Supportive Care in Patients undergoing Haematopoietic Stem Cell Transplant (HSCT)

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Objectives

• Discuss strategies for antifungal prevention and treatment in HEM/BMT patients

• Discuss important antifungal PK considerations in HEM/BMT

• Evaluate current literature on GVHD prevention strategies

• Discuss the management of Graft Versus Host Disease (GVHD)
Competences addressed

Standard 4.2:
• Consider the appropriateness of prescribed medicines

Standard 7.1:
• Contribute to therapeutic decision-making

Standard 7.2:
• Provide ongoing medication management

Standard 7.3:
• Influence patterns of medicine use
Fungal Infections-Background

- Traditionally, many invasive fungal infections were associated with a poor prognosis, because effective therapeutic options were limited.

- With these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs.

- Understanding the PK and PD properties of the different classes of antifungal agents is vital for the effective management of invasive fungal infection.

Dodds Ashley ES et al. Clin Infect Dis 2006
# Mortality Due to Invasive Fungal Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida spp.</td>
<td>40%*1,2</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>62%#3</td>
</tr>
<tr>
<td>Invasive moulds (Aspergillus, Fusarium, Zygomycetes)</td>
<td>~80%§4</td>
</tr>
<tr>
<td>Scedosporium</td>
<td>100%§4</td>
</tr>
</tbody>
</table>

*Adult patients hospitalised in the US
#Hospitalised patients with invasive aspergillus
§ HSCT recipients

4-Marr KA et al. Clin Infect Dis 2002
Antifungal agents used in HEM/BMT

• Azoles:
  – Fluconazole (1990)
  – Itraconazole (1992)
  – Voriconazole (2002)
  – Posaconazole liquid (2006)

• Liposomal Amphotericin B (Ambisome) (1996)

• Echinocandins:
  – Caspofungin (2001)
  – Anidulafungin (2006)
Factors affecting need for antifungal prophylaxis

- Patient population
- Type of chemotherapy
- Type of transplant (sibling, MUD, mismatch) and source of cells (BM, PBSC)
- Incidence of invasive fungal infections (IFI) at a treating centre
- Environmental factors e.g. building and construction work
- The availability of diagnostic tests within a centre

MUD= Matched Unrelated Donor
BM= Bone Marrow
PBSC= Peripheral Blood Stem Cells

Factors to consider when choosing antifungal prophylaxis

- Antifungal spectrum
- Patient risk and period of neutropenia
- Toxicity profile
- Drug interactions
- Need for & cost of TDM
- Cost of drug
- Route of administration

## Sources of donors in Adult BMT

<table>
<thead>
<tr>
<th>Graft Source</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Neutropenic period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling adult donor</td>
<td>Good outcomes</td>
<td>Availability (5-10%)</td>
<td>Short (7-10 days)</td>
</tr>
<tr>
<td></td>
<td>Less GVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrelated adult donor</td>
<td>Good outcomes</td>
<td>Availability (~50%)</td>
<td>Short if PBSC</td>
</tr>
<tr>
<td></td>
<td>“Gold standard”</td>
<td>Time delay</td>
<td>(7-14 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Longer if BM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(14-21 days)</td>
</tr>
<tr>
<td>Umbilical cord blood</td>
<td>Availability (&gt;95%)</td>
<td>Low cell number</td>
<td>Very long</td>
</tr>
<tr>
<td></td>
<td>↓GVHD</td>
<td>Infection</td>
<td>(21-35 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slower to engraft</td>
<td></td>
</tr>
<tr>
<td>HLA-haploidentical related donor</td>
<td>Availability (&gt;95%)</td>
<td>↑↑GVHD</td>
<td>Short if PBSC</td>
</tr>
<tr>
<td></td>
<td>Speed to BMT</td>
<td>↑Non-relapse mortality</td>
<td>(7-14 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Longer if BM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(14-21 days)</td>
</tr>
</tbody>
</table>

BMT= Bone Marrow Transplant, GVHD= Graft Versus Host Disease
PBSC= Peripheral blood stem source, BM= Bone marrow
Australasian Antifungal Guidelines

HIGHER-RISK PATIENT

- Intensive chemotherapy of AML: induction, re-induction, consolidation with high-dose therapy
  Posaconazole solution 200 mg tds (with fatty food/drink). Start 24 hours after last anthracycline or on day of chemotherapy in patients not receiving anthracycline. Continue until neutropenia has resolved and patient in complete remission

- Higher risk allogeneic SCT, pre-engraftment, e.g. cord blood, unrelated donor transplant with bone marrow stem cell source or likely delayed engraftment
  Posaconazole solution 200 mg tds (with fatty food/drink). Other options: voriconazole 200 mg bd or itraconazole 200 mg bd or lipid formulation amphotericin 50 mg/day 3 times a week. Start after conditioning. Continue until neutropenia resolves. If no GVHD develops, use fluconazole through to day 75

- Allogeneic SCT with grade 2–4 GVHD
  Posaconazole solution 200 mg tds until day 112 post-onset GVHD or resolution

LOWER-RISK PATIENT

- Less intensive chemotherapy AML or standard consolidation
  Fluconazole 200 mg/day. Start on admission and continue until neutropenia resolved

- Autologous SCT
  Fluconazole 200–400 mg/day. Start on admission and continue until neutropenia resolved

- Standard allogeneic SCT, pre-engraftment eg: sibling, matched, peripheral blood stem cell source
  Fluconazole 400 mg daily from admission to day 75

- Autologous SCT with non-mucositis regimen, chemotherapy for solid organ tumours
  No prophylaxis needed
Case Study #1

Antifungals-Chemotherapy Drug Interactions
Case Study #1

• Miss NL, 20-year old University student.

• Diagnosed with Acute Lymphoblastic Leukaemia (ALL) in May 2014.

• Received intensive chemotherapy treatment with BFM protocol-achieved complete remission.

• Presents for myeloablative allogeneic matched unrelated donor stem cell transplant in October 2014.

• Source of stem cells-bone marrow.

• Expected period of neutropenia is ≥ 14 days.
Case Study #1

• Conditioning chemotherapy regimen
  – IV Busulfan 3.2mg/kg/day (D-7 to D-4)
  – IV Cyclophosphamide 60mg/kg/day (D-3 and D-2)

• Patient is not on antifungal prophylaxis upon admission.

• Team wants to start patient on itraconazole as prophylactic antifungal upon admission i.e. day -7

• ? issues
Itraconazole-Cyclophosphamide drug interaction

Paper in the Blood 2004

• A randomized trial that included 197 patients comparing the safety and efficacy of itraconazole and fluconazole in preventing fungal infections in patients undergoing allogeneic stem cell transplantation.

• Itraconazole and fluconazole were administered with the start of conditioning therapy, until at least 120 days after SCT.

• The most common conditioning regimen was cyclophosphamide (60 mg/kg) and total body irradiation (TBI).

Itraconazole-Cyclophosphamide drug interaction (cont’d)

Findings:

• Patients who received itraconazole concurrent with cyclophosphamide (CY) conditioning developed higher serum bilirubin and creatinine values in the first 20 days after SCT.

• Analysis of CY metabolism in a subset of patients demonstrated higher exposure to toxic metabolites (mainly 4-hydroxy-cyclophosphamide) among recipients of itraconazole compared with fluconazole.

Marr K et al. Blood 2004
Azoles Drug Interactions In the Australian Antifungal Guidelines

• The Australian antifungal guidelines mentions that Itraconazole is not the ideal antifungal when cyclophosphamide is used as part of the conditioning.

• Antifungal prophylaxis with itraconazole/posaconazole/voriconazole should start after conditioning for High risk allogeneic HSCT, pre-engraftment, e.g. cord blood, unrelated donor transplant with bone marrow stem cell source or likely delayed engraftment.

Case Study #1-outcome

• Team decided to withhold starting itraconazole until cyclophosphamide is finished (D-1).

• Start Itraconazole liquid as it is more efficiently absorbed when compared to the capsule formulation.

• Patient achieved therapeutic levels by D+5. Itraconazole level on D+5 1200 μg/L (Tagret 500-2000 micg/L).

• Itraconazole levels continued to be therapeutic whilst neutropenic.

• Switched to itraconazole capsules upon discharge.
Case Study #2

Antifungal-Calcineurin Inhibitors

Drug Interactions
Case Study #2

- Mr BG, a 35 year-old male presents for an allogeneic stem cell transplant for follicular lymphoma in September 2014.
- Reduced intensity transplant-sibling.
- Source of stem cells - Peripheral blood.
- Average duration of neutropenia (7-10 days).
- Chemotherapy conditioning regimen - flubarabine and melphalan.
Case Study #2

- Day +13 post transplant
- Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin</td>
<td>80 mg IV BD</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>400mg PO daily</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>500mg PO ONCE daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40mg PO ONCE daily</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>500mg PO ONCE daily</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8mg IV TDS PRN</td>
</tr>
</tbody>
</table>

*Cyclosporin trough level on D+13= 189 μg/L*

*St Vincent’s BMT unit target level = 100-210 μg/L*
Case Study #2

• D+13 patient develops signs of acute Graft Versus Host Disease (rash and diarrhoea)

• Plan-escalation of immunosuppression
  – Methylprednisolone 1mg/kg TWICE a day

• Patient is now at high risk of fungal infection due to higher immunosuppression

• Infectious Diseases consult-switch to IV voriconazole

• ? Issues
Metabolism

• Azole antifungals undergo hepatic metabolism (through CYP-450 enzymes)
  – For fluconazole, the role of hepatic metabolism in drug elimination is minimal.

  – Itraconazole, voriconazole, and posaconazole, which are highly dependent on hepatic metabolism for drug elimination.

Summary of Azole-mediated cytochrome P450 drug-drug interactions.

<table>
<thead>
<tr>
<th>Enzyme inhibition</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP-2C19</td>
<td>+</td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>CYP-2C9</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>CYP-3A4</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

# Azole-Calcineurin Inhibitors Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cyclosporin</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Reduce cyclosporin dose by 30%</td>
<td>Reduce tacrolimus dose by 50%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Reduce cyclosporin dose by 50-80%</td>
<td>Consider reducing tacrolimus dose by at least 50%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Reduce cyclosporin dose by 50%</td>
<td>Reduce tacrolimus by up to 75%</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Reduce cyclosporin dose by 25-30%</td>
<td>Reduce tacrolimus by 30%</td>
</tr>
</tbody>
</table>

Case Study #2

- IV voriconazole started with no down titration of cyclosporin dose.

- Repeat cyclosporin level in 6 days came back high at 507 μg/L! (range 100-219μg/L).

- Cyclosporin dose was reduced to 50mg IV BD (dose cut by 40%)
Case Study #2

Voriconazole added

Cyclosporin IV Reduced to 50mg BD
Azoles Drug interactions

- Allazole antifungals inhibit CYP450 enzymes to some degree. As a result, careful consideration must be given when an azole agent is added to a patient’s drug regimen.

- Similarly, when an azole agent is discontinued, the change in metabolism that occurs may have profound clinical implications.

- For example, organ rejection has been reported after discontinuation of an azole antifungal that was not accompanied by the necessary upward dose adjustments in the affected immunosuppressant agent (cyclosporin).

Groll AH et al. Pharmacokinetic interaction between voriconazole and cyclosporin following allogeneic bone marrow transplantation. J Antimicrob Chemother 2004
Metabolism of Echinocandins

- Echinocandins:
  - Caspofungin undergoes hepatic metabolism to produce two distinct inactive metabolites.
  - Anidulafungin is not hepatically metabolized but undergoes nonenzymatic degradation.
**Echinocandins drug-drug interactions**

- Although caspofungin is not major substrates for the CYP450 enzyme system, it still has interactions that appear to be mediated via this mechanism.

- Caspofungin concentrations are decreased when administered with CYP450 inducers, such as rifampicin and phenytoin. Cyclosporin can increase caspofungin concentration and risk of toxicities.

- Anidulafungin does not appear to exhibit these CYP450-mediated interaction. *But...*
Toxicities of Antifungals

• Amphotericin B:
  – Nephrotoxicity and infusion related-reactions.

• Fluconazole:
  – LFTs elevation and rash.

• Itraconazole:
  – GI disturbances, rash, LFTs elevation, QT prolongation and hypokalaemia.
Toxicities of Antifungals cont’d

• Voriconazole:
  – Visual disturbances (up to 30%), rash, LFTs elevation, thrombocytopenia, QT prolongation and acute renal failure.

• Posaconazole:
  – LFTs elevation, neutropenia, fever and hypokalaemia.
  – Posaconazole has lower potential for prolonging QT interval.
Toxicities of Antifungals cont’d

• Echinocandins
  – Caspofungin: LFTs elevation, headache and hypotension
  – Anidulafungin: hyperkalaemia and thrombocytopenia
Therapeutic Drug Monitoring (TDM) of Antifungals

• Why TDM is important?
  – Optimize the potential for a favorable patient outcome (efficacy).
  – Minimise the potential for side effects (safety).

• For most antibiotics (including antifungals), the activity of the agent is related to one or more of the following:

  1-Time that the serum concentration exceeds the MIC of the organism (t>MIC)
  2-Maximum serum concentration (Cmax) to MIC ratio (Cmax/MIC)
  3-The area under the serum concentration – time curve (AUC) in relation to MIC (AUC/MIC)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Range</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>500-2000 micg/L</td>
<td>Start measuring trough levels after 5 days</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>1.5-5.5 mg/L</td>
<td>Start measuring after 2 days</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>&gt; 700ng/mL</td>
<td>Start monitoring after 7 days</td>
</tr>
</tbody>
</table>

Conclusions-Fungal Infections

• Antifungal agents have provided clinicians with a tool previously lacking in the management of these life threatening fungal infections.

• Along with new options, however, comes the need to understand the uniqueness of each agent, including its role in therapy, toxicity profile, and interactions with concomitant medications.

• In order to attain the maximum effect from these agents, clinicians should also become familiar with strategies to optimise efficacy through an understanding of pharmacokinetic and pharmacodynamic properties.

• TDM monitoring is crucial to guide antifungal prophylaxis and treatment.
Graft Versus Host Disease (GVHD)
GVHD-Background

- Acute GVHD (aGVHD) and chronic GVHD (cGVHD) remain a major contributor to transplantation related deaths.

- Most significant barrier to allogeneic stem cell transplant (alloSCT).

- Despite prophylactic immunosuppressive agents, ~50% of patients develop GVHD.

- Most GVHD reactions are undesirable and affect multiple organs e.g. skin, GIT, lungs and liver.

- GVHD among haematopoietic targets are desirable and critical for the cure of haematological malignancies via graft-versus-tumor (GVT) effect.
CAUSE OF DEATH IN THE FIRST YEAR AFTER TRANSPLANT – ALLOGENEIC TRANSPLANTS
Classification of GVHD

Shulman Classification 1980

- **ACUTE**
  - Red skin rash, GIT and liver

- **CHRONIC**
  - Skin, eyes, mouth, GIT, liver, lung and genitals

NIH Classification 2005

- **CLASSIC ACUTE**

- **LATE ACUTE**

- **OVERLAP**

- **CLASSIC CHRONIC**
1960: Methotrexate (MTX)

1978: Cyclosporine (CsA)

1985: MTX + CsA better than monotherapy for GVHD prevention and improving survival

1990s: TAC + MTX

Late 1990s: MMF/CsA

MMF, mycophenolate mofetil; SIR, sirolimus; TAC, tacrolimus.
ATG-Antithymocyte Globulin
# ATG for GVHD Prophylaxis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ATG</th>
<th>Placebo</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD Grade II-IV</td>
<td>33%</td>
<td>52%</td>
<td>.008</td>
</tr>
<tr>
<td>Acute GVHD Grade III-IV</td>
<td>11.7%</td>
<td>25.5%</td>
<td>.039</td>
</tr>
<tr>
<td>Extensive cGVHD at 3 years</td>
<td>12.2%</td>
<td>45%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Relapse</td>
<td>32.6%</td>
<td>19.4%</td>
<td>.47</td>
</tr>
<tr>
<td>Non-relapse mortality</td>
<td>28.2%</td>
<td>33.5%</td>
<td>.18</td>
</tr>
<tr>
<td>Survival free of immunosuppression</td>
<td>52.9%</td>
<td>16.9%</td>
<td></td>
</tr>
</tbody>
</table>

**ATG-Future Directions**

- Randomized, double-blind, prospective, placebo-controlled, multicenter Phase III trial of ATG prophylaxis as a supplement to standard of care to prevent moderate to severe chronic GVHD
  - AML, ALL, and MDS after allogeneic transplant from unrelated donors

- Primary endpoint
  - Moderate to severe cGVHD free survival
  - Higher relapse rates with less cGVHD
### Sirolimus for GVHD Prophylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>(N)</th>
<th>GVHD prophylaxis</th>
<th>aGVHD</th>
<th>cGVHD</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutler C, <em>Blood</em>. 2007</td>
<td>53 MRD 30 MUD</td>
<td>SIR/TAC</td>
<td>Grade II-IV 20.5% Grade III-IV 4.8%</td>
<td>59.1%</td>
<td>TRM @ 100 d 4.8% TMA 7.3% VOD 8.4%</td>
</tr>
<tr>
<td>Rosenbeck L, <em>BBMT</em>. 2011.</td>
<td>106 MUD and MMUD</td>
<td>SIR/TAC/ +/- ATG (59) vs. MTX/CNI (47)</td>
<td>Grade II-IV 18.6% SIR arm vs. 48.9% MTX Grade III-IV 5% vs. 17%, p = 0.045</td>
<td>40.4% vs. 41.9%</td>
<td>TMA 10% SIR vs. 4.3% MTX (P = .296) VOD 20.3% SIR vs. 4.2% MTX</td>
</tr>
<tr>
<td>Perez-Simon Sr, J. <em>Blood</em>. 2011.</td>
<td>90 MUD</td>
<td>CsA/MMF (45) vs. SIR/TAC (45)</td>
<td>Grade II-IV 49% SIR vs. 50% CsA Grade III-IV 15% SIR vs. 26% CsA</td>
<td>55% SIR vs. 88% CsA, P = .00002</td>
<td>TMA 12% SIR No VOD</td>
</tr>
<tr>
<td>Cutler C. <em>BMT</em>. 2011.</td>
<td>32 Cord</td>
<td>SIR/TAC</td>
<td>Grade II-IV 9.4%</td>
<td>12.5%</td>
<td>NRM @ 100 d 12.5%</td>
</tr>
</tbody>
</table>

CNI = calcineurin inhibitor; CsA = cyclosporine; MUD = matched unrelated donor; MMUD = mismatched unrelated donor; SIR = sirolimus; TAC = tacrolimus; TMA = thrombotic microangiopathy; VOD = veno-occlusive disease
### Sirolimus in GVHD Prophylaxis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>aGVHD</th>
<th>cGVHD (any grade)</th>
<th>Causes of Death</th>
</tr>
</thead>
</table>
| TAC/SIR | Grade III-IV 16% | 53% | • Relapse (2)  
• GVHD (2)  
• Infection (2)  
• Septicemia (2)  
• VOD (1)  
• Multiorgan failure (1) |
| TAC/MTX | Grade III-IV 13%  
*P = .16* | 70%  
*P = .678* | • Relapse (7)  
• DAH (1)  
• GVHD (1) |
GVHD Prevention

• Ideally
  – Death of host reactive donor lymphocytes within days of transplant
    • Leaving behind unharmed donor T cells with memory for pathogens (recovery of immune function and allow graft vs. host tolerance)
  – Increase T regulatory cells

Post-transplantation Cyclophosphamide

T-cell activation

- Peptide-MHC
- CD80/CD86
- TCR
- CD28
- CD40
- CD40L

Alloreactive T cells → Dendritic cell

T-cell proliferation

- IL-2
- Activated effector T cell
- Receptor

Calcineurin inhibitor

Cy day +3

Non-alloreactive T cells

Haplo-identical HSCT

Used with permission (Dr E. Fuchs)
Protocol also available from eviQ
Graft-versus-host disease

Acute

Chronic

Luznik L et al. Blood. 2010
Relapse and non-relapse mortality
Overall survival, by diagnosis

Luznik L et al. *Blood*. 2010
Causes of death (n=113)

• Relapse: 79
• Non-relapse mortality: 34
  – Infection ~ 40% infections
  – GVHD ~ 15%

Luznik L et al. *Blood.* 2010
Interesting point!

• Increased HLA mismatch-improved EFS without GVHD.
• \(\uparrow graft\text{-}versus\text{-}tumor \text{ without } \uparrow GVHD\)
GVHD Treatment

Predictisone: The all the time eating, shaking, bone thinning, weight gaining, B!@&h making, so you can never sleep again medicine!

1-ASH Education Book 2012- Are we making Progress in GHVD prophylaxis and treatment?
2-BCSH/BSBMT Guideline; Diagnosis and Management of a GVHD and cGVHD
Acute GVHD Treatment

- Patients requiring systemic therapy (grades II-IV) are started on methylprednisolone 2mg/kg/day in two divided doses or prednisolone equivalent
  - No advantage in using higher than 2mg/kg/day of methylprednisolone.
  - Consider dose escalation when aGVHD manifestations start showing major improvement.

- Only about 60% of patients respond to systemic steroids

- Grade I disease-optimise calcineurin inhibitor levels and consider topical steroids

- Attempts at intensifying initial regimen have failed

Van Lint MT et al. Blood 1998
MacMillan et al. Blood 2010
**Mycophenolate + Steroids as 1st line for aGVHD**

- BMT CTN 0802 trial – multicentre, double blind, placebo controlled study steroids/placebo vs. steroids/mycophenolate mofetil for the first therapy for acute GVHD

- Prednisolone 2mg/kg/day with either MMF 1g PO/IV TDS or placebo

- Primary endpoint was GVHD free survival at day 56

- No difference in GVHD-free survival, OS, or chronic GVHD rates from adding mycophenolate to steroids

- More cytopenias in the MMF arm

- Steroids alone continue to remain the standard of care for the frontline treatment of acute GVHD

*Bolanes-Meade J et al. 2013 BMT tandem meeting abstract # 50*
Patient with aGVHD
Patient with aGVHD
Patient with aGVHD
aGVHD Second-Line Therapy

- aGVHD progresses within 3 days or is not improved after 5-7 days of initial treatment with 2mg/kg/day of methylprednisolone i.e. steroid refractory

- Second line treatments are associated with toxicities, high failure rates and 1-year survival of 20-30%

- Methotrexate, mycophenolate, basiliximab, alemtuzumab, ATG, etanercept, infliximab and sirolimus

- 50% of patients respond (CR or partial response)

- Non-absorbable steroids like budesonide can be considered for acute GIT-aGVHD- helps to reduce the dose of systemic steroids

- No evidence that one agent is better than the other!
# aGVHD Second-Line Therapy

## Table 2. Selected studies of aGVHD frontline therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Regimens tested*</th>
<th>N</th>
<th>Response day</th>
<th>CR</th>
<th>CR/PR</th>
<th>NRM</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacMillian75</td>
<td>Retrospective cohort</td>
<td>PDN</td>
<td>864</td>
<td>28</td>
<td>53%</td>
<td>57%</td>
<td>36%</td>
<td>NA</td>
</tr>
<tr>
<td>Cahn76</td>
<td>Randomized</td>
<td>Basiliximab + PDN vs Placebo + PDN</td>
<td>35/34</td>
<td>20</td>
<td>44%/54%</td>
<td>71%/63%</td>
<td>NA</td>
<td>@ 1 y: 66%/59%</td>
</tr>
<tr>
<td>Van Lint71</td>
<td>Randomized</td>
<td>HD PDN vs PDN</td>
<td>48/47</td>
<td>NA</td>
<td>NA</td>
<td>71%/68%</td>
<td>32%/28</td>
<td>@ 3 y: 62%/63%</td>
</tr>
<tr>
<td>Cragg78</td>
<td>Randomized</td>
<td>Horse ATG + PDN vs PDN</td>
<td>50/46</td>
<td>42</td>
<td>NA</td>
<td>76%/76%</td>
<td>54%/35%</td>
<td>@ 2 y: 40%/50%</td>
</tr>
<tr>
<td>Lee77</td>
<td>Randomized</td>
<td>Daclizumab + PDN vs Placebo + PDN</td>
<td>53/49</td>
<td>42</td>
<td>43%/49%</td>
<td>51%/53%</td>
<td>39%/28%</td>
<td>@ 1 y: 26%/60% (P = .002)</td>
</tr>
<tr>
<td>Levine80</td>
<td>Phase 2 Single arm</td>
<td>Etanercept + PDN</td>
<td>61</td>
<td>28</td>
<td>69%</td>
<td>NA</td>
<td>NA</td>
<td>@ 6 mo: 69%</td>
</tr>
<tr>
<td>Couriæ79</td>
<td>Randomized</td>
<td>Infliximab + PDN vs PDN</td>
<td>29/28</td>
<td>28</td>
<td>55%/54%</td>
<td>62%/58%</td>
<td>52%/36%</td>
<td>@ 2 y: 17%/28%</td>
</tr>
<tr>
<td>Alousi81</td>
<td>Phase 2 4-arm randomized</td>
<td>Etanercept + PDN vs MMF + PDN vs Denileukin + PDN vs Pentostatin + PDN</td>
<td>46/45/47/42</td>
<td>28</td>
<td>26%/60%/38%</td>
<td>48%/78%/60%/62%</td>
<td>NA</td>
<td>@ 9 mo: 47%/64%/49%/47%</td>
</tr>
<tr>
<td>Pidala82</td>
<td>Pilot single arm</td>
<td>Sirolimus (no PDN)</td>
<td>10</td>
<td>Best</td>
<td>50%</td>
<td>NA</td>
<td>0%</td>
<td>@ 18 mo: 79%</td>
</tr>
</tbody>
</table>

Meeting quality criteria per American Society for Blood and Marrow Transplantation recommendations.27
PDN indicates prednisone or equivalent dose of another corticosteroid; NA, not available; and HD PDN, high-dose prednisone or equivalent.
*All typically administered in addition to a calcineurin inhibitor.
Important considerations

• Patients are considered very high risk of infections
• PJP/Toxoplasmosis prophylaxis
• HSV/VZV prophylaxis
• Mould active antifungal prophylaxis
• Close CMV monitoring
• CRP
• Fever can be masked by steroids!
Chronic GVHD Treatment

• cGVHD more than 100 days after transplant

• NIH criteria established scoring system and algorithm for calculating global severity to improve consistency in documentation across centers, reduce biased response assessments

• Systemic therapy should be considered for patients who meet criteria for moderate to severe global severity (involvement of 3 or more organs or with an NIH score of 2 or greater in any single organ or any lung involvement)

cGVHD-Organs Affected

- Skin
- Mouth
- Lungs
- Eyes
- Gut
- Liver
- Genitals
cGVHD-Systemic Treatment

• 1mg/kg methylprednisolone or oral equivalent

• Calcineurin inhibitor e.g. cyclosporin or tacrolimus.

• Addition of mycophenolate if no response or progression—also used as a steroid sparing agent.
# Steroid Refractory Chronic GVHD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab</strong></td>
<td>C-2 II</td>
<td>• Cutaneous and musculoskeletal symptoms respond best</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infection most common complication</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>C-3 II</td>
<td>• Sedation, constipation and neuropathy are main side effects</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>C-1 III-I</td>
<td>• Response rates 56 to 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of Thrombotic microangiopathy (TAM)</td>
</tr>
<tr>
<td>Entanercept and Infliximab</td>
<td>C-4 III-3</td>
<td>• Responses seen in skin and GI GVHD</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>C-1 III-I</td>
<td>• Response rates 40-75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Infectious complications 10-50%</td>
</tr>
<tr>
<td>Photopheresis</td>
<td>C-1 II</td>
<td>• No treatment schedule has demonstrated superior response rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Steroid sparing effects</td>
</tr>
<tr>
<td>Imatinib</td>
<td>C-2 III-I</td>
<td>• Activity in pulmonary and sclerodermatous GVHD</td>
</tr>
</tbody>
</table>

Oral cGVHD
Oral cGVHD

Flowers M et al. Blood 2002
Oral cGVHD

- Oral cGVHD common, may be initial site
- Topical corticosteroids & tacrolimus
- Avoid irritating food/drink/toothpaste
- Salivary stimulants & moisturizing agents
- Oral cancer surveillance
- May require treatment for many years

<table>
<thead>
<tr>
<th>Oral mucosal cGVHD</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized disease</td>
<td>Dexamethasone solution 0.5 mg/5 mL, 5 mL swish 5 minutes and spit, 2-4 times/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clobetasol 0.05% solution</td>
<td>Instruct patients to wait 10-15 minutes after topical therapy before eating/drinking</td>
</tr>
<tr>
<td></td>
<td>Budesonide mouthwash (3 mg/10 mL)</td>
<td>Gels can be applied with gauze and left in place 10-15 minutes</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus 0.1% solution</td>
<td>Solutions: begin with dexamethasone, if inadequate response after 2-4 wks (4 times a day), substitute with clobetasol (budesonide can also be used). If after 2-4 wks still inadequate control, add tacrolimus and use equal parts with clobetasol as a single combined rinse.</td>
</tr>
<tr>
<td>Focal disease (eg, solitary painful ulcers)</td>
<td>Fluocinonide 0.05% gel, 2-4 times/day</td>
<td>Secondary candidiasis, typically occurs in first week, in addition to treatment most will require prophylaxis. Prophylaxis regimens include daily topical antifungal therapy or fluconazole 200 mg once/wk</td>
</tr>
<tr>
<td>Lips</td>
<td>Tacrolimus 0.1% ointment, 2-4 times/day</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salivary gland cGVHD</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xerostomia</td>
<td>Salivary stimulants (gum/candy)</td>
<td>Sugar-free or xylitol-containing gum/candy</td>
</tr>
<tr>
<td></td>
<td>Oral-moisturizing agents</td>
<td>Sialogogues may take 8-12 wks for full efficacy</td>
</tr>
<tr>
<td></td>
<td>Sialogogue therapy</td>
<td>Avoid sialogogues in patients with pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>• Pilocarpine 5 mg 3 times a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cevimeline 30 mg 3 times a day</td>
<td></td>
</tr>
<tr>
<td>Dental caries</td>
<td>Good oral hygiene</td>
<td>See Table 4 for detailed guidelines</td>
</tr>
<tr>
<td></td>
<td>Avoid sugary foods/drinks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical fluoride therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remineralization therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular dental visits</td>
<td></td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Fluconazole</td>
<td>Topical steroid therapy increases risk of candidiasis</td>
</tr>
<tr>
<td></td>
<td>Disinfect removable prosthesis nightly</td>
<td>Antifungal prophylaxis for recurrent candidiasis</td>
</tr>
</tbody>
</table>

| Sclerotic cGVHD             | Physical therapy                                                         | Condition is generally progressive and requires ongoing therapy                |
|                             | Intrallesional steroid therapy                                            |                                                                                |
|                             | Surgery to disrupt mucosal bands                                          |                                                                                |
Topical corticosteroids according to potency

1. Betamethasone dipropionate 0.05% optimised vehicle (Diprosone ointment OV)

1. Clobetasol propionate 0.05% (Eumovate, cream only)

2. Betamethasone dipropionate 0.05%(Diprosone ointment)

1. Betamethasone valerate 0.1% (Celestone ointment)

2. Triamcinolone acetonide 0.1% (Aristocort ointment)

1. Triamcinolone acetonide (Kenalog in orabase)
Lung-cGVHD

• Pulmonary complications significantly contribute to late mortality after allo-HSCT

• Bathia et al. found a 15-fold increased risk of late mortality because of pulmonary dysfunction compared with the general population

• Bronchiolitis obliterans organizing pneumonia (BOOP) or bronchiolitis obliteratans syndrome (BOS), non-infectious pulmonary complication forms are strongly associated with cGVHD

Savani BN et al. BBMT 2006
Management of Lung GVHD

- Systemic steroids
- Inhaled corticosteroids
- Calcinerin inhibitors
- Mycophenolate
- Azithromycin (Khaled et al Eur Respir J 2005) 250mg thrice weekly PO
  - 8/153 patients had developed BO after HSCT
  - azithromycin 500 mg once daily for 3 days, followed by 250 mg 3 × /week for 12 weeks.
  - Clinically significant improvement was achieved in both FEV1 and FVC in seven out of eight patients.
- Imatinib

Hildebrant GC et al. BMT 2011
Role of the Pharmacist

- Provide advise re correct agent choice, correct dose and treatment duration.
- Patient education.
- Checking for drug-drug interactions.
- Therapeutic Drug Monitoring.
- Assessing need for dose modification e.g in renal or hepatic impairment.
- Assessing for side effects.
- Transition to oral therapy when appropriate.
- Monitoring for cost effectiveness.
Conclusions-GVHD

• aGVHD and cGVHD remain serious barriers to successful allo-HCT

• It is had to say if we are making progress in the management of GVHD in the last 20 years

• The current reality is that no single agent has yet been approved by the FDA for GVHD!

• The primary goal is to prevent the life-threatening and disabling GVHD manifestations.

• Post-transplant cyclophosphamide- A game changer?
Questions?