 14, 2013

Drug interactions with sirolimus

- P-gp substrate
  - P-gp inducers
    - carbamazepine, dexamethasone (systemic), doxorubicin, nefazodone, phenobarbital, phenytoin, prazosin, rifampin, St Johns Wort, tenofovir, tipranavir, vinblastine
  - P-gp inhibitors
    - abiraterone acetate, amiodarone, atorvastatin, carvedilol, clarithromycin, cobicistat, crizotinib, cyclosporine (systemic), darunavir, dipyridamole, dronedarone, erythromycin (systemic), grapefruit juice, itraconazole, ivacaftor, ketoconazole (systemic), lapatinib, lomitapide, lopinavir, mefloquine, nelfinavir, nicardipine, nilotinib, progesterone, propranolol, quinidine, quinine, ranolazine, reserpine, ritonavir, saquinavir, sunitinib;, tacrolimus (systemic), tamoxifen, telaprevir, ulipristal, vandetanib, vemurafenib, verapamil, voriconazole
- *Please refer to Appendix 2 in your handout*

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Table 3. Sirolimus Drug-Drug Interactions

Drug	Mechanism	Data Type	Effect	Recommendation
Inhibitors				
Amiodarone	CYP3A4 inhibition	CR; no clinical effect	Increased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [76].
Azoles	CYP3A4 and P-gp inhibition	PK, CR, HSCT; volunteers	Increased sirolimus level	Adjust according to Table 5.
Corticosteroids	CYP3A4 inhibition	PK	Increased levels of both drugs	If used concurrently, monitor sirolimus level; monitor for signs of steroid side effects [71].
Cyclosporine	CYP3A4 inhibition	PK; renal, volunteers	Increased sirolimus AUC	Sirolimus should be administered 4 hours after oral cyclosporine [60].
Macrolide antibiotics	CYP3A4 inhibition (potent)	CR; acute renal failure	Increased sirolimus level	Coadministration is not recommended [72,75].
Micafungin	Unknown	PK; volunteers	Increased sirolimus level	If used concurrently, monitor sirolimus levels and adjust dose [122].
Non-dihydropyridine diltiazem/verapamil	CYP3A4 inhibition	PK; volunteers	Increased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [73].
Inducers				
Phenytoin	CYP3A4 induction	CR; no clinical effect	Decreased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [74].
Competition at CYP3A				
Tacrolimus	CYP3A4 competition	Prospective/CR renal; no clinical effect	Decreased tacrolimus level	If used concurrently, monitor tacrolimus level and adjust dosage [51].

PK indicates pharmacokinetic studies; CR, case reports.

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006

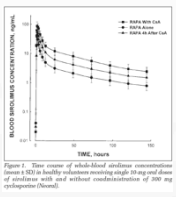
Drug interactions with sirolimus

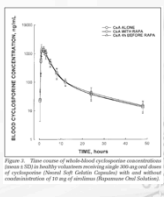
- Zimmerman et al evaluated the optimal timing of CSA and sirolimus administration in 24 healthy volunteers
  - Sirolimus Cmax ↑ 116% and AUC ↑ 230% with simultaneous administration with CSA
  - Sirolimus Cmax ↑ 37% and AUC ↑ 80% when administered 4 hours after CSA

☐ Sirolimus + CSA

△ Sirolimus 4 hrs after CSA

○ Sirolimus alone





Zimmerman JJ et al. *J Clin Pharmacol*. 2003;43:1168-1176.

Drug interactions with sirolimus

- Zimmerman cont.
  - Authors' conclusions
    - Why does CSA increases sirolimus bioavailability?
      - P-gp substrate competition
      - P-gp and/or CYP3A4 inhibition by CSA
      - Greater P-gp and CYP3A affinity by CSA
    - Administer sirolimus at least 4 hours after CSA and consider sirolimus dose reduction
- Kaplan and colleagues had similar results when they performed similar study in 24 kidney transplant patients
- PK study by MacAlister et al. looked at tacrolimus and sirolimus and DID NOT see this same effect

Zimmerman JJ et al. *J Clin Pharmacol*. 2003;43:1168-1176.
Kaplan B et al. *Clin Pharmacol Ther*. 1998;63:48-53.
MacAlister VC et al. *Ther Drug Monit*. 2002;24:346-350.

Drug interactions with sirolimus

- Marty and colleagues evaluated the coadministration of sirolimus and voriconazole in 11 allogeneic SCT patients
  - 8 of 11 patients decreased sirolimus by 90% upon voriconazole initiation

Patient	Siro dose before vori	Siro dose adjustment	Siro level before vori	Highest siro level after vori
1	2	0.2	7.4	11.7
2	3	0.3	9.1	6.1
3	4	0.4	7.8	9.9
4	2	2	4.5	**29.6**
5	4	0.4	8.2	13.9
6	4	0.4	5.9	6.0
7	4	0.4	4.0	3.2
8	4	0.0	<1.5	4.6
9	1	0.1	2.5	1.9
10	3	3	4.0	**23.4**
11	3	3	9.1	**23.5**

Marty FM et al. *Biol Blood Marrow Transplant*. 2006;12:552-559.

Drug interactions with sirolimus

- Marty cont.
  - No significant adverse effects were reported
  - Authors conclusions:
    - Voriconazole strongly inhibits the metabolism of sirolimus mediated by CYP3A4 and P-gp
    - An empiric 90% dosage reduction in sirolimus and frequent monitoring of sirolimus levels

Marty FM et al. *Biol Blood Marrow Transplant*. 2006;12:552-559.

Drug interactions with other immunosuppressive agents

- Mycophenolate mofetil (MMF)
  - CSA inhibits mycophenolic acid (MPA) enterohepatic recirculation resulting in ↓ MPA AUC
  - MMF dose may need adjustment if CSA started or stopped
  - Same interaction NOT seen with tacrolimus or sirolimus
- Methotrexate
  - Concomitant administration of other antifolates i.e., trimethoprim/sulfamethoxazole, should be avoided
  - PK interaction has not been identified

Canttaneo D. et al. *Am J Transplant*. 2005;5:2937-2944
Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006

Audience Response Question

- Concomitant administration of phenytoin and cyclosporine puts the patient at most risk for which of the following events?

  a. Breakthrough seizures
  b. Cyclosporine-induced hypertension
  c. Relapse of malignancy
  d. GVHD

Drug interactions by class: Antimicrobials

Drug interactions with antibiotics

- Fluoroquinolones
  - Absorption is ↓ when coadministered with medications containing divalent cations
    - aluminum, calcium, magnesium and iron
  - Administer fluoroquinolones at least 2 hours before or after ingestion of these products
- Metronidazole
  - Increase Bu trough levels by CYP3A4 inhibition and glutathione competition
  - Increase CSA and tacrolimus trough levels by CYP3A4 inhibition

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006
Lexicomp Online, Lexi-Drug Online, Hudson, Ohio: Lexi-Comp, Inc; 2013; December 14, 2013

Drug interactions with antifungals

- Azoles
  - Fluconazole
    - Minor CYP3A4 substrate, strong CYP2C19/CYP2C9 inhibitor, moderate CYP3A4 inhibitor
  - Itraconazole
    - Major CYP3A4 substrate, strong CYP3A4 inhibitor, P-gp inhibitor
  - Ketoconazole
    - Major CYP3A4 substrate, strong CYP3A4 inhibitor, moderate CYP2C19/CYP2C9/CYP2D6 inhibitor, weak CYP2B6/CYP2C8 inhibitor, P-gp inhibitor
  - Posaconazole
    - Metabolized by UDP glucuronidation, Strong CYP3A4 inhibitor
  - Voriconazole
    - Major CYP2C19/CYP2C9 substrate, minor CYP3A4 substrate, strong CYP3A4 inhibitor, moderate CYP2C19/CYP2C9 inhibitor, P-gp inhibitor
- *Please refer to Appendix 3 in your handout*

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Table 5. Pharmacokinetic Effect of Azole Antifungals: Changes in AUC of Tacrolimus, Cyclosporine, and Sirolimus

	Tacrolimus		Cyclosporine		Sirolimus	
Azole	AUC	Reduction in Tacrolimus Dose	AUC	Reduction in Cyclosporine Dose	AUC	Reduction in Sirolimus Dose
Fluconazole oral 400 mg daily [30,31,33]	310% increase	50%	85% increase	40%	*3.5-fold increased in $C_{minimum}$ with 100-mg fluconazole	33%
Fluconazole i.v. 400 mg daily [5,35]	16% increase [35]	40%	21% increase [35]	25%	↑	25%
Voriconazole oral or i.v. 200 mg twice daily [32,34,94]	300% increase	66%	70% increase	55%	1,000% increase	90%
Posaconazole oral 200 mg three times/day [68,77]	350% increase	75%	33% increase	25%	8.9-fold increase	50%

*Monitoring of blood levels of calcineurin inhibitors is recommended when the route of fluconazole administration is switched from i.v. to oral [5]. AUC indicates area under the curve.

Table 6. Other Azole Drug Interactions

Drug	Antifungal	Data Type	Effect	Recommendation
Busulfan	Flz	Nonrandomized SCT	Busulfan AUC increased	No action needed [11].
	Itz	Nonrandomized SCT	Busulfan clearance decreased	Avoid combination [11].
	Vrz	Theoretical (based on metabolism; no studies)	Busulfan clearance decreased	Consider starting Vrz after day 1 [11,13].
Calcium channel blockers	Itz	Randomized healthy volunteers	Felodipine AUC increased	Decrease felodipine dosage [108].
	Flz, Vrz, Psz	In vitro	Felodipine AUC increased	Monitor blood pressure.
Dexamethasone	Itz	Randomized healthy volunteers	Dexamethasone AUC increased	Monitor for toxicity [83].
Estrogens	Vrz	Nonrandomized healthy volunteers	Vrz and estrogen AUC increased	Monitor for Vrz toxicity [111].
	Flz	Randomized healthy volunteers	Estrogen AUC increased	No action needed [104].
Fentanyl/oxycodone	Flz, Vrz	Randomized healthy volunteers	Fentanyl AUC increased	Monitor for sedation [100].
Glipizide/glimepiride	Flz	Randomized healthy volunteers	Glimepiride AUC increased	Decrease glimepiride dose [103].
Methadone	Vrz	Randomized patients taking methadone	Methadone AUC increased	Monitor for methadone toxicity, QTinterval prolongation [110].
	Flz	Randomized patients taking methadone	Methadone AUC increased	Monitor for methadone toxicity, QTinterval prolongation [98].
Phenytoin	Psz	Nonrandomized volunteers	Psz AUC decreased	Avoid combination [114].
	Vrz	Randomized volunteers	Vrz AUC decreased; phenytoin AUC increased	Increase Vrz maintenance dose to 400 mg twice daily [109].
	Flz	Randomized volunteers	Phenytoin AUC increased	Monitor for phenytoin toxicity [99].
PPIs	Itz	Nonrandomized volunteers	Itz and omeprazole AUC increased	Do not use Itz capsules; solution okay [107].
	Vrz/Flz	Randomized/nonrandomized volunteers	Both AUC increased	No clinically relevant effect; start with low-dose PPI [102].
Statins	Itz/Psz	Randomized volunteers	Statin AUC increased	Avoid combination [115].
	Flz	Randomized volunteers	Statin AUC increased	Start low-dose statin [101].
	Vrz	In vitro	Statin AUC increased	Monitor for statin toxicity [112].
TKIs	Vrz/Psz	In vitro	TKI metabolism decreased	Avoid use with dasatinib/nilotinib, which also increases the risk of QTinterval prolongation; decrease dose if necessary. If using with imatinib, consider using lowest dose and closely follow for toxicity [43].

Flz indicates fluconazole; Itz, itraconazole; Psz, posaconazole; Vrz, voriconazole; PK, pharmacokinetic studies; CR, case reports.

Glotzbecker B et al. *Biol Blood Marrow Transplant*. 2012;18:989-1006

Drug interactions with antifungals

- Echinocandins (Caspofungin and Micafungin)
  - Caspofungin and CSA
    - 2 adult studies evaluated concomitant administration
      - ↑ caspofungin AUC ~35%
      - transient increase in LFT
    - Some evidence suggests that CSA inhibits the uptake of caspofungin into hepatocytes
    - Concomitant administration is not recommended unless benefit outweighs the risk
  - Caspofungin and tacrolimus
    - Study in healthy adults showed ↓ tacrolimus $AUC_{0\text{-}12}$ ~20% when administered with caspofungin
    - Routine monitoring of tacrolimus levels recommended
  - Micafungin: weak CYP3A4 inhibitor yet NO significant PK interactions have been reported

Cancidas [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2010.
Sanz-Rodriguez C et al. *Bone Marrow Transplant*. 2004;34:13-20.

Drug interactions with antivirals

- No significant PK drug interactions reported with acyclovir, valacyclovir, ganciclovir, valganciclovir or foscarnet
- Cidofovir with probenecid
  - Probenecid is given with cidofovir to reduce nephrotoxicity
  - Coadministration of probenecid and meropenem resulted in 56% ↑ in meropenem AUC
    - Probenecid competes with meropenem for active tubular secretion
    - Coadministration is contraindicated

Merrem (meropenem). Wilmington, DE: AstraZeneca Pharmaceuticals LP, July 2009
Lexicomp Online, Lexi-Drug Online, Hudson, Ohio: Lexi-Comp, Inc; 2013; December 14, 2013

Audience Response Question

- RA has started myeloablative conditioning with Bu-CY for his matched unrelated donor transplant. His *clostridium difficile* culture just returned positive. What would be the best course of treatment?

a. 10 day course of IV or oral metronidazole
b. 10 day course of oral vancomycin
c. 10 day course of IV vancomycin
d. 10 day course of IV metronidazole and oral vancomycin

Adverse effects of polypharmacy and drug interactions

- Toxicity and/or treatment failure
  - Chemotherapy
    - Toxicities: myelosuppression, SOS, mucositis
    - Treatment failure: malignant disease relapse, auto-engraftment
  - Immunuosuppression
    - Toxicities: myelosuppression, malignant hypertension, nephrotoxicity, posterior-reversible encephalopathy syndrome, loss of graft
    - Treatment failure: graft versus host disease (GVHD), lack of engraftment
  - Antimicrobial
    - Toxicities: nephrotoxicity, ototoxicity, myelosuppression, superinfections
    - Treatment failure: infection not erradicated

Recommendations

- Medication profile evaluation EVERYDAY
- Closely monitor drug levels when interacting medication is started or stopped
- Assess for adverse effects when interacting medication is started or stopped
- Utilize drug interaction tools/websites
  - Lexi-Interact by Lexi-Comp
  - Micromedex
  - www.drug-interactions.com
  - www.depts.washington.edu/didbase/
- Empirically alter dosage regimens when applicable or find alternative therapy when concomitant administration is contraindicated

Questions?