Polypharmacy and BMT: Finding a Happy Medium

Gabriel Bartoo, PharmD, BCPS, BCOP

ASBMT Regional Conference for NPs, PAs and Fellows
October 13, 2016
Disclosures

• No Relevant Financial Disclosures
Polypharmacy – What does it mean?

• Use of six or more concomitant drugs
• Drug used to treat side effect of another
• Two or more drugs used to treat one condition
• Drugs prescribed more than twice a day
• Complicated drug regimen that negatively impacts adherence
OSCILLATIONS and sudden shifts in the center of gravity of therapeutics have been occurring with increasing frequency during recent years. It is imperative that those responsible for setting standards in medical practice look squarely at the changes. A most impressive advance has been the discovery of many specifics. We have now a number of drugs with great therapeutic power.

“It is necessary for leaders of American medicine and leaders of American drug manufacture to join forces...to see that a tendency to relapse into the mystique of polypharmacy be brought to a quick and complete halt.”
Polypharmacy in BMT

RELAPSE PREVENTION

IMMUNO-SUPPRESSION

Polypharmacy in BMT

SUPPORTIVE CARE

ANTIMICROBIAL PROPHYLAXIS

Nausea
Insomnia
Pain
Rash/pruritis
Oral care
Vitamin/mineral deficiencies

Hypertension
Dyslipidemia
Depression
Diabetes
Hypothyroidism
Osteoporosis
Liver injury prophylaxis
Objectives

• Review risks of polypharmacy, focusing on adverse effects and drug interactions
  • Immunosuppressants
  • Antimicrobial agents
  • BCR-ABL tyrosine kinase inhibitors
  • Supportive care
• Outline strategies to minimize pill burden
• Outline strategies to maximize medication adherence
Immunosuppressants

- Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus
- Sirolimus
- Mycophenolate
Calcineurin Inhibitors
Adverse Effects

- Nephrotoxicity
- Hypertension
- Hypomagnesemia
- Hyperkalemia
- Hyperglycemia (T>C)
- Hepatotoxicity
- GI side effects
  - Anorexia/nausea/vomiting
  - Diarrhea
- Hirsutism (C)/Alopecia (T)
- Gingival Hyperplasia (C)
- Thrombotic microangiopathy
- Neurotoxicity
  - Tremor
  - Headache
  - Seizures
  - Peripheral neuropathy
  - Encephalopathy

T = tacrolimus
C = cyclosporine

Pharmacology and side effects of cyclosporine and tacrolimus. In: UpToDate, Waltham, MA. (Accessed 9/18/16)
Calcineurin Inhibitors
Medication Management

• Dosage forms
  • Modified cyclosporine preferred over Sandimmune
  • CSA smell, size, packaging less desirable than TAC
  • IV adsorption to plastic tubing

• Timing of dosing
  • Twice a day dosing, monitor a 12-hour post-dose level
  • Frequent dose adjustments, recheck level ≥ 2 days after
  • Once daily extended release TAC products available

• Metabolism
  • Extensively metabolized in the liver (CYP3A4)
  • Excreted into bile; minimally excreted unchanged in urine

  TAC = tacrolimus
  CSA = cyclosporine
  CYP = cytochrome P450

BMT 1999; 24:1053-1056
## Calcineurin Inhibitors
### Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA</td>
<td>Fluconazole, Posaconazole, Voriconazole</td>
<td>CYP3A4</td>
<td>Variable effects, Dose and time dependent</td>
</tr>
<tr>
<td>TAC</td>
<td>Fluconazole, Posaconazole, Voriconazole</td>
<td>CYP3A4</td>
<td>Variable effects, Dose and time dependent</td>
</tr>
<tr>
<td>CSA/TAC</td>
<td>Imatinib, Dasatinib, Nilotinib</td>
<td>CYP3A4, P-GP</td>
<td>Variable effects, Dose and time dependent</td>
</tr>
<tr>
<td>CSA/TAC</td>
<td>Azithromycin, CCBs, PPIs</td>
<td>P-GP, CYP3A4</td>
<td>Possible ↑ exposure</td>
</tr>
</tbody>
</table>

**CSA** = cyclosporine  
**TAC** = tacrolimus  
**CCB** = calcium channel blocker  
**P-GP** = P-glycoprotein  
**CYP** = Cytochrome P450  
**PPI** = proton pump inhibitor

BMT 2004; 33:137-152  
Biol Blood Marrow Transplant 2012; 18: 989-1006
Sirolimus Adverse Effects

- Myelosuppression
- Dyslipidemia, hyperglycemia
- Edema
- Hypertension
- GI Effects
  - Diarrhea/constipation
  - Abdominal pain
  - Nausea
  - Stomatitis
- Arthralgia/myalgia
- Neurotoxicity
  - Headache
  - Dizziness
- Hepatotoxicity
- Skin Rash
- Nephrotoxicity
- Impaired wound healing
- Noninfectious pneumonitis

J Clin Oncol 2012; 30:2919-2928
Sirolimus
Medication Management

• Typical daily dosing
  • Avoid post-dose levels, trough level ideal
  • Long half life makes timing less critical
  • Steady state level may take $\geq 1$ week after change

• Price and insurance coverage can be a barrier

• Metabolism
  • Extensively metabolized via CYP3A4 and P-GP
  • Excreted in feces via P-GP efflux into gut

CYP = Cytochrome P450
P-GP = P-glycoprotein

Overview of immunosuppressive agents used for prevention and treatment of graft-versus-host disease
In: UpToDate, Waltham, MA. (Accessed 9/18/16)
Mycophenolate
Adverse Effects – Medication Management

• Toxicity
  • Dose-related cytopenia and gastrointestinal toxicity

• Typically BID to TID dosing

• TDM not routine in BMT patients
  • AUC monitoring predicts outcomes better than trough levels
  • Trough monitoring reasonable if toxicity suspected

• REMS program for premenopausal females

REMS = risk evaluation and mitigation strategy
TDM = therapeutic drug monitoring

Overview of immunosuppressive agents used for prevention and treatment of
graft-versus-host diseaseIn: UpToDate, Waltham, MA. (Accessed 9/18/16)
## Sirolimus and Mycophenolate Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus (SIR)</td>
<td>Fluconazole</td>
<td>CYP3A4</td>
<td>Variable effects Dose and time dependent↑SIR exposure up to 1100%</td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus (SIR)</td>
<td>Diltiazem</td>
<td>CYP3A4</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sirolimus (SIR)</td>
<td>Azithromycin</td>
<td>P-GP</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus (SIR)</td>
<td>Cyclosporine</td>
<td>CYP3A4 P-GP</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑SIR exposure up to 230%</td>
</tr>
<tr>
<td>Mycophenolate (MMF)</td>
<td>Gastric Acid</td>
<td>pH</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Suppression</td>
<td></td>
<td>↓MMF exposure up to 37%</td>
</tr>
</tbody>
</table>

**SIR** = Sirolimus  
**MMF** = Mycophenolate mofetil  
**P-GP** = P-glycoprotein  
**CYP** = Cytochrome P450  

Biol Blood Marrow Transplant 2006; 12:552-559  
BMT 2004; 33:137-152  
Biol Blood Marrow Transplant 2012; 18: 989-1006
Supportive Care

- Hypertension
- Hyperlipidemia
- Diabetes
- Hypothyroidism
- Osteoporosis
- Depression
Hypertension

• Often secondary to calcineurin inhibitor use
• Choice based on comorbidities and side effects
• Once daily regimens preferred
  • Amlodipine
    • Relatively high incidence of lower extremity swelling
  • ACE inhibitors/Angiotensin-receptor blockers
    • Possible increased risk of angioedema with sirolimus
    • Possible hyperkalemia with calcineurin inhibitors
  • Beta blockers
  • Thiazide diuretics

JAMA 2014;311:507-520
Blood 2010; 117:3002-9
Biol Blood and Marrow Transplant 2012; 18:348-71
# Hypertension

## Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>Fluconazole</td>
<td>CYP2C9</td>
<td>Variable ↑ exposure</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
<td>Heart rate</td>
</tr>
<tr>
<td>Amlodipine Nifedipine</td>
<td>Fluconazole</td>
<td>CYP3A4</td>
<td>Variable ↑ exposure</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem Verapamil</td>
<td>Fluconazole</td>
<td>CYP3A4</td>
<td>Variable ↑ exposure</td>
<td>Blood pressure</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
<td></td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Start with low dose of antihypertensive and titrate slowly to effect

**CYP = Cytochrome P450**
Hyperlipidemia

- Exacerbated by immunosuppressant use
- Allogeneic BMT 7x risk of cardiovascular event
- Statins are primary therapy
  - Possible immunomodulatory effects
  - Muscle and liver toxicity
- Hypertriglyceridemia
  - Fibrates
  - Fish Oil
# Hyperlipidemia Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Simvastatin Lovastatin Atorvastatin* Fluvastatin* | Fluconazole Posaconazole Voriconazole | Variable ↑ statin exposure up to 8-fold | Use alternate statin
*Low-dose possible Monitor myopathy Monitor LFTs |
| Simvastatin Lovastatin Atorvastatin Pitavastatin Fluvastatin* Pravastatin* Rosuvastatin* | Cyclosporine | Variable ↑ statin exposure up to 25-fold | Avoid concomitant use
*Use pravastatin ≤ 20 mg
*Use rosuvastatin ≤ 5 mg
*Use fluvastatin ≤ 20 mg BID Monitor myopathy Monitor LFTs |

**CYP** = Cytochrome P450  
**OATP** = Organic anion-transporting polypeptide  
**LFT** = Liver function test
Diabetes

- Prevalence roughly 10% after allogeneic BMT
- Insulin commonly used
  - Lacks drug interactions
  - Individualize dosing
  - Preferred for short-term use or unstable patient
- Daily intermediate-acting insulin useful to counteract steroid-related hyperglycemia
- Oral agents reasonable if no contraindications

BMT 2016; 51:1041–1049
Blood. 2011; 117:3002-9
Oral Hypoglycemic Agents

- Metformin
  - GI side effects, caution in renal dysfunction

- Sulfonylureas
  - Hypoglycemia, long-acting agents can outlast steroid effect

- Incretin agents (DPP-4 inhibitors, GLP-1 agonists)
  - Nausea/vomiting, effective for steroid hyperglycemia

- Glinides
  - Hypoglycemia risk

- Thiazolidinediones, SGLT2 inhibitors, Alpha-glucosidase inhibitors

DPP = dipeptidyl peptidase IV enzyme
GLP = glucagon-like peptide
SGLT = sodium-glucose cotransporter

BMT 2016; 51:1041–1049
Blood. 2011; 117:3002-9
## Diabetes Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Fluconazole Voriconazole</td>
<td>CYP2C9</td>
<td>Variable ↑ up to 138%</td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Nephrotoxic agents</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Cyclosporine</td>
<td>P-GP</td>
<td>Variable increases</td>
</tr>
<tr>
<td>Linagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Fluconazole Voriconazole Posaconazole</td>
<td>CYP3A4</td>
<td>Variable increases</td>
</tr>
<tr>
<td>Linagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Fluconazole Voriconazole Posaconazole</td>
<td>CYP2C9 CYP3A4</td>
<td>Variable increases</td>
</tr>
<tr>
<td>Repaglinide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-GP = P-glycoprotein  
CYP = cytochrome P450

BMT 2004; 33: 137-152  
Biol Blood Marrow Transplant 2012; 18: 989-1006  
Trends in Pharmacological Sciences 2012; 33: 312-22
Hypothyroidism

- Long-term prevalence 20-40% after allogeneic BMT
- Can be secondary to medications
- Levothyroxine replacement
  - Optimal administration sometimes difficult

Blood. 2010; 117:3002-9
Biol Blood and Marrow Transplant 2012; 18:348-71
## Hypothyroidism

### Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine</td>
<td>Imatinib, Dasatinib, Bosutinib, Nilotinib, Ponatinib</td>
<td>Inhibitor of MCT8 transporter</td>
<td>N/A</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Ca, Mg, Fe, Al, Zn, Sevelamer, Kayexalate, Orlistat, Simethicone, Sucralfate, Bile acid sequestrants</td>
<td>↓ Absorption</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**MCT8** = Monocarboxylate transporter 8

---

J Clin Endocrinol Metab 2012; 97: E100–E105

©2016 MFMER | slide-24
Osteoporosis

• Common after BMT
• Prophylaxis warranted with long-term corticosteroid use
• Lifestyle interventions
  • Optimize dietary calcium intake
  • Weight bearing exercise, fall prevention, smoking cessation
• Treatment
  • Bisphosphonates typical used initially
  • Calcium + vitamin D supplementation if needed
  • Caution with oral bisphosphonates in esophageal GVHD
  • Hormone replacement for younger patients if deficient

Blood 2011; 117:3002-9
BMT 2011; 46:1-9
Transplant Int. 2011; 24:867-79
Depression

• Long-term incidence at least 10% post-BMT

• Antidepressant preferred for comorbid conditions
  • Appetite stimulation - mirtazapine
  • Peripheral neuropathy - venlafaxine, duloxetine

• Antidepressants to avoid
  • Oral graft vs. host disease
    • TCA, mirtazapine, paroxetine, sertraline
  • Hypertension
    • Venlafaxine, duloxetine, bupropion
  • Arrhythmias, cardiovascular disease, hypotension
    • TCA

TCA = tricyclic antidepressant

Blood 2011;118:4723-4731
Antimicrobial Prophylaxis

- Antifungal prophylaxis
- Viral prophylaxis
- Pneumococcal prophylaxis
- Pneumocystis prophylaxis
Antifungal Prophylaxis

• Fluconazole
  • Relatively well tolerated, once daily regimen
  • Less potent CYP inhibition

• Broader coverage for those at risk
  • Voriconazole, twice daily regimen
    • Safety concerns with long-term use
  • Posaconazole, 3 delayed-release tabs once daily
  • Itraconazole rarely used – less well tolerated
  • Increased risk of drug interactions
  • Cost/insurance issues can be barrier to use
Antimicrobial Prophylaxis

• Long-term voriconazole use
  • Fluoride excess, bone pain
  • Cutaneous squamous cell carcinoma

• Photosensitivity
  • Voriconazole
  • Sulfamethoxazole/trimethoprim
  • Dapsone
  • Doxycycline
  • Levofloxacin
Antimicrobial Prophylaxis

- **Viral prophylaxis**
  - Acyclovir, valacyclovir

- **Pneumococcal prophylaxis**
  - Penicillin, doxycycline, azithromycin

- **Pneumocystis prophylaxis**
  - Sulfamethoxazole/trimethoprin, dapsone, pentamidine, atovaquone

- **Optimal duration unknown**
## Antimicrobial Prophylaxis Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole/Voriconazole</td>
<td>Rifampin</td>
<td>CYP3A4</td>
<td>Variable ↓ up to 96%</td>
</tr>
<tr>
<td>Posaconazole Suspension</td>
<td>PPIs, H2A</td>
<td>pH</td>
<td>Variable ↓ up to 50%</td>
</tr>
<tr>
<td>Voriconazole/Posaconazole</td>
<td>Phenytoin</td>
<td>CYP3A4</td>
<td>Variable ↓ up to 70%</td>
</tr>
</tbody>
</table>

**PPI** = proton pump inhibitor  
**H2A** = histamine 2 antagonist  
**CYP** = cytochrome P450

BMT 2004; 33: 137-152  
Biol Blood Marrow Transplant 2012; 18: 989-1006
Relapse Prevention

- Multiple Myeloma
- CML, Ph(+) ALL
  - BCR-ABL tyrosine kinase inhibitors
## BCR-ABL Tyrosine Kinase Inhibitors
### Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Approximate Change</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosutinib, Dasatinib, Nilotinib</td>
<td>PPIs, H2A</td>
<td>pH</td>
<td>Avoid PPIs if possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable ↓ up to 60%</td>
<td>Timing of H2A</td>
</tr>
<tr>
<td>Bosutinib, Dasatinib, Nilotinib</td>
<td>Posaconazole, Voriconazole</td>
<td>CYP3A4</td>
<td>Variable ↑ 40 to 500%</td>
</tr>
<tr>
<td>Bosutinib, Dasatinib, Nilotinib</td>
<td>Rifampin, Phenytoin, Carbamazepine</td>
<td>CYP3A4</td>
<td>Variable ↓ up to 90%</td>
</tr>
</tbody>
</table>

**CYP** = cytochrome P450  
**PPI** = proton pump inhibitor  
**H2A** = histamine 2 antagonist
Barriers to Medication Adherence

- Memory
- Beliefs
- Difficulty with dosage form
- Cost
Maximizing Medication Adherence Memory

- Pill box, medication calendar, blister pack, electronic dispensing device, smart phone app
- Simplify regimen, reduce pill burden, enlist caregiver
- Use internet or electronic adherence aids/reporting

JAMA 2010; 304:1592-1601
CS is tapered off cyclosporine at day + 180. He is currently on Acyclovir BID, Penicillin BID, Bactrim daily, Metoprolol BID, and Magnesium TID. His magnesium is 2 mg/dL. What can be done to reduce pill burden?

1. Change Metoprolol to XL daily
2. Change Acyclovir to Valacyclovir daily
3. Discontinue Magnesium
4. All of the above
Maximizing Medication Adherence

Memory

• Discuss concerns, establish shared goal
• Provide education
• Simplify regimen, reduce pill burden
  • Acyclovir → Valacyclovir
  • Penicillin → Doxycycline or Azithromycin
  • Voriconazole → Posaconazole tablets
  • Tacrolimus → Extended release products

JAMA 2010;304: 1592-1601
Maximizing Medication Adherence
Dosage Form

- Alternative dosage form
  - Liquid (e.g. cyclosporine)
  - Smaller dosage form (e.g. doxycycline)
  - Capsule vs. tablet (e.g. ursodiol)
  - Pill splitter or crusher

- Spacer for inhaler or dry powder inhaler

- Insulin pen
Maximizing Medication Adherence Cost

• Change to lower-cost medication
  • Ursodiol tablets vs. capsules

• Discontinue unnecessary medications
  • Magnesium, proton pump inhibitor

• Patient assistance programs
  • Needymeds.org
Summary

• Polypharmacy in BMT is common/necessary
  • Focus on avoiding associated adverse outcomes
  • Medication management consumes time/resources

• Minimize risks of polypharmacy
• Improve adherence
  • Simplify medication regimen
  • Elicit patient cooperation
Questions & Discussion