Introduction to Graft-versus-Host Disease (GVHD)

Celebrating a Second Chance at Life
Survivorship Symposium

April 27 – May 3, 2024

Luke Mountjoy DO
Assistant Member Physician,
Colorado Blood Cancer Institute
Graft-versus-Host Disease: The Basics

BMTinfonet.org - Symposium 2024
April 27 2024

Luke Mountjoy, DO
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Colorado Blood Cancer Institute
Denver, CO
Introduction to Graft-versus-Host Disease (GVHD)

- Allotransplant: A quick introduction.
- Mechanisms leading to GVHD
- Incidence and risk factors GVHD
- Clinical presentation of GVHD
- GVHD prophylaxis
- GVHD treatment
Transplant from Donor

Blood forming cells: STEM CELLS
➢ Replace Host’s stem cells

Immune Cells:
➢ They can attack the recipient
  ➢ “Graft versus host disease”
➢ They can destroy cancer cells
  ➢ “Graft Versus Tumor”

Recipient

“Host”
Graft-versus-Host Disease (GVHD)

- Biological consequence of the transfer of a donor’s immune cells into the recipient
- Immunosuppressive medications are necessary to prevent GVHD
- GVHD can be eliminated by removing immune cells (T-cells) from the donor collection
GVHD How Does It Happen? Elements of Over-Reactivity

Chemo and radiation: Tissue damage

Damage to intestinal environment

Cytokines and inflammatory mediators

Donor immune cells discover host targets

Cells cross talk amplifies and direct fight to many directions

Issues in control and education the immune cells
GVHD: Acute and Chronic

Acute GVHD: Skin, GI, Liver

Chronic GVHD: Skin, Mouth, Eyes GI, Liver, MSK, Fascia, Lungs, etc

Alloreactivity

Immunodeficiency

Classic Acute

Late Acute Chronic Overlap

Classic chronic

Day 0 50 100 180 1 yr 2 yrs 3 yrs 5 yrs

Activity

Inflammation

Injury

Repair

Damage

Fibrosis

Cutler BMTinfo 2020
Acute Graft-versus-Host Disease (GVHD)

- Leading cause of mortality
- Grade II-IV occurs in ~70% pts
- Grade III-IV occurs in 10-15%
- ~2-6 weeks after transplant
- 30-40% refractory to 1st line of treatment
# Acute GVHD - Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>↑ Risk of acute GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor-recipient factors</strong></td>
<td></td>
</tr>
<tr>
<td><em>HLA disparity (HLA class I, II)</em></td>
<td><em>HLA mismatched &gt; matched donor</em></td>
</tr>
<tr>
<td>Minor HLA disparity (mHA)</td>
<td>Unrelated donor &gt; related donor</td>
</tr>
<tr>
<td>Sex matching</td>
<td>Mismatch &gt; match</td>
</tr>
<tr>
<td><strong>Donor parity</strong></td>
<td><em>Multiparity &gt; nulliparity</em></td>
</tr>
<tr>
<td>Donor age</td>
<td>Older donor &gt; younger donor</td>
</tr>
<tr>
<td>ABO type</td>
<td>ABO mismatch &gt; ABO match</td>
</tr>
<tr>
<td>Donor CMV serostatus</td>
<td>CMV positive &gt; CMV negative</td>
</tr>
<tr>
<td>Cytokine gene polymorphisms</td>
<td>Numerous associated with acute GVHD</td>
</tr>
<tr>
<td><strong>Stem cell graft factors</strong></td>
<td></td>
</tr>
<tr>
<td>Stem cell source</td>
<td>PBSC &gt; BM &gt; UCB</td>
</tr>
<tr>
<td>Graft composition</td>
<td>Higher CD34+ count &gt; lower CD34+ cell count</td>
</tr>
<tr>
<td></td>
<td>Higher T-cell dose &gt; lower T cell dose</td>
</tr>
<tr>
<td><strong>Transplantation factors</strong></td>
<td></td>
</tr>
<tr>
<td>Conditioning intensity</td>
<td>Myeloablative &gt; reduced-intensity regimens</td>
</tr>
</tbody>
</table>
# Acute GVHD: Clinical Features and Grading - MAGIC

## GVHD Target Organ Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin (Active Erythema Only)</th>
<th>Liver (Bilirubin)</th>
<th>Upper Gl</th>
<th>Lower Gl (stool output/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No active (erythematous) GVHD rash</td>
<td>&lt;2 mg/dL</td>
<td>No or intermittent nausea, vomiting, or anorexia</td>
<td>&lt;500 mL/day or &lt;3 episodes/day</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% BSA</td>
<td>2-3 mg/dL</td>
<td>Persistent nausea, vomiting or anorexia</td>
<td>500-999 mL/day or 3-4 episodes/day</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25-50% BSA</td>
<td>3.1-6 mg/dL</td>
<td></td>
<td>1000-1500 mL/day or 5-7 episodes/day</td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular rash &gt;50% BSA</td>
<td>6.1-15 mg/dL</td>
<td></td>
<td>&gt;1500 mL/day or &gt;7 episodes/day</td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythroderma (&gt;50% BSA) plus bullous formation and desquamation &gt;5% BSA</td>
<td>&gt;15 mg/dL</td>
<td>Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).</td>
<td></td>
</tr>
</tbody>
</table>

**Overall clinical grade (based on most severe target organ involvement):**
- Grade 0: No stage 1-4 of any organ.
- Grade I: Stage 1-2 skin without liver, upper Gl, or lower Gl involvement.
- Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper Gl and/or stage 1 lower Gl.
- Grade III: Stage 2-3 liver and/or stage 2-3 lower Gl, with stage 0-3 skin and/or stage 0-1 upper Gl.
- Grade IV: Stage 4 skin, liver, or lower Gl involvement, with stage 0-1 upper Gl.

Harris et al, BBMT 2016
Chronic Graft-versus-Host Disease (GVHD)

- Most serious and common long-term complication of transplant
- Occurs in 30% - 55% of patients
- ~4-6 months after transplant
- 50% of patients have 3 or more organs involved
- On average, therapy is required for 2-3 years
<table>
<thead>
<tr>
<th>Organ/site</th>
<th>Diagnostic</th>
<th>Distinctive (insufficient for diagnosis)</th>
<th>Features seen in acute &amp; chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>• Poikiloderma</td>
<td>• Depigmentation</td>
<td>• Erythema</td>
</tr>
<tr>
<td></td>
<td>• Lichen planus-like</td>
<td>• Papulosquamous</td>
<td>• Maculopapular</td>
</tr>
<tr>
<td></td>
<td>• Sclerosis</td>
<td></td>
<td>• pruritus</td>
</tr>
<tr>
<td></td>
<td>• Morphea-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lichen sclerosis-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Onycholysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nails</td>
<td>• Alopecia (scarring or nonscarring)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Scaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp/body hair</td>
<td>• Lichen planus-like</td>
<td>• New dry, gritty, or painful eyes (sicca)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• lichen sclerosis-like</td>
<td>• Keratoconjunctivitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vaginal or urethral scarring/stenosis</td>
<td>• Punctate keratopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Labial agglutination</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Phimosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>• Lichen planus-like</td>
<td>• Erosion</td>
<td>• Gingivitis</td>
</tr>
<tr>
<td></td>
<td>• lichen sclerosis-like</td>
<td>• Fissures</td>
<td>• Mucositis</td>
</tr>
<tr>
<td></td>
<td>• Vaginal or urethral scarring/stenosis</td>
<td>• Ulcers</td>
<td>• Erythema</td>
</tr>
<tr>
<td></td>
<td>• Labial agglutination</td>
<td></td>
<td>• pain</td>
</tr>
<tr>
<td>Genitalia</td>
<td>• Phimosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>• Lichen planus-like</td>
<td>• Xerostomia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lichen planus-like</td>
<td>• Mucoceles</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Xerostomia</td>
<td>• Mucosal Atrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mucoceles</td>
<td>• Pseudomembranes</td>
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<tr>
<td>------------</td>
<td>------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
</tbody>
</table>
| GI tract   | • Esophageal web  
• Esophageal strictures | | • Diarrhea  
• Anorexia  
• Nausea vomiting  
• Malabsorption  
• Wasting syndrome/FTT |
| Liver      | | | • Mixed hepatitis,  
• Increased TBili, ALP, ALT |
| Muscles, fascia, joints | • Fasciitis  
• Joint stiffness or contractures due to sclerosis | • Myositis  
• Polymyositis | |
| Lung       | • Bronchiolitis obliterans (bx) | • Cryptogenic organizing pneumonia (COP or BOOP)  
• Restrictive lung disease | |
| Heme/Immuno| | | • Thrombocytopenia  
• Eosinophilia  
• Hypo-hypergamma  
• Autoantibodies  
• Raynaud phenomenon |
| Others     | | | • Serositis/effusions  
• Nephrotic syndrome  
• Myasthenia gravis  
• Peripheral neuropathy  
• Whole body anasarca |
# Chronic GVHD: 2014 NIH Consensus

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Mild** | 1 or 2 organs or sites (except lung) with score 1  
- Mild oral symptoms, no decrease in oral intake  
- Mild dry eyes, lubricant eyedrops ≤ 3x/day |
| **Moderate** | 3 or more organs with score 1  
- At least 1 organ or site with score 2  
  - 19-50% body surface area involved or superficial sclerosis  
  - Moderate dry eyes, eyedrops > 3x/day or punctal plugs  
- Lung score 1 (FEV1 60-79% or dyspnea with stairs) |
| **Severe** | At least 1 organ or site with score 3  
  - > 50% body surface area involved  
  - Deep sclerosis, impaired mobility or ulceration  
  - Severe oral symptoms with major limitation in oral intake  
  - Severe dry eyes affecting ADL  
- Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground) |
Transplant from Donor: How to Define Success

- Cure the blood cancer
- NO Graft-versus-Host Disease
Transplant from Donor: General Schema

Infusion of Cells from Donor

**CONDITIONING**
- ✓ Chemo +/- Radiation
- ✓ More or less intense
- ✓ Prevent Rejection
- ✓ Destroy cancer cells

**POST TRANSPLANT IMMUNOSUPPRESSION**
- ✓ Drugs given in vein or by pills
- ✓ Prevent GVHD
Transplant from Donor: General Schema

Infusion of Cells from Donor

Day -6 0 +15 +30 +100 +180

CONDITIONING
✓ Chemo +/- Radiation
✓ Prevent Rejection
✓ Destroy cancer cells

Cyclosporine + Methotrexate Tacrolimus + Methotrexate
Tacrolimus + MMF
Tacrolimus + Sirolimus + MMF
Tacrolimus + Methotrexate + Abatacept
Other Ways to Reduce GVHD: Look at the Donation

➢ In the donor collection bag there is a mix of many kinds of cells:
  • Stem cells and LOTS and LOTS of immune cells.

➢ Some cells can induce GVHD (Naïve T cell)
  • ALLOREACTIVE – BAD guys

➢ Some cells can prevent or reduce GVHD (Regulatory T cells)
  • TOLERANCE – GOOD guys
Strategies to Avoid GVHD

- Post-transplant Cytoxan (PTCy)
- Graft manipulation
How Post-Transplant Cytoxan (PTCy) Works

Alloreactive T-cell cause GVHD (the BAD ones)

Alloreactive T-cell expand and are destroyed by Cytoxan

All other T-cells thrive
Post-Transplant Cytoxan (PTCy): Study and Clinical Data

➢ PTCy (+TAC/MMF) already used worldwide for transplant from children or parents (haploidentical transplants)

➢ BMT CTN 1203 clinical trial showed promising results in transplants from siblings and unrelated donors.

➢ Phase III BMT CTN 1703 study evaluated outcomes after reduced-intensity conditioning transplant in patients randomized to receive PTCy + TAC + MMF vs standard TAC + MTX

PTCy = post-transplant cyclophosphamide
TAC = tacrolimus
MMF = mycophenolate mofetil
MTX = methotrexate
## BMT CTN 1703: Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (n)</th>
<th>Patients living without disease and without GVHD 1 year post transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCy + TAC + MMF (n = 214)</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>TAC + MTX (n = 217)</td>
<td></td>
<td>35%</td>
</tr>
</tbody>
</table>

PTCy = post-transplant cyclophosphamide
TAC = tacrolimus
MMF = mycophenolate mofetil
MTX = methotrexate

*Holtan et al ASH 2022*
# BMT CTN 1703: Results

<table>
<thead>
<tr>
<th></th>
<th>PTCy + TAC + MMF ((n = 214))</th>
<th>TAC + MTX ((n = 217))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with acute GVHD 100 days post transplant</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Patients with chronic GVHD 1 year post transplant</td>
<td>12%</td>
<td>25%</td>
</tr>
<tr>
<td>Patients with Cancer Relapse 1 year post transplant</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Transplant mortality 1 year post transplant</td>
<td>12%</td>
<td>17%</td>
</tr>
</tbody>
</table>
Other Ways to Reduce GVHD

Donor collection:

➢ Let’s remove the bad guys
➢ Let’s help the good guys
“Let’s Remove the BAD Guys” Approach

“Naïve” Tcells are removed [CD45RA+]

Stem Cells + “Memory” Tcells infused to the recipient

138 patients with leukemia,
Donors were fully matched

Bleakley et al JCO 2022

Day

-6   0   +15   +30   +100   +180

Chemo Conditioning

Tacrolimus +/- MTX
“Let’s Remove the BAD Guys” Approach

“Naïve” T-cell depleted (n = 138)

Patients with acute GVHD grade ≥3
180 days post transplant

- 4%
- None severe

Patients with chronic GVHD
1 year post transplant

- 7%
- None severe

Patients living without disease and without GVHD
3 years post transplant

- 68%

Overall Survival
3 years post transplant

- 77%

Bleichley et al. JCO 2022
“Let’s Help the GOOD Guys” Approach

ORCA-T

Donor cells → Stem Cells → Regulatory T cell [CD4⁺CD127lo] → The GOOD guys

Conventional T cell

Oliai et al, ASH 2022
ORCA-T: Clinical Trials

- **127 patients**, with high-risk blood cancers
- Donors were fully matched related (n=66) or unrelated (n=61).
- Transplant was with high dose chemo or radiation
- Post transplant single-agent tacrolimus
- Outcomes were compared with 375 matched patients from the CIBMTR registry

NCT04013685
NCT01660607

Oliai et al, ASH 2022
## ORCA-T: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ORCA-T (n = 127)</th>
<th>CIBMTR Control (n = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with acute GVHD grade $\geq$3 180 days post transplant</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Patients with chronic GVHD 1 year post transplant</td>
<td>6%</td>
<td>38%</td>
</tr>
<tr>
<td>Relapse free survival 1 year post transplant</td>
<td>81%</td>
<td>62%</td>
</tr>
<tr>
<td>Non Relapse mortality 1 year post transplant</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Overall Survival 1 year post transplant</td>
<td>91%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Oliai et al, ASH 2022
ORCA-T: Results

<table>
<thead>
<tr>
<th>ORCA-T</th>
<th>CIBMTR Control</th>
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</thead>
<tbody>
<tr>
<td>(n = 127)</td>
<td>(n = 375)</td>
</tr>
<tr>
<td>Patients living without disease and without GVHD 1 year post transplant</td>
<td>76%</td>
</tr>
</tbody>
</table>

A multi-center randomized controlled phase 3 trial comparing Orca-T to standard of care is currently enrolling across the US (NCT05316701).

Oliai et al ASH 2022
Steroids: mainstay of systemic treatment

- Acute: 40-60% respond < 5 days
- Chronic: need longer course (ie. weeks to months)
- When steroids don’t work: several options are available
GVHD: Challenges

- No one treatment fits all patients
- Some therapies are ineffective
- Treatment has side effects, immunosuppressive, might be needed lifelong
- Impact on quality of life, return to family life, relationships, work
## New Drugs Approved for GVHD Treatment

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Type of GVHD</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (Imbruvica®)</td>
<td>Chronic</td>
<td>2/8/2017</td>
</tr>
<tr>
<td>Ruxolitinib (Jakafi®)</td>
<td>Acute</td>
<td>5/24/2019</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>9/22/2021</td>
</tr>
<tr>
<td>Belomosudil (Rezurock®)</td>
<td>Chronic</td>
<td>7/16/2021</td>
</tr>
</tbody>
</table>
Ibrutinib (Imbruvica®)

➢ Original study included 42 patients with bad GVHD, resistant to steroids
  • In 31% of patients, GVHD went away completely
  • 38% of patients had partial resolution of GVHD
  • In 55% of patients, the response lasted at least 11 months
  • 64% of patients could reduce the usage of steroids like prednisone

➢ It works on sclerotic GVHD:
  • 61% of patients with sclerosis showed improvement and in 39%, tightening of the skin went away

Waller EK, BBMT 2019
PCYC-1129-CA
Ibrutinib (Imbruvica®)
Adverse Effects

- In > 20% of Patients
  - Fatigue
  - Bruising
  - Low platelets
  - Muscle spasm
  - Nausea
  - Pneumonia
  - Mouth sores

- In ~5% of patients
  - Irregular heartbeat

In ~5% of patients
Ruxolitinib (Jakafi®)

- **Pill:** twice a day
- **Already used for other blood diseases (myelofibrosis and Polycythemia Vera)**
- **How does it work?**
  - *Modulates immune system* to switch off GVHD
  - Regulates the development, proliferation, and activation of several immune cell types.
Ruxolitinib (Jakafi®)

REACH2 Trial : Acute GVHD

➢ Randomly assigned 309 patients with severe steroid-refractory acute GVHD to receive ruxolitinib 10 mg twice daily (n = 154) or best available therapy (n = 155)

➢ Improvement was seen in 62% of patients compared to 39%.

➢ GVHD went completely away in 34% of patients on ruxolitinib vs 19% in the control group

➢ The good response was maintained after 2 months of treatment for more patients in the ruxolitinib group than in the control group (40% vs. 22%)

Zeiser R, NEJM 2020
Ruxolitinib (Jakafi®)

REACH3 Trial: chronic GVHD

➢ Randomly assigned 329 patients with moderate or severe steroid-refractory or dependent chronic GVHD to receive ruxolitinib 10 mg twice daily (n = 165) or best available therapy (BAT; n = 164)

➢ The improvement was seen in 50% of patients compared to 26%.

➢ The responses lasted up to 1 year and 7 months

➢ Patients reported improved quality of life and symptoms

Zeiser R, NEJM 2021
Lee S, et al, Blood. 2021
Ruxolitinib (Jakafi®)
Adverse Effects

➢ >35%
  • Anemia
  • Low platelets

➢ >20%
  • Infection, fungal, viral
  • Liver tests go up
Belumosudil (Rezurock®)

- **Pill:** once or twice a day with food
- **Totally new drug designed to fight fibrosis (ROCK inhibitor)**
- **How does it work?**
  - Modulates immune system to switch off GVHD, does not depress the immune system
  - Anti-fibrosis
Belumosudil (Rezurock®)

- 77% of patients treated improved
  - responses noted in all affected organs
- In 50% of patients, the response lasted at least 14 months
- Very well tolerated
- Signals of response in patients who experienced treatment failure with ruxolitinib and ibrutinib.

Cutler et al, Blood 2021
Study: ROCKstar
Belumosudil (Rezurock®)  
Adverse Effects  

➢ >20%  
  • Fatigue  
  • Edema  
  • Muscular pain  
  • Liver tests go up  
  • Headache  
  • GI upset
Summary

➢ GVHD is a major complication of transplant

➢ We are getting better!

➢ Substantial strides have been made to prevent GVHD

➢ Promising additional therapies on the horizon

➢ Treatment for GVHD rapidly improving
Thank you !!!

BMTinfoNet
Questions?

Luke Mountjoy DO
Assistant Member Physician,
Colorado Blood Cancer Institute

Luke
Let Us Know How We Can Help You

Visit our website:  bmtinfonet.org

Email us:  help@bmtinfonet.org

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