LATE COMPLICATIONS OF ALLOGENEIC TRANSPLANT: CHRONIC GRAFT VS. HOST DISEASE

Asmita Mishra, MD and Marian Dam, DNP
FLASCO 2019 Great Strides Together
May 17, 2019
OPTIMIZING SUCCESS AFTER TRANSPLANT

• Understanding the problem at hand

• Identification and grading of chronic GVHD

• Therapy for chronic GVHD
Allogeneic Hematopoietic Cell Transplantation (HCT)

Conditioning

Immune Suppression

Desired end - goal:
- Cure of malignancy
- Resolution of all GVHD
- Successful liberation from IS (i.e. immune tolerance)

Acute GVHD

Chronic GVHD

GVHD: - Significant source of TRM - Major barrier to otherwise potentially curative anti-malignancy activity of HCT
Causes of Death after Unrelated Donor HCT done in 2015-2016

Died within 100 days post-transplant:
- Primary Disease: 24%
- Infection: 20%
- GVHD: 11%
- Hemorrhage: 18%
- Organ Failure: 3%
- Graft Rejection: 2%
- Second Malignancy: 1%
- Other: 1%

Died at or beyond 100 days post-transplant:
- Primary Disease: 48%
- GVHD: 13%
- Infection: 12%
- Second Malignancy: 10%
- Graft Rejection: 13%
- Other: 1%

*Data reflects 3-year mortality
Chronic GVHD causes late HCT mortality

<table>
<thead>
<tr>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>32%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>62%</td>
<td>86%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Chronic GVHD remains major obstacle to HCT success

BMT CTN 0402

BMT CTN 0201

Cumulative Incidence, %

Years

Cumulative Incidence of Chronic GVHD (%)

P=0.01

Peripheral blood

Bone marrow

Cutler, Blood 2014
Anasetti, NEJM 2012
OPTIMIZING SUCCESS AFTER TRANSPLANT

• Understanding the problem at hand
  • Long term transplant specific issue
  • Impacts many transplanted patients
  • Major cause of death after transplant

• Identification and grading of chronic GVHD
Chronic GVHD Diagnosis

- Major proposed changes in diagnosis, classification, and severity grading following 2005 NIH Consensus Conference
- Distinction of acute and chronic
- Definitions of classic vs. overlap chronic
- Individual organ severity grading, summarized in global composite score of mild, moderate, severe

Table 2. Categories of acute and chronic graft-versus-host disease (GVHD). Reprinted from Filipovich et al.\textsuperscript{7}

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI</th>
<th>Presence of acute GVHD features</th>
<th>Presence of chronic GVHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute</td>
<td>≤ 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent</td>
<td>&gt; 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>or late-onset acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Filipovich. BBMT, 2005.
<table>
<thead>
<tr>
<th>Mild</th>
<th>• 1 or 2 organs or sites (except lung) with score 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>• 3 or more organs with score 1</td>
</tr>
<tr>
<td></td>
<td>• At least 1 organ or site with score 2</td>
</tr>
<tr>
<td></td>
<td>• Lung score of 1</td>
</tr>
<tr>
<td>Severe</td>
<td>• At least 1 organ or site with score 3</td>
</tr>
<tr>
<td></td>
<td>• Lung score 2</td>
</tr>
</tbody>
</table>
Diagnostic Manifestations

**SKIN**
- Poikiloderma
- Lichen-planus
- Sclerosis
- Morphea
- Lichen sclerosis

**MOUTH/EYES**
- Lichen-planus
- Dry eyes

**GI**
- Esophageal web, stricture
- Liver abnormalities

**JOINTS**
- Fasciitis
- Contractures or joint stiffness

**LUNG**
- Bronchiolitis obliterans

**GENITAL**
- Lichen planus
- Lichen sclerosis
- Vaginal scarring
- (male – phimosis, or urethral/meatus stenosis)
Poikiloderma: Atrophy and pigmentary changes

Lichen planus: Erythematous/violaceous flat-topped papules or plaques with or without surface reticulation or silvery/shiny appearance on direct light

Lichen sclerosis: Discrete to coalescent gray to white moveable papules or plaques, with shiny appearance and leathery consistency
Cutaneous sclerosis: thickened or tight skin, ranges from superficial sclerosis (thickened skin) to deep sclerosis (hidebound) -> at most severe, limited mobility, Ulceration, and poor wound healing

Morphea: localized, patchy area of moveable skin with leathery-like consistency, often with dyspigmentation
P-ROM

Shoulder

1 (Worst) 2 3 4 5 6 7 (Normal)

Elbow

1 (Worst) 2 3 4 5 6 7 (Normal)

Wrist/finger

1 (Worst) 2 3 4 5 6 7 (Normal)

Ankle

1 (Worst) 2 3 4 (Normal)
# NIH Mouth Score

<table>
<thead>
<tr>
<th>MOUTH</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus-like features present:</td>
<td>□ No symptoms</td>
<td>□ Mild symptoms with disease signs but not limiting oral intake</td>
<td>□ Moderate symptoms with disease signs with partial limitation of oral intake</td>
<td>□ Severe symptoms with disease signs on examination with major limitation of oral intake</td>
</tr>
<tr>
<td>□ Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Lichen planus-like changes:** white lines and lacy-appearing lesions on the buccal mucosa, tongue, palate, or lips

**Hyperkeratotic plaques:** leukoplakia

**Sclerosis:** decreased oral range of motion
# NIH GI tract score

<table>
<thead>
<tr>
<th>GI Tract</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Check all that apply:</strong>&lt;br&gt;☐ Esophageal web/proximal stricture or ring&lt;br&gt;☐ Dysphagia&lt;br&gt;☐ Anorexia&lt;br&gt;☐ Nausea&lt;br&gt;☐ Vomiting&lt;br&gt;☐ Diarrhea&lt;br&gt;☐ Weight loss ≥5%*&lt;br&gt;☐ Failure to thrive&lt;br&gt;☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td>☐ No symptoms</td>
<td>☐ Symptoms without significant weight loss* (&lt;5%)</td>
<td>☐ Symptoms associated with mild to moderate weight loss* (5-15%) OR moderate diarrhea without significant interference with daily living</td>
<td>☐ Symptoms associated with significant weight loss* &gt;15%, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living</td>
</tr>
</tbody>
</table>
Esophageal web: Barium swallow and endoscopic visualization demonstrate esophageal narrowing due to web
## NIH Liver score

<table>
<thead>
<tr>
<th></th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER</td>
<td>□ Normal total bilirubin and ALT or AP &lt; 3 x ULN</td>
<td>□ Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN</td>
<td>□ Elevated total bilirubin but ≤ 3 mg/dL or ALT &gt; 5 ULN</td>
<td>□ Elevated total bilirubin &gt; 3 mg/dL</td>
</tr>
</tbody>
</table>

- Abnormality present but explained entirely by non-GVHD documented cause (specify):
Bronchiolitis Obliterans Syndrome (BOS)
OPTIMIZING SUCCESS AFTER TRANSPLANT

• Understanding the problem at hand

• Identification and grading of chronic GVHD
  • Can occur any time but usually 100 days after HCT
  • Any organ can get impacted: skin most common
  • Significant impact on morbidity

• Therapy for chronic GVHD
Chronic GVHD: Secondary treatment

• Second-line therapy
  – Many IS agents used
  – Frequent failure, multiple lines of therapy

• Many novel agents being evaluated

• Recent FDA approved treatment option available

Inamoto. Blood 2013
Chronic GVHD: Primary treatment

- Standard first-line treatment
  - 1mg/kg/day prednisone
  - CNI – spare steroid exposure

- Expected outcome
  - ORR 6-9 months ~ 60%
  - CR 6-9 months ~ 30%
Novel agents for chronic GVHD

**Phase 1**
Acute inflammation & Tissue injury

- Innate immunity
  - Cytokines
  - TLR agonists
  - Neutrophils
  - Platelets
  - Vascular inflammation

**Phase 2**
Chronic inflammation & dysregulated immunity

- Adaptive immunity
  - Thymic Injury and dysfunction
  - T cells
  - B cells
  - NK cells
  - Antigen presenting cells
  - Regulatory Cells
    - Treg, Breg
    - IL-10 producing regulatory T cells (Tr1)

**Phase 3**
Aberrant tissue repair & fibrosis

- Innate & adaptive
  - TGFβ
  - PDGFα
  - TNFα
  - IL-17
  - Macrophages
  - Fibroblasts

Cooke, BBMT 2017
## Novel agents for chronic GVHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baricitinib</td>
<td>JAK1/2 inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Proteasome inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Proteasome inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>KD025</td>
<td>ROCK2 inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA4-Ig fusion protein</td>
<td>T-cell costimulatory pathway</td>
</tr>
<tr>
<td>Ponesimod</td>
<td>S1P1 receptor modulator</td>
<td>T-cell homing</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>CD30 antibody-drug conjugate</td>
<td>T-cell responses</td>
</tr>
<tr>
<td><strong>Ibrutinib</strong></td>
<td>BTK/ITK inhibitor</td>
<td><strong>B cells</strong></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Anti-CD20 antibody</td>
<td><strong>B cells</strong></td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>Syk inhibitor</td>
<td><strong>B cells</strong></td>
</tr>
<tr>
<td>Entospletinib</td>
<td>Syk inhibitor</td>
<td><strong>B cells</strong></td>
</tr>
<tr>
<td>Dose escalated IL-2</td>
<td>Induction of T-regs</td>
<td><strong>T-regs</strong></td>
</tr>
<tr>
<td>IL-2+T-regs</td>
<td>Induction of T-regs</td>
<td><strong>T-regs and Cellular therapies</strong></td>
</tr>
<tr>
<td>Autologous MSCs</td>
<td>Suppressive population</td>
<td><strong>Cellular therapies</strong></td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Suppressive population</td>
<td><strong>Cellular therapies</strong></td>
</tr>
<tr>
<td>AZD9668</td>
<td>Neutrophil elastase inhibitor</td>
<td><strong>Non-lymphocyte target</strong></td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Hedgehog inhibitor</td>
<td><strong>Non-lymphocyte target</strong></td>
</tr>
<tr>
<td>LDE225</td>
<td>Hedgehog inhibitor</td>
<td><strong>Non-lymphocyte target</strong></td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Multiple</td>
<td><strong>Non-lymphocyte target</strong></td>
</tr>
</tbody>
</table>
IBRUTINIB FOR CHRONIC GVHD

- Multiple targets in GVHD inducing pathways
  - Inhibition of Bruton tyrosine kinase in B cells
  - Interleukin-2 inducible T cells kinase in T cells

- Multicenter open label study, N=42
- Steroid dependent or refractory cGVHD
Durable Response with Ibrutinib

**Chart:**
- **ORR 67%**
- **CR 9**
- **SD 19**
- **PD 2**

**Table:**

<table>
<thead>
<tr>
<th>Organ</th>
<th>No. of responders</th>
<th>Best ORR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Mouth</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organs showing response at baseline among responders</th>
<th>Best ORR, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 organs</td>
<td>20 (80)</td>
</tr>
</tbody>
</table>

**Adverse event (N = 42):**

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>5 (12)</td>
<td>14 (33)</td>
<td>5 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (17)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>8 (19)</td>
<td>3 (7)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (19)</td>
<td>3 (7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bruising</td>
<td>6 (14)</td>
<td>4 (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Miklos et al, Blood 2017
Scenario 1

• 39 Y.O. Caucasian Male
• Disease: AML t (8,21) (q22, q22), relapsed
• DOT: 2015
• Type of transplant: allogeneic matched unrelated
• Donor 43 y.o. M, ABO compatible
• Match grade 10/12 (DPB1 permissive)
• Conditioning: Fludarabine + Busulfan 5300.
• Stem cell source: Peripheral blood.
• GVHD prophylaxis: Tacrolimus/Sirolimus
Post Transplant Complication

• During a routine 2 month follow up patient was found to have approx. 45% maculopapular rash (Gr2 skin) with Gr 2 LFT elevation.
  – Treatment plan was to optimize Tacrolimus/Sirolimus levels
  – Started Prednisone 1mg/kg (~100mg)
    • Topical betamethasone cream
Post Transplant Complication

- **02/20/2016:** Skin GVHD resolved and started steroid taper with weekly visits.
- Recurrence of liver transaminases 2x ULN at prednisone taper dose of 50mg.
  - **Moderate GVHD score:** Prednisone dose increased to 80mg

- **04/02/2016:** Scleroderma to 25% of BSA. Extracorporeal photopheresis (ECP) started 2 times a week.
  - Plan to taper steroid as tolerated every 3 weeks
Post Transplant Complication

• **01/2017**: Patient remained on GVHD therapy for scleroderma and Grade 2 abnormal liver transaminases. He began to experience irritability, AMS, and probable seizures was referred to Neuro-Oncology.
  
  • *MRI brain w/wo later revealed enhancement & progression of white matter lesions*
    
    o Started on levetiracetam 1gm BID and IVIG X 2 days
    
    o **Severe GVHD score**: Initiated Ibrutinib
Post Transplant Complication

-Brain (biopsy proven) tissue w/ encephalitis, perivascular inflammation and microglial activation and gliosis

-Predominately CD3+ T-cells, mixture of CD4/CD8 cells
Long Term Follow-up

- Resolution of brain GVHD as evidenced by MRI. Tapered off levetiracetam.
- GVHD: PR. Now off ECP. Remains on low dose Tacrolimus daily, Sirolimus on alternating days, prednisone 10 mg. Reduced ibrutinib dose due to muscle cramping.
- He now follows up twice a year, attends baseball games with spouse.
CONCLUSION

• Understanding the problem at hand
  ▪ Obstacle to otherwise curative potential of HCT
  ▪ GVHD poses major risks: morbidity including disability, impaired QOL, and death

• Therapy for chronic GVHD
  ▪ Steroids remain first line therapy
  ▪ Ibrutinib is the first FDA approved therapy for GVHD

• CONTACT A FRIEND: asmita.mishra@moffitt.org
  marian.dam@moffitt.org
Acknowledgments

• The Patients
• Moffitt BMT-CI Department