Chronic Graft-versus-Host Disease: Utilizing the NIH Consensus Guidelines

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Fred Hutchinson Cancer Research Center
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Disclosures: Astellas, research grant; All therapeutics are off-label

Outline

• Overview of chronic GVHD
• Chronic GVHD Consensus conference
• Organ-specific and global severity scoring
• Two clinical examples
• Treatment
• Information resources

Chronic GVHD

• Most common long-term complication of allogeneic hematopoietic cell infusion
  – Affects 30-70% of allogeneic recipients
  – Median onset 4-6 months
  – 90-95% of cases diagnosed within 1 year
  – Leading cause of non-relapse mortality
    • 25% of deaths in 2 year survivors
    • 11% of deaths in 5 year survivors

• Both inflammatory and fibrotic components
  – Symptoms vary
  – 50% have 3 or more involved organs

• Treatment is prolonged and may contribute to morbidity and mortality
  – Median duration of treatment is 2-3 years
  – 15% still require treatment after 7 years
  – Infections cause 60-85% of deaths

Health status

Fraser et al. Blood 2006;108:2867-2873

Impetus for the NIH Consensus Conference

• No change in first line therapy since 1980’s
• No standard second line therapy
• No FDA approved therapies
• Literature sparse, heterogeneous
• Difficult to interpret clinical trials
  – Diagnosis not standardized
  – Severity scale dichotomous
  – Response measures not defined
NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (June 6, 2005)

Chairs: Steve Pavletic & Georgia Vogelsang

- Diagnosis and scoring (Filipovich et al)
- Pathology (Shulman et al)
- Biomarkers (Schultz et al)
- Response criteria (Pavletic et al)
- Supportive care (Couriel et al)
- Clinical trials (Martin et al)

**Diagnosis and Scoring**

- Criteria for chronic GVHD diagnosis
  - 1 Diagnostic finding OR 1 Distinctive finding plus biopsy/test confirmation
- Categories of organ-specific severity (0-3)
  - Skin, Mouth, Eyes, Lung, GI tract, Liver, Joints and Fascia, Genital Tract
- Calculation of overall (global) severity
  - Mild, Moderate, Severe

*Filipovich et al, BBMT 2005; 11: 945*

**Diagnostic Manifestations**

- **SKIN**
  - Poikiloderma
  - Lichen-planus
  - Sclerosis
  - Morphea
  - Lichen sclerosis
- **MOUTH**
  - Lichen-planus
  - Hyperkeratotic plaques
  - Sclerosis
- **GI**
  - Esophageal web, stricture
- **Joints**
  - Fasciitis
  - Contractures
- **Genital**
  - Lichen planus
  - Stenosis

*Filipovich et al, BBMT 2005; 11: 945*

**Acute and Chronic GVHD**

- ACUTE
- CHRONIC

*Seattle 1980-2008 N=5050 100d DFS All allogeneic Tx Clinical ext chronic GVHD Storer, unpublished data*
NIH Skin Score

- No Symptoms
- <18% BSA with disease signs but no sclerotic features
- 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)
- >50% BSA OR deep sclerotic features "hidebound" (unable to pinch)

% BSA involved

+ % BSA and degree of sclerosis

NIH Lung Score

- No Symptoms
- Mild symptoms (shortness of breath after climbing one flight of steps)
- Moderate symptoms (shortness of breath after walking on flat ground)
- Severe symptoms (shortness of breath at rest; requiring O2)

- FEV1 > 80%
- FEV1 69-79% OR LFS 3-5
- FEV1 40-59% OR LFS 6-9
- FEV1 <39% OR LFS 10-12

LFS = FEV1 score + DLCO score

- 80% = 1
- 70-79% = 2
- 60-69% = 3
- 50-59% = 4
- 40-49% = 5
- < 40% = 6

+ Symptoms and PFTs

NIH Mouth Score

- No Symptoms
- Mild symptoms (requiring eyedrops <3 x per day or punctual plugs) WITHOUT vision impairment
- Moderate symptoms (requiring drops >3 x per day or punctual plugs) WITHOUT vision impairment
- Severe symptoms (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca

+ Symptoms and interventions

NIH Eye Score

- No Symptoms
- Mild dry eye symptoms (requiring eyedrops <3 x per day OR asymptomatic signs of keratoconjunctivitis sicca)
- Moderate dry eye symptoms partially affecting ADL
- Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca

+ Symptoms and interventions

Other organs

- Liver
  - Total bilirubin, alkaline phosphatase, ALT/AST
- Gastrointestinal
  - Dysphagia, anorexia, nausea, vomiting, diarrhea, abdominal pain, weight loss
- Joint and fascia
  - Tightness, contractures, range of motion, ADLs
- Genital
  - Physical findings, pain
**Example 1**
- Diane, a 36 y/o woman
  - Maculopapular rash on her face and upper chest
  - Food sensitivity, lichen-planus-like oral changes
  - Dry eyes, using eyedrops twice a day

**NIH Skin Score**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular rash</td>
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<td>&gt;50% BSA OR deep sclerotic features &quot;hidebound&quot; (unable to pinch) OR impaired mobility, ulceration or severe pruritus</td>
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</table>

% BSA involved: 10%

- % BSA and degree of sclerosis

**NIH Eye Score**

<table>
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<tr>
<th>0</th>
<th>1</th>
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<tr>
<td>No Symptoms</td>
<td>Mild dry eye symptoms not affecting ADL (requiring eyedrops &lt; 3 x per day) OR asymptomatic signs of keratoconjunctivitis sicca</td>
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<td>Severe dry eye symptoms significantly affecting ADL. (special eyeware to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by keratoconjunctivitis sicca</td>
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Dry eyes, using eyedrops twice a day

- Symptoms and interventions

**Example 2**
- Mark, a 49 y/o man
  - Sclerosis involving his arms
  - Oral ulcers, unable to eat spicy foods
  - No other organs involved

**NIH Skin Score**

<table>
<thead>
<tr>
<th>Clinical features</th>
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% BSA involved: 18%

- % BSA and degree of sclerosis

**NIH Mouth Score**

| No Symptoms | Mild symptoms with disease signs but NO sclerotic features | Moderate symptoms with disease signs with partial limitation of oral intake | Severe symptoms with disease signs on examination with major limitation of oral intake |

Food sensitivity, lichen-planus-like oral changes

- Symptoms and limitation of oral intake

**NIH Skin Score**

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Sclerosis involving his arms (BSA 18%)

- % BSA and degree of sclerosis
**NIH Mouth Score**

<table>
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<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Mild symptoms with disease signs but not limiting oral intake significantly</td>
</tr>
<tr>
<td>2</td>
<td>Moderate symptoms with disease signs with partial limitation of oral intake</td>
</tr>
<tr>
<td>3</td>
<td>Severe symptoms with disease signs on examination with major limitation of oral intake</td>
</tr>
</tbody>
</table>

- Oral ulcers, unable to eat spicy foods

**Symptoms and limitation of oral intake**

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**NIH Eye Score**

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**Symptoms and interventions**

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**Examples**

- **Diane:**
  - Skin 1
  - Mouth 1
  - Eyes 1

- **Mark:**
  - Skin 3
  - Mouth 2
  - Eyes 0

**Chronic GVHD Consortium**

Clinical sites: Fred Hutchinson Cancer Research Center, Stanford University, University of Minnesota, Dana-Farber Cancer Institute, Vanderbilt University, Medical College of Wisconsin, H. Lee Moffitt, Washington University, Memorial Sloan Kettering

Additional laboratory site: University of North Carolina

Funded by: NCI CA118953, ORD/NCI CA163438

ClinicalTrials#: NCT00637689, Patient Advocacy Organizations:

- National Marrow Donor Program
- nbmtLINK
- BMT InfoNet

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Filipovich et al, BBMT 2005; 11: 945
Organ Involvement (n=298)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>85</td>
<td></td>
<td></td>
<td>109</td>
</tr>
<tr>
<td>Lung</td>
<td>62</td>
<td></td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td></td>
<td></td>
<td>80</td>
</tr>
</tbody>
</table>

10% score 1 in >3 organs
85% skin, 3 or lung
28% either criterion

Arai et al, Blood 2011

Overlap has a worse prognosis

Non-relapse mortality and Survival

Median FU of survivors = 18.5 mos

Not significant: donor type, recipient age, disease stage

Arai et al, Blood 2011

Response Criteria

- **Response criteria**
  - Clinician-reported scales (10-20 min)
  - Patient-reported outcomes (15-20 min)
  - Definitions for complete response, partial response, stable, progressive

- **Additional measures for use in clinical trials**
  - Functional testing – walk test, grip strength, Schirmer’s (15 min)

Pavlatic et al, BBMT 2006; 12: 252

Non-relapse mortality and Survival

Median FU of survivors = 18.5 mos

**NIH Skin response measure**

<table>
<thead>
<tr>
<th>Skin</th>
<th>Percent Rule of 9a</th>
<th>Index % of body part affected</th>
<th>erythematous</th>
<th>induration</th>
<th>papular lesions</th>
<th>Non-recorded skin injuries or fascia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Head/neck, lip</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>2.</td>
<td>Anterior trunks</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>3.</td>
<td>Pectoral fascia</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>4.</td>
<td>L. upper extremity</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>5.</td>
<td>R. upper extremity</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>6.</td>
<td>L. lower extremity</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>7.</td>
<td>R. lower extremity</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>8.</td>
<td>Genitalia</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

NRM OS

Mark (severe) 32% 62%
Diane (moderate) 9% 86%
Someone else (mild) 3% 97%
**NIH Mouth response measure**

<table>
<thead>
<tr>
<th>Oral Cavity</th>
<th>None</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>None</td>
<td>Minimal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Ulcers</td>
<td>None</td>
<td>Minimal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>None</td>
<td>0-1 Macroglossia</td>
<td>2-4 Macroglossia</td>
<td>5+ Macroglossia</td>
<td></td>
</tr>
</tbody>
</table>

**Initial Therapy**

- Steroids at 1 mg/kg/day
  - Data do not support the need for a calcineurin inhibitor (Koc Blood 2002; 100:49)
  - About 30% of people respond and never need additional treatment (Flowers Blood 2002; 100: 415)
  - No evidence that initial therapy should be modified based on anticipated response or risk of recurrent malignancy
  - Consider a clinical trial: Clinical Trials Network Protocol 0801

**Summary**

- Chronic GVHD diagnosis requires at least one diagnostic manifestation OR one distinctive finding plus biopsy/test confirmation
- Scoring criteria (0-3) are available to record chronic GVHD severity in 8 organ systems
- Overall mild, moderate and severe categories
  - Are calculated from severity scoring
  - Predict non-relapse mortality and survival
  - The terms “limited” and “extensive” are no longer used

**BMT-Clinical Trials Network 0801**

(PIs: Paul Carpenter / Mukta Arora)

- Phase II/III design (N=400)
  - any chronic GVHD within 4 months of diagnosis
  - prednisone + sirolimus +/- CNI

<table>
<thead>
<tr>
<th>Prednisone + Sirolimus</th>
<th>Prednisone + CNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II: CR/PR after 6 mos</td>
<td></td>
</tr>
<tr>
<td>Phase III: Complete resolution of all GVHD after 2 yrs</td>
<td></td>
</tr>
</tbody>
</table>

Measuring therapeutic response in chronic GVHD Trials: An instructional manual
http://www.asbmt.org/GVHDForms.htm

Recommended post-transplant care
http://www.marrow.org/md-guidelines
How to Conduct a Comprehensive Chronic GVHD Assessment
www.fhcrc.org/science/clinical/gvhd/

How I conduct a comprehensive chronic graft-versus-host disease assessment
Carpenter PA.

Ancillary and Supportive Care

Ancillary Therapy and Supportive Care of Chronic Graft-versus-Host Disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: Y. Ancillary Therapy and Supportive Care Working Group Report

http://www.asbmt.org
>>> Guidelines, Policy Statements, and Reviews
>>>>Data collection forms and information for measuring disease response
>>>>>Dispensary guidelines

Thank You

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Consortium Investigators
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Sally Arak
Dan Waldorf
Makia Acora
Cory Cutler
Malan Jagasia
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Jeanne Palmer
Joseph Polato
Iskra Pusic
Kirsten Williams
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Stefanie Sarantopolous

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