Introduction to Chronic Graft-versus-Host Disease

Celebrating a Second Chance at Life Survivorship Symposium

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Dana-Farber Cancer Institute
Introduction to Chronic Graft-versus-Host Disease

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Chronic GVHD - Background

- >50% of ‘Related’ and ‘Unrelated’ donor recipients
  - Incidence increasing as early transplant-related outcomes improve
  - Exception: Cord transplant and Haplo transplant, where incidence is lower
- Very important cause of morbidity in the later post-transplant period
- Median 2-3 years of treatment
- Associated with quality of life and functional deficits
GVHD

- Caused by the interaction between the transplanted immune system (Graft) and recipient tissues (Host)
GVHD after Allogeneic Hematopoietic Cell Transplant (HCT)

- 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

- Activity Inflammation Injury Repair Damage Fibrosis
- Day 0 50 100 180 1 yr 2 yrs 3 yrs 5 yrs
GVHD Classification

Clinical sign(s) compatible with GvHD

Chronic GvHD
✓ Skin (lichenoid, sclerotic...)
✓ Mouth
✓ Nails and hair
✓ Eyes
✓ Lung
✓ Musculoskeletal
✓ Hematopoietic
✓ Gastro-intestinal (esophageal)
✓ Liver
✓ Other

Acute GvHD
✓ Skin
✓ Gastro-intestinal
✓ Liver

Subsequent episode
Recurrent
Persistent
New Onset or late acute

Any sign of Acute GvHD?
No
Classical Chronic GvHD
Yes
Overlap Syndrome

1st episode
Classical
GVHD Pathology: Acute and Chronic GVHD

MacDonald et al, Blood 2017;129:13-21
3 Biologic Phases of 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
    - $T_{REG}$, $B_{REG}$
    - IL-10 producing regulatory T-cells

**Phase 3: Aberrant Tissue Repair & Fibrosis**
- Innate & Adaptive
  - TGFβ
  - PDGFα
  - TNFα
  - IL-17
  - Macrophages
  - Fibroblasts

Chronic GVHD: Organ Involvement

### GVHD Signs and Symptoms

<table>
<thead>
<tr>
<th>Skin and related structures</th>
<th><strong>Skin</strong>: Hyper/hypopigmentation, lichenoid, sclerodermal, papulosquamous, ichthyosiform and psoriasiform changes; atrophy, poikiloderma, and ulcers</th>
<th>Pruritus, dryness, pain, infection, rigidity, decreased range of motion, photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nails</strong></td>
<td>Dystrophy, longitudinal ridging, onycholysis, pterygium, destruction</td>
<td>Nail and hair loss</td>
</tr>
<tr>
<td><strong>Scalp</strong></td>
<td>Scaling, fibrosis, scarring and non-scarring alopecia, papulosquamous changes</td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichenoid changes, erythema, ulcers, xerostomia, fibrosis, leukoplakia; dental caries</td>
<td>Pain, odynophagia, dysphagia, dysgeusia, dryness, sensitivity to food</td>
</tr>
<tr>
<td>Eyes</td>
<td>Keratoconjunctivitis sicca, corneal ulcerations</td>
<td>Pain, dryness photophobia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polymyositis, muscle weakness, myalgias, arthritis, arthralgias, fasciitis</td>
<td>Weakness, arthralgias, myalgias, decrease ROM</td>
</tr>
<tr>
<td>GI tract</td>
<td><strong>Upper</strong>: Abnormal motility, esophageal fibrosis, ulcerations, strictures</td>
<td>Odynophagia and lower dysphagia, pain, heartburn, nausea, anorexia, vomiting, abdominal pain, diarrhea/malabsorption, dehydration, weight loss</td>
</tr>
<tr>
<td></td>
<td><strong>Lower</strong>: Mucosal abnormalities/malabsorption, submucosal fibrosis</td>
<td></td>
</tr>
<tr>
<td>System</td>
<td>Signs</td>
<td>Symptoms</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Liver</td>
<td>Hyperbilirubinemia, elevated ALP, elevated ALT/AST, fibrosis</td>
<td>Fatigue, jaundice, pruritus</td>
</tr>
<tr>
<td>Lung</td>
<td>Obstructive (BO/BOOP) or restrictive (scleroderma of the chest) dysfunction; air trapping, bronchiectasis, pneumothorax, pneumomediastinum, subcutaneous emphysema; microbial colonization or pneumonia</td>
<td>Dyspnea, wheezing, productive or non productive cough</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neuropathy, myasthenic syndromes</td>
<td>Pain, burning, dysesthesias, paresthesias, muscle weakness</td>
</tr>
<tr>
<td>Vaginal mucosa</td>
<td>Erythema, lichenoid changes, dryness, ulcers, strictures/stenosis</td>
<td>Pain, burning, dryness, dyspareunia</td>
</tr>
<tr>
<td>Serosal</td>
<td>Serositis, pericardial, pleural and peritoneal effusions</td>
<td>Dyspnea, chest pain, pleuritic pain, abdominal pain, ascites</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Isolated or combined cytopenias, eosinophilia, hemolysis</td>
<td>Fatigue, fever, infection, bleeding</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Repeated infections of various etiologies, lymphopenia, hyper/hypogammaglobulinemia</td>
<td>Increased susceptibility to infection</td>
</tr>
</tbody>
</table>
Chronic GVHD: Skin Involvement
Chronic GVHD: Mouth Involvement
Chronic GVHD: Eye Involvement
### Chronic GVHD: Fascia Involvement

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Flexibility</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Shoulder</td>
<td></td>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>4</td>
<td>5</td>
<td>6</td>
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<td>7</td>
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<tr>
<td></td>
<td>Elbow</td>
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<td>4</td>
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<td>7</td>
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<tr>
<td></td>
<td>Wrist and fingers</td>
<td></td>
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<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>4</td>
<td>5</td>
<td>6</td>
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<td>7</td>
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<tr>
<td></td>
<td>Foot Dorsiflexion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>Findings</td>
<td>Scoring (see skin score worksheet)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Skin</td>
<td>Erythematous rash of any sort</td>
<td>% BSA (max 100%)</td>
</tr>
<tr>
<td></td>
<td>Moveable sclerosis</td>
<td>% BSA (max 100%)</td>
</tr>
<tr>
<td></td>
<td>Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis</td>
<td>% BSA (max 100%)</td>
</tr>
<tr>
<td></td>
<td>Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer</td>
<td>Location: ___________________</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Largest dimension: __________cm</td>
</tr>
<tr>
<td>Eyes</td>
<td>Bilateral Schirmer’s Tear Test (without anesthesia) in persons 9 years or older</td>
<td>mm of wetting</td>
</tr>
<tr>
<td></td>
<td>Right Eye:</td>
<td>mm of wetting</td>
</tr>
<tr>
<td></td>
<td>Left Eye:</td>
<td>mm of wetting</td>
</tr>
<tr>
<td>Mouth</td>
<td>Mucosal change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence of cGVHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild erythema or moderate erythema (&lt;25%)</td>
<td>Moderate (&gt;25%) or Severe erythema (&lt;25%)</td>
</tr>
<tr>
<td></td>
<td>Lichenoid</td>
<td>Hyperkeratotic changes (25-50%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Hyperkeratotic changes (&gt;50%)</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
<td>Ulcers involving (&lt;20%)</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0</td>
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<tr>
<td></td>
<td>1-5 mucocles</td>
<td>6-10 scattered mucocles</td>
</tr>
<tr>
<td></td>
<td>Mucoceles*</td>
<td>*Mucocles scored for lower labial and soft palate only</td>
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<tr>
<td></td>
<td></td>
<td>Total score for all mucosal changes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Counts</th>
<th>Platelet Count</th>
<th>ULN</th>
<th>K/uL</th>
<th>Total WBC</th>
<th>ULN</th>
<th>K/uL</th>
<th>% Eosinophils</th>
<th>%</th>
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<tbody>
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</table>

<table>
<thead>
<tr>
<th>Liver Function Tests</th>
<th>Total serum bilirubin</th>
<th>ULN</th>
<th>mg/dL</th>
<th>ALT</th>
<th>ULN</th>
<th>U/L</th>
<th>Alkaline Phosphatase</th>
<th>ULN</th>
<th>U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal-Upper GI</td>
<td>0 = no symptoms 1 = mild, occasional symptoms, with little reduction in oral intake during the past week 2 = moderate, intermittent symptoms, with some reduction in oral intake during the past week 3 = more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week</td>
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<tr>
<td>Gastrointestinal-Esophageal</td>
<td>0 = no esophageal symptoms 1 = occasional dysphagia or odynophagia with solid food or pills during the past week 2 = intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week 3 = Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week</td>
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<tr>
<td>Gastrointestinal-Lower GI</td>
<td>0 = no loose or liquid stools during the past week 1 = occasional loose or liquid stools, on some days during the past week 2 = intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion 3 = voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion</td>
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</tr>
<tr>
<td>Lungs</td>
<td>Pulmonary Function Tests with Diffusing Capacity (attach report for person &gt; 5 yrs old) FEV-1 % Predicted Single Breath DLCO (adjusted for hemoglobin) % Predicted</td>
<td></td>
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</tr>
<tr>
<td>Health Care Provider Global Ratings:</td>
<td>Where would you rate the severity of this patient's chronic GVHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible: 0 = none 1 = mild 2 = moderate 3 = severe Most severe cGVHD symptoms possible Over the past month would you say that this patient's cGVHD is: +3 = Very much better +2 = Moderately better +1 = A little better 0 = About the same -1 = A little worse -2 = Moderately worse -3 = Very much worse</td>
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</tr>
<tr>
<td>Functional Performance (in persons &gt;4 years old)</td>
<td>Total Distance Walked in 2 Minutes: Number of laps: _______ (x 50 feet) + final partial lap: _______ feet = _______ feet walked in 2 minutes Grip Strength (Dominant Hand) Trial #1 Trial #2 Trial #3 psi psi psi</td>
<td>Range of Motion: ○ Not performed ○ Physical Therapy Report Attached</td>
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</tr>
</tbody>
</table>
**cGVHD Assessment**

<table>
<thead>
<tr>
<th>PERFORMANCE</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ECOG LPS</td>
<td>Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)</td>
<td>Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)</td>
<td>Symptomatic, ambulatory, capable of self-care, &gt;50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)</td>
<td>Symptomatic, limited self-care, &gt;50% of waking hours in bed (ECOG 3-4, KPS or LPS &lt;60%)</td>
</tr>
</tbody>
</table>

**SKIN?**

<table>
<thead>
<tr>
<th>SCORE % BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD features to be scored by BSA:</td>
</tr>
<tr>
<td>☐ No BSA involved</td>
</tr>
</tbody>
</table>

**Check all that apply:**

- Maculopapular rash/erythema
- Lichen planus-like features
- Sclerotic features
- Papulosquamous lesions or ichthyosis
- Keratotic pilaris-like GVHD

**SKIN FEATURES SCORE:**

| ☐ No sclerotic features | ☐ Superficial sclerotic features “not hidebound” (able to pinch) |

**Check all that apply:**

- Deep sclerotic features
- “Hidebound” (unable to pinch)
- Impaired mobility
- Ulceration

**Other skin GVHD features (NOT scored by BSA)**

**Check all that apply:**

- Hyperpigmentation
- Hypopigmentation
- Poikiloderma
- Severe or generalized pruritus
- Hair involvement
- Nail involvement
- Abnormality present but explained entirely by non-GVHD documented cause (specify):

<table>
<thead>
<tr>
<th>MOUTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen planus-like features present:</td>
</tr>
<tr>
<td>☐ Yes</td>
</tr>
</tbody>
</table>

- No symptoms | Mild symptoms with disease signs but not limiting oral intake significantly |
- Moderate symptoms with disease signs with partial limitation of oral intake | Severe symptoms with disease signs on examination with major limitation of oral intake |

**Abnormality present but explained entirely by non-GVHD documented cause (specify):**
## cGVHD Assessment

<table>
<thead>
<tr>
<th>EYES</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No symptoms</td>
<td>Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)</td>
<td>Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops &gt;3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS</td>
<td>Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS</td>
</tr>
</tbody>
</table>

Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:
- Yes
- No
- Not examined

### Abnormality present but explained entirely by non-GVHD documented cause (specify):

<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></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>

**GI Tract Check all that apply:**
- Esophageal web/ proximal stricture or ring
- Dysphagia
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Weight loss ≥5%
- Failure to thrive

### Abnormality present but explained entirely by non-GVHD documented cause (specify):

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

**Liver**

### Abnormality present but explained entirely by non-GVHD documented cause (specify):

<table>
<thead>
<tr>
<th>LUNGS**</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No symptoms</td>
<td>Mild symptoms (shortness of breath after climbing one flight of steps)</td>
<td>Moderate symptoms (shortness of breath after walking on flat ground)</td>
<td>Severe symptoms (shortness of breath at rest; requiring 6L)</td>
</tr>
</tbody>
</table>

**Lung symptom score:**

<table>
<thead>
<tr>
<th>Lung score</th>
<th>% FEV1</th>
<th>% FEV1</th>
<th>% FEV1</th>
<th>% FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV1 ≥80%</td>
<td>FEV1 60-79%</td>
<td>FEV1 40-59%</td>
<td>FEV1 ≤39%</td>
</tr>
</tbody>
</table>

**Pulmonary function tests**

- Not performed

**Abnormality present but explained entirely by non-GVHD documented cause (specify):**
**cGVHD Assessment**

<table>
<thead>
<tr>
<th>Joints and Fascia</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-ROM score (see below)</td>
<td>No symptoms</td>
<td>Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL</td>
<td>Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL</td>
<td>Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)</td>
</tr>
<tr>
<td>Shoulder (1-7): ____</td>
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<tr>
<td>Elbow (1-7): ____</td>
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<tr>
<td>Wrist/finger (1-7): ____</td>
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<td>Ankle (1-4): ____</td>
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</tbody>
</table>

- Abnormality present but explained entirely by non-GVHD documented cause (specify):
- Abnormality present but explained entirely by non-GVHD documented cause (specify):

**Genital Tract** (See Supplemental figure)
- No signs
- Mild signs¹ and females with or without discomfort on exam
- Moderate signs² and may have symptoms with discomfort on exam
- Severe signs¹ with or without symptoms

**Other indicators, clinical features or complications related to chronic GVHD** (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none = 0, mild = 1, moderate = 2, severe = 3)
- Ascites (serositis)____
- Myasthenia Gravis____
- Pericardial Effusion____
- Peripheral Neuropathy____
- Eosinophilia > 500/µl____
- Pleural Effusion(s)____
- Polymyositis____
- Platelets <100,000/µl____
- Nephrotic syndrome____
- Weight loss>5% without GI symptoms____
- Others (specify):____

**Overall GVHD Severity** (Opinion of the evaluator)
- No GVHD ______
- Mild ______
- Moderate ______
- Severe ______

**Photographic Range of Motion (P-ROM)**

NIH Individual Organ Severity Score

- 0 – no clinical manifestations/symptoms
- 1 – clinical manifestations with no more than mild disability
- 2 – clinical manifestations with moderate disability
- 3 – clinical manifestations with severe disability

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of organs</th>
<th>Maximum Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>$\leq 2$</td>
<td>1 (0 for lung)</td>
</tr>
<tr>
<td>Moderate (a)</td>
<td>$\geq 3$</td>
<td>1 (0 for lung)</td>
</tr>
<tr>
<td>Moderate (b)</td>
<td>Any</td>
<td>2 (1 for lung)</td>
</tr>
<tr>
<td>Severe</td>
<td>Any</td>
<td>3 (2 for lung)</td>
</tr>
</tbody>
</table>
Treatment Strategy

▪ Local symptoms → Local Rx
  – Early identification is crucial
  – Two types of local therapies
    – Supportive
    – Locally immunosuppressive

▪ Systemic symptoms or multiple local sites → Systemic Rx
  – Prednisone 1 mg/kg/day + Tacrolimus or Cyclosporine
  – Complete response rate: 50%-55%
  – Median time to discontinue immune therapy: 1.6-2.2 years
  – Additional agents at onset of GVHD: Not shown to be beneficial
Indications for Secondary Treatment of Chronic GVHD

- Progression of symptoms
- No improvement after ~ 1 mo of treatment
- Inability to taper prednisone below 1 mg/kg/day within 4-8 weeks without worsening
- Toxicity

The chance that a patient starting initial therapy for chronic GVHD will never need additional therapy is only 21.3%

Lee, BBMT 2017
Second-Line Therapy for Chronic GHVD

- After failure of corticosteroids, no current consensus on optimal second-line treatment choice
- Many retrospective and prospective studies suggest high response rates with second-line treatment options
  - Results are hard to interpret because of suboptimal study designs
- Treatment choices are based on:
  - Physician experience
  - Ease of use
  - Need for monitoring
  - Risk of toxicity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>65-70</td>
</tr>
<tr>
<td>Rituximab</td>
<td>66-86</td>
</tr>
<tr>
<td>Imatinib</td>
<td>22-79</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>53-56</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>26-64</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>76</td>
</tr>
<tr>
<td>IL-2</td>
<td>52</td>
</tr>
</tbody>
</table>
Mechanistic Interventions for the Prevention or Treatment of Chronic GVHD

Stem cell graft engineering
- Antithymocyte globulin
- Posttransplant cyclophosphamide
- CD34 selection
- Ex vivo pan-T-cell depletion
- Ex vivo selective T-cell depletion
- Donor IL-2 therapy

Adoptive Treg Therapy
- Purified donor Treg
- Ex vivo expanded Treg
- Antigen-specific Treg

Inhibit T-cell signaling
- ITK inhibition: ibrutinib
- JAK1/2 inhibition: ruxolitinib
- ROCK2 inhibition: KD025
- Bortezomib

Treg-sparing therapy
- Sirolimus
- Mycophenolate mofetil
- Ruxolitinib
- Bortezomib

In vivo Treg expansion
- ECP
- Low-dose IL-2

Inhibit B-cell signaling
- BTK inhibition: ibrutinib
- SYK inhibition: fostamatinib

B-cell depletion in vivo
- Rituximab
- Ofatumumab
- Obinutuzumab

Allo-reactive T-cells

CD4+ FOXP3+ regulatory T-cells

Allo and auto-reactive B-cells

Other Health Issues Related to Chronic GVHD

- Long-term survivors of allogeneic BMT with chronic GvHD are 3 times as likely to have 2 or more chronic health conditions.

- Specific conditions associated with chronic GvHD include:
  - oral and ocular complications
  - pulmonary compromise
  - gastrointestinal complications
  - neurological problems

- Patients with chronic GvHD are 2.7-fold more likely to be frail.
Phase 1b/2 Study of Ibrutinib in cGVHD (NCT02195869)

Key eligibility criteria:
- Steroid dependent/refractory
- ≤3 prior treatments for cGVHD
- Other systemic immunosuppressants, if used, were continued
- >25% body surface area with “erythematous rash”, by NIH-defined criteria or
- >4 total mouth score, by NIH-defined criteria

Primary end point:
- cGVHD response per 2005 NIH response criteria

Secondary end points:
- Rate of sustained response
- Change in Lee cGVHD symptom scale
- Changes in steroid requirement over time
- Safety end points

Exploratory end points:
- Effect on lymphoid and myeloid signaling pathways and plasma cytokines and chemokines

Patients with cGVHD who have failed frontline steroids (N = 42)

Ibrutinib 420 mg\(^a\) orally continued until progression of cGVHD or unacceptable toxicity

\(^a\)Recommended phase 2 dose identified in phase 1 of the study
Ibrutinib Produced a High Rate of Response That Was Sustained

- 1/3 of responders had a CR
- 79% responded at the time of 1st response assessment
- 71% of the 28 responders had a sustained cGVHD response of at least 5 mo

*5 patients had no response assessment during the study but are included in the denominator.
Chronic GVHD Responses Were Observed Across Multiple Organs

- 80% (20/25) of patients with ≥2 involved organs at baseline responded in at least 2 organs
- 56% (5/9) of patients with ≥3 involved organs at baseline responded in at least 3 organs

Response by Organ

<table>
<thead>
<tr>
<th>Organ</th>
<th>Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>88%</td>
</tr>
<tr>
<td>Mouth</td>
<td>88%</td>
</tr>
<tr>
<td>Gl</td>
<td>91%</td>
</tr>
<tr>
<td>Liver</td>
<td>67%</td>
</tr>
</tbody>
</table>

(n = 24) (n = 24) (n = 11) (n = 3)
Ibrutinib Produced Clinically Meaningful Improvement in Lee Symptom Scale Score Among Responders

- Consistent with improvement in chronic GVHD symptoms, clinician-assessed and patient-reported reductions in overall chronic GVHD severity were also reported.

*5 patients had no Lee symptom scale assessment during the study.
Second-line Chronic GVHD Treatment Options: Ruxolitinib

- Europe and US, retrospective survey
- N= 41 steroid-refractory moderate to severe cGvHD
- Median follow-up 22.4 weeks
- ORR: 85.4% (35/41)
- 5.7% (2/35) cGVHD relapse rate

Key eligibility criteria
- ≥12 years old with moderate to severe steroid-refractory classical cGVHD
- Myeloid and platelet engraftment
- Only prior treatments, corticosteroids ± CNI for cGVHD
- If prior JAK inhibitor for aGVHD, CR or PR, and off for >8 weeks

REACH3
- Primary endpoint: ORR
- Secondary endpoints: Δ symptom scale score, DOR, OS, ↓ steroid use, QOL, toxicity

Ruxolitinib BID at protocol-defined starting dose

Best available treatment
Optional crossover after cycle 6

Interim Analysis of KD025-213: A Phase 2, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Chronic Graft Versus Host Disease (cGVHD) after at Least 2 Prior Lines of Systemic Therapy (The ROCKstar Study)

Corey Cutler, MD, MPH, Stephanie Lee, MD, MPH, Sally Arai, MD, Marcello Rotta, MD, Behyar Zoghi, MD, Aravind Ramakrishnan, MD, Aleksandr Lazaryan, MD, MPH, PhD, David A Eiznhamer, PhD, Olivier Schueller, PhD, Zhongming Yang, PhD, Laurie S. Green, MEd, Sanjay K. Aggarwal, MD, The ROCKstar Study Group, Bruce R. Blazar, MD, Steven Z. Pavletic, MD and Madan Jagasia, MD

1 Department of Hematologic Malignancies, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, 2 Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 3 Stanford University, Stanford, CA, 4 James Cancer Center, Ohio State University, Columbus, OH, 5 Texas Transplant Institute, Methodist Hospital, San Antonio, TX, 6 Blood and Marrow Transplant, Texas Transplant Institute at St. David's South Austin Medical Center, Austin, TX, 7 Blood and Marrow Transplantation and Cellular Immunotherapy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, 8 Kadmon Corporation, LLC, New York, NY, 9 The ROCKstar Study Group, New York, NY, 10 Division of Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN, 11 Experimental Transplantation and Immunology Branch, Center for Cancer Research (CCR), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, 12 Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN
KD025-213: Primary Endpoint Met at Interim Analysis

- Interim analysis occurred 2 months after last patient was enrolled
- KD025 achieved clinically meaningful and statistically significant ORRs in both arms
  - Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%
- Three patients achieved a complete response (CR)

64% (95% CI: 51%, 75%)\(^1\)  
67% (95% CI: 54%, 78%)\(^2\)

\( ^1 \text{p}<0.0001; \ ^2 \text{p}<0.0001 \)
GvHD Treatment-Induced Long-Term Effects

- Immune deficiency
- Cataracts
- Chronic kidney injury
- Steroid-induced diabetes
- Dyslipidemia
- Steroid myopathy
- Adrenal insufficiency
- Osteoporosis
- Neuropathy
- Poor wound healing
- Second malignancies/PTLD

Long-Term Morbidity Associated with Chronic Graft versus Host Disease

A Report from the Blood or Marrow Transplant Survivor Study (BMTSS)

## Frequency of Late Effects in Survivors with and without chronic GVHD

<table>
<thead>
<tr>
<th>Condition</th>
<th>No cGvHD (%)</th>
<th>cGvHD (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>52.4</td>
<td>63.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Oral</td>
<td>17</td>
<td>30.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11.9</td>
<td>23</td>
<td>0.0005</td>
</tr>
<tr>
<td>GI</td>
<td>7.6</td>
<td>12.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Neurology</td>
<td>23.1</td>
<td>33.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Frailty</td>
<td>6.1</td>
<td>17.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endocrine</td>
<td>42.6</td>
<td>48</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7.2</td>
<td>9.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Renal</td>
<td>1.8</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>26.7</td>
<td>26.3</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Conclusions

- Chronic GVHD
  - Common
  - Potentially serious unless caught early
  But......
  - Treatable
  - Lots of advances – drug approvals coming
  - Tons of research......Stay tuned!
Questions?

Celebrating a Second Chance at Life Survivorship Symposium

July 11-17, 2020

bmtinfonet.org ✦ help@bmtinfonet.org ✦ 847-433-3313