An Introduction to Chronic Graft-versus-Host Disease

Madan Jagasia, MBBS; MS
Outline

• What is chronic GVHD?
• When does it occur?
• Which organs does it affect?
• How do we treat it?
• How successful is the treatment?
• How does it affect quality of life?
The Basics of Transplant

- Preparative Regimen
- The Stem cell graft
- GVHD Prophylaxis
- Graft-versus-tumor effect
The Failure and Success See-Saw

- Relapse
- GVHD
- Early mortality

- Overcoming GVHD
- GVT

FAILURE  SUCCESS
Graft-versus-Host Disease

• Immune phenomenon
  – Mediated by both T cells and B cells

• Acute GVHD
  – Skin
  – Gastrointestinal tract
  – Liver

• Chronic GVHD
Chronic GVHD

- Most serious and common long-term complication of allogeneic transplantation
- Occurs in
  - 30% (young, with sibling donors) to
  - 70% (older, unrelated donors)
- Median time to development is 4-6 months after transplant
- 50% have 3 or more involved organs/tissues
- On average therapy is required for 2-3 years
- 15% still require therapy 7+ years after diagnosis
NIH Consensus Criteria

• Definition of Chronic GVHD
  – Presence of diagnostic criteria
    • Skin 5 manifestations
    • Mouth 3 manifestations
    • Genitalia 2 manifestations
    • GI esophagus 2 manifestations
    • Lung 1 manifestation (requiring biopsy)
    • Muscles/fascia/joints 1 manifestation
  – Distinctive criteria plus biopsy
When Does It Occur?

Which Organs Does It Affect?

- Ocular
- Oral Ulcers
- Nail Dystrophy
- Sclerosis
- Bronchiolitis Obliterans
- Sclerodermaous Lesions
- Bile Duct Damage
- Skin Ulcers
- Fasciitis
How do we assess chronic GVHD?

- NIH grading and scoring
  - 8 organ domains
    - Skin
    - Mouth
    - Eyes
    - GI
    - Liver
    - Lungs
    - Joints/Fascia
    - Genitalia
  - Score 0-3 (none-worst)
How do we assess chronic GVHD?

<table>
<thead>
<tr>
<th>Score definition</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18% BSA with disease signs but NO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19%-50% BSA OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep sclerotic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involved with superficial sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>feature “not hidebound” (able to pinch)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50% BSA OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impaired mobility, ulceration or severe pruritus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erythema*

<table>
<thead>
<tr>
<th></th>
<th>154 (60%)</th>
<th>30 (12%)</th>
<th>30 (12%)</th>
<th>8 (3%)</th>
<th>17 (7%)</th>
<th>4 (2%)</th>
<th>14 (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moveable sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-moveable sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jacobsohn D et al, Blood 2012; 120 (13): 2545-2552
Lichenoid GVHD
Sclerosis with rippling
Severe sclerosis with blister formation
How do we assess chronic GVHD Severity?

• **Mild**
  – 1 or 2 organs (excluding lung) *and*
  – Maximum score of 1 in all affected organ or sites

• **Moderate**
  – 1 organ with score 2 *or*
  – 3 or more organs with score 1 *or*
  – Lung score 1

• **Severe**
  – 1 or more organs with score 3 *or*
  – Lung score 2 or higher
The Spectrum of Chronic GVHD

Frequency of Organ Involvement

- Skin: 75%
- Mouth: 51-63%
- Liver: 21-51%
- Eye: 22-33%
- GI: 23-45%
- Lung: 4-19%
- Esophagus: 7%
- Joints: 6%
Who is at Risk for Chronic GVHD?

- HLA mismatch or unrelated donor
- Age-recipient and donor
- Female donor to male recipient
- Parity of female donor
- Stem cell source
- Prior acute GVHD
Who is at Risk for Chronic GVHD?

How Do We Treat Chronic GVHD?

• Factors affecting treatment
  – Organ involvement
  – Severity
• Treatment Options
  – Topical therapy
  – Systemic therapy
cGVHD- Local Treatment

- Local Skin:
  - steroid creams
  - cyclosporine or tacrolimus creams and ointments

- Local Oral:
  - Dexamethasone rinses

- Local Eye:
  - Tear drops, cyclosporine eye drops
  - Punctal occlusions, contact lenses, scleral lenses
cGVHD- Systemic Treatment

• Immunosuppression
• Different from acute GVHD
• Calcineurin inhibitors (Cyclosporine, Tacrolimus)
• Steroids
• Photopheresis
• Organ specific therapy
How Successful is the Treatment?

• How do we define success?
  – Ideal: Complete resolution of all symptoms and signs
    • Often difficult in some organs (e.g. dry eye from ocular GVHD)
  – Improvement in signs and symptoms
    • Patient reported
    • Provider reported
  – ?Coming off all immunosuppressive agents without any worsening
Does Severity Matter?

Does Severity Matter?

<table>
<thead>
<tr>
<th>Score definition</th>
<th>0 (No symptoms)</th>
<th>1 (&lt; 18% BSA with disease signs but NO sclerotic feature)</th>
<th>2 (19%-50% BSA OR Involvement with superficial sclerotic feature “not hidebound” (able to pinch))</th>
<th>3 (&gt; 50% BSA OR Deep sclerotic features “hidebound” (unable to pinch) OR impaired mobility, ulceration or severe pruritus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-year overall survival</td>
<td>86%</td>
<td>83%</td>
<td>81%</td>
<td>69%</td>
</tr>
<tr>
<td>Two-year nonrelapse mortality</td>
<td>10%</td>
<td>13%</td>
<td>15%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Jacobsohn D et al *Blood* 2012; 120 (13): 2545-2552
Impact on Quality of Life

• GVHD consortium data
  – Physical and Mental attributes of QOL as affected increasingly with mild, moderate and severe chronic GVHD
  – Physical and Mental attributes were compared to other chronic disease
    • Physical – severe chronic GVHD was comparable to uncontrolled lupus, angina, myocardial infarction
    • Mental-severe chronic GVHD was comparable to major depression
Late Effects of Transplantation

• Late effects after transplantation is common
  – More common in patients with chronic GVHD

• Follow-up should ideally be coordinated by long-term clinic of the transplant center
  – Focus on primary care
  – Multidisciplinary approach
    - Dermatologist
    - Ophthalmologist
    - Endocrinologist
    - Renal
    - Pulmonary
    - Infectious disease
    - Symptom management
    - Psychiatrist
    - Social worker
    - Case manager

  – Screening for common medical problems associated with chronic GVHD and transplant
Late Effects of Transplantation

• Common medical problems
  – Lipids
  – Hypertension
  – Diabetes
  – Chronic kidney insufficiency
  – Thyroid
  – Other hormonal changes
  – Bone loss
  – Dry eye and cataracts

Savani B N. Blood 2011 Mar 17;117(11):3002-9
Late Effects of Transplantation

- Late infections
- Vaccinations
- Pulmonary complications
- Second malignancies

Savani B N. Blood 2011 Mar 17;117(11):3002-9
Some recommendations......

• Take ownership of your health
• Educate yourself
• Ask questions
• Follow directions…they are designed to safeguard your health and not inconvenience you
Some recommendations......

• Sun exposure
• Maintain primary care:
  – Mammograms
  – Pap smears
  – Colonoscopy
  – PSA if indicated
  – Vaccination
• Travel and vaccinations
Impact Beyond the Patient

- Caregiver in transplant
- Chronic GVHD
  - Family
  - Finances
  - Return to work
  - Return to normalcy
Summary

• Chronic GVHD remains a
  – Common problem
  – Affects multiple organs
  – Affects quality of life
• We are doing better at
  – Understanding of the spectrum
  – Assessment of severity
  – Response assessment in some organs
• We need to do better
  – In predicting chronic GVHD
  – Identifying new targets that can be affected by medicines
• Transplant centers need to
  – Provide or coordinate
    Complete and comprehensive care of the patient and family
Acknowledgements

• Chronic GVHD Consortium
• Long Term Transplant Clinic-VUMC
• Vanderbilt-Ingram Cancer Center

Patients, Caregivers and Friends/Family