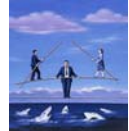


Chronic Graft-versus-Host Disease: Utilizing the NIH Consensus Guidelines

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February 3, 2012

Disclosures: Astellas, research grant; All therapeutics are off-label

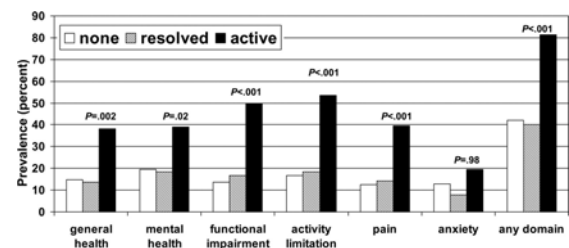
- Both inflammatory and fibrotic components
 - Symptoms vary
 - 50% have 3 or more involved organs
- Treatment is prolonged and may contribute to morbidity and mortality
 - Median duration of treatment is 2-3 years
 - 15% still require treatment after 7 years
 - Infections cause 60-85% of deaths



Outline

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

Health status



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

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

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

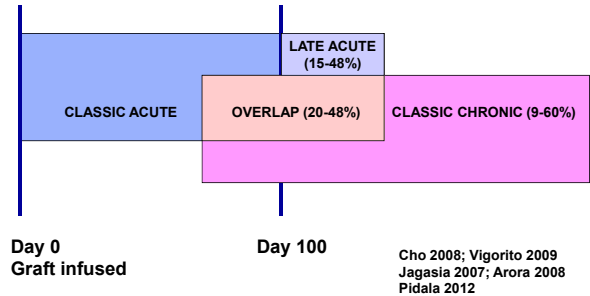
NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD (June 6, 2005)

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)

BBMT
2005; 11: 945
2006; 12: 31
12: 126
12: 252
12: 375
12: 491

2005 NIH Revision



Diagnosis and Scoring

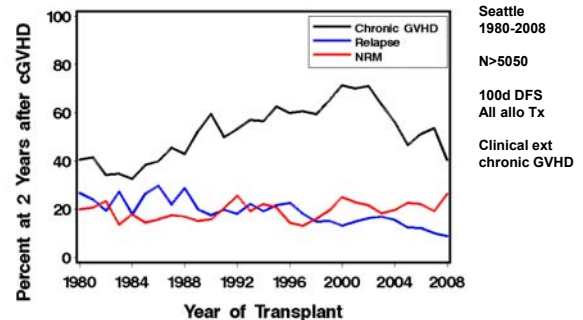
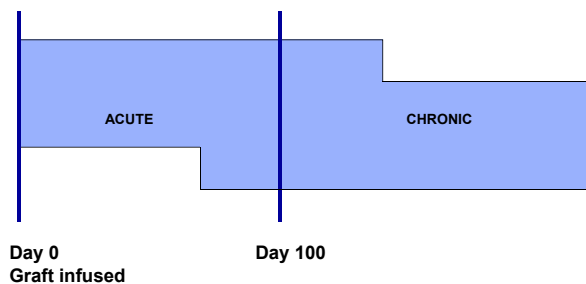
- Criteria for chronic GVHD diagnosis
 - 1 Diagnostic finding OR 1 Distinctive finding plus biopsy/test confirmation
- Categories of organ-specific severity (0-3)
 - Skin, Mouth, Eyes, Lung, GI tract, Liver, Joints and Fascia, Genital Tract
- Calculation of overall (global) severity
 - Mild, Moderate,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

Filipovich et al, BBMT 2005; 11: 945

Diagnostic Manifestations

- | | |
|---|---|
| <p><u>SKIN</u></p> <ul style="list-style-type: none"> • Poikiloderma • Lichen-planus • Sclerosis • Morphea • Lichen sclerosis <p><u>MOUTH</u></p> <ul style="list-style-type: none"> • Lichen-planus • Hyperkeratotic plaques • Sclerosis <p><u>Lung</u></p> <ul style="list-style-type: none"> • Bronchiolitis obliterans on bx | <p><u>GI</u></p> <ul style="list-style-type: none"> • Esophageal web, stricture <p><u>Joints</u></p> <ul style="list-style-type: none"> • Fasciitis • Contractures <p><u>Genital</u></p> <ul style="list-style-type: none"> • Lichen planus • Stenosis |
|---|---|

Acute and Chronic GVHD



NIH Skin Score

	0	1	2	3
Clinical features	<input type="checkbox"/> No Symptoms	<input type="checkbox"/> $\leq 18\%$ BSA with disease signs but NO sclerotic features	<input type="checkbox"/> 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	<input type="checkbox"/> $> 50\%$ BSA OR deep sclerotic features " hidebound " (unable to pinch) OR impaired <u>mobility</u> , <u>ulceration</u> or severe <u>pruritus</u>
% BSA involved				

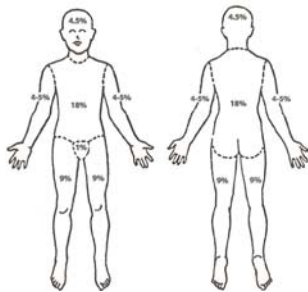
♦ % BSA and degree of sclerosis

- Clinical features**
- Maculopapular rash
 - Lichen planus-like
 - Papulosquamous
 - Ichthyosis
 - Hyperpigmentation
 - Hypopigmentation
 - Keratosis pilaris
 - Erythema
 - Erythroderma
 - Poikiloderma
 - Sclerotic features
 - Pruritus
 - Hair involvement
 - Nail involvement

NIH Lung Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input type="checkbox"/> Mild symptoms (shortness of breath after climbing one flight of steps)	<input type="checkbox"/> Moderate symptoms (shortness of breath after walking on flat ground)	<input type="checkbox"/> Severe symptoms (shortness of breath at rest; requiring O ₂)
<input type="checkbox"/> FEV1 $\geq 80\%$ OR LFS=2	<input type="checkbox"/> FEV1 60-79% OR LFS 3-5	<input type="checkbox"/> FEV1 40-59% OR LFS 6-9	<input type="checkbox"/> FEV1 $\leq 39\%$ OR LFS 10-12
LFS = FEV1 score + DLCO score			
		$\geq 80\%$ = 1 70-79% = 2 60-59% = 3 50-49% = 4 40-49% = 5 $\leq 40\%$ = 6	♦ Symptoms and PFTs

Body Surface Area – Rule of 9s



NIH Eye Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) OR asymptomatic signs of kerato-conjunctivitis sicca	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs) WITHOUT vision impairment	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by kerato-conjunctivitis sicca
♦ Symptoms and interventions			

NIH Mouth Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input type="checkbox"/> Mild symptoms with disease signs but not limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs with <u>partial</u> limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with <u>major</u> limitation of oral intake
♦ Symptoms and limitation of oral intake			

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 Eye Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input checked="" type="checkbox"/> Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) OR asymptomatic signs of kerato-conjunctivitis sicca	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs) WITHOUT vision impairment	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by kerato-conjunctivitis sicca
Dry eyes, using eyedrops twice a day			
♦ Symptoms and interventions			

NIH Skin Score

	0	1	2	3
Clinical features	<input type="checkbox"/> No Symptoms	<input checked="" type="checkbox"/> $\leq 18\%$ BSA with disease signs but NO sclerotic features	<input type="checkbox"/> 19-50% BSA with superficial sclerotic features "not hidebound" (able to pinch)	<input type="checkbox"/> $> 50\%$ BSA OR deep sclerotic features " <u>hidebound</u> " (unable to pinch) OR impaired <u>mobility</u> , <u>ulceration</u> or severe <u>pruritus</u>
% BSA involved		Maculopapular rash on her face and upper chest (10%)		
		♦ % BSA and degree of sclerosis		

Example 2

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

NIH Mouth Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input checked="" type="checkbox"/> Mild symptoms with disease signs but <u>not</u> limiting oral intake significantly	<input type="checkbox"/> Moderate symptoms with disease signs with <u>partial</u> limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with <u>major</u> limitation of oral intake
Food sensitivity, lichen-planus-like oral changes			
♦ Symptoms and limitation of oral intake			

NIH Skin Score

	0	1	2	3
Clinical features	<input type="checkbox"/> No Symptoms	<input type="checkbox"/> $\leq 18\%$ BSA with disease signs but NO sclerotic features	<input type="checkbox"/> 19-50% BSA OR involvement with superficial sclerotic features "not hidebound" (able to pinch)	<input checked="" type="checkbox"/> $> 50\%$ BSA OR deep sclerotic features " <u>hidebound</u> " (unable to pinch) OR impaired <u>mobility</u> , <u>ulceration</u> or severe <u>pruritus</u>
% BSA involved			Sclerosis involving his arms (BSA 18%)	
		♦ % BSA and degree of sclerosis		

NIH Mouth Score

0	1	2	3
<input type="checkbox"/> No Symptoms	<input type="checkbox"/> Mild symptoms with disease signs but <u>not</u> limiting oral intake significantly	<input checked="" type="checkbox"/> Moderate symptoms with disease signs with <u>partial</u> limitation of oral intake	<input type="checkbox"/> Severe symptoms with disease signs on examination with <u>major</u> limitation of oral intake
Oral ulcers, unable to eat spicy foods			
♦ Symptoms and limitation of oral intake			

Examples

- Diane:
 - Skin 1
 - Mouth 1
 - Eyes 1
- Mark:
 - Skin 3
 - Mouth 2
 - Eyes 0

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

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

NIH Eye Score

0	1	2	3
<input checked="" type="checkbox"/> No Symptoms	<input type="checkbox"/> Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) OR asymptomatic signs of kerato-conjunctivitis sicca	<input type="checkbox"/> Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs) WITHOUT vision impairment	<input type="checkbox"/> Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision caused by kerato-conjunctivitis sicca
♦ Symptoms and interventions			

Examples

- Diane: overall 2 (moderate)
 - Skin 1
 - Mouth 1
 - Eyes 1
- Mark: overall 3 (severe)
 - Skin 3
 - Mouth 2
 - Eyes 0

Mild	<ul style="list-style-type: none"> • 1 or 2 organs or sites (except lung) with score 1 <ul style="list-style-type: none"> • $< 18\%$ BSA, no sclerotic features • Mild oral symptoms, no decrease in oral intake • Mild dry eyes, eyedrops < 3x/day
Moderate	<ul style="list-style-type: none"> • 3 or more organs with score 1 • At least 1 organ or site with score 2 <ul style="list-style-type: none"> • $19-50\%$ BSA or superficial sclerosis • Moderate oral symptoms, partial decrease in intake • Lung score 1 (FEV1 $< 80\%$ or SOB with stairs)
Severe	<ul style="list-style-type: none"> • At least 1 organ or site with score 3 <ul style="list-style-type: none"> • $> 50\%$ BSA or deep sclerosis • Severe oral symptoms with major limitation in oral intake • Severe dry eyes affecting ADL • Lung score 2 (FEV1 $< 60\%$ or SOB on flat ground)

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

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



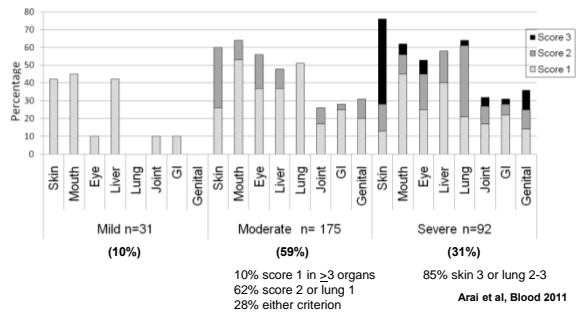
Additional laboratory site:
 University of North Carolina

Funded by: NCI CA118953
 ORD/NCI CA163438

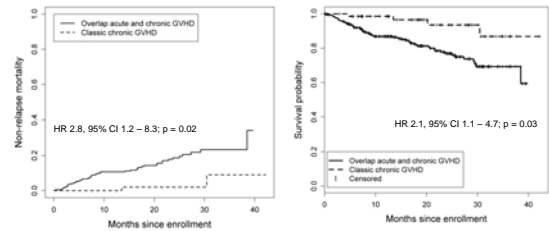
ClinicalTrials#: NCT00637689

Patient Advocacy Organizations:
 National Marrow Donor Program
 nbmLINK
 BMT InfoNet

Organ Involvement (n=298)



Overlap has a worse prognosis

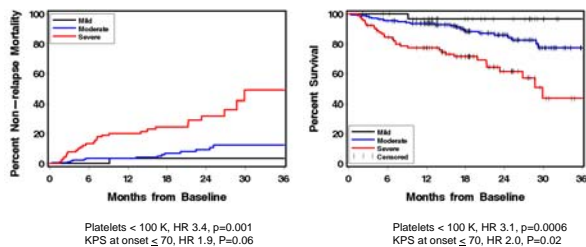


Overlap has worse functional status (2 min walk test, HAP) and higher symptom burden (skin, nutrition)

Pidalá et al, Haematologica

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

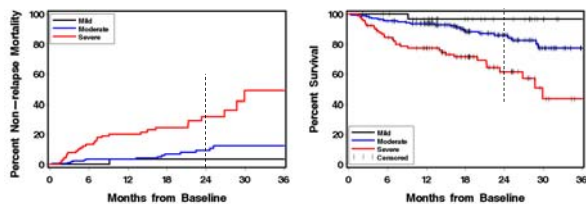
Response Criteria

- 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)

Pavletic et al, BBMT 2006; 12: 252

Non-relapse mortality and Survival

Median FU of survivors = 18.5 mos



	NRM	OS
Mark (severe)	32%	62%
Diane (moderate)	9%	86%
Someone else (mild)	3%	97%

NIH Skin response measure

SKIN				
Do not use Rule of 9s Indicate % of body part affected	Check ONE area of the body as the sentinel lesion	Erythematous rash of any sort	Moveable sclerosis	Non-moveable subcutaneous sclerosis or fasciitis
1. Head/neck/scalp	<input type="checkbox"/>	%	%	%
2. Anterior torso	<input type="checkbox"/>	%	%	%
3. Posterior torso	<input type="checkbox"/>	%	%	%
4. L. upper extremity	<input type="checkbox"/>	%	%	%
5. R. upper extremity	<input type="checkbox"/>	%	%	%
6. L. lower extremity, (incl. L buttock)	<input type="checkbox"/>	%	%	%
7. R. lower extremity, (incl. R buttock)	<input type="checkbox"/>	%	%	%
8. Genitalia	<input type="checkbox"/> not examined	<input type="checkbox"/>	%	%

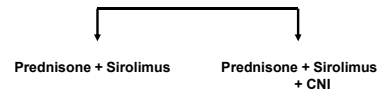
NIH Mouth response measure

Mouth	Erythema	<input type="checkbox"/> None	<input type="checkbox"/> Mild erythema OR Moderate erythema (<25%)	<input type="checkbox"/> Moderate (≥25%) OR Severe erythema (<25%)	<input type="checkbox"/> Severe erythema (≥25%)
	Lichenoid	<input type="checkbox"/> None	<input type="checkbox"/> Hyperkeratotic changes (<25%)	<input type="checkbox"/> Hyperkeratotic changes (25-50%)	<input type="checkbox"/> Hyperkeratotic changes (>50%)
	Ulcers	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> Ulcers involving (≤20%)	<input type="checkbox"/> Severe ulcerations (>20%)
	Mucocoeles (of lower labia and soft palate only)	<input type="checkbox"/> None	<input type="checkbox"/> 1-5 mucocoeles	<input type="checkbox"/> 6-10 scattered mucocoeles	<input type="checkbox"/> Over 10 mucocoeles

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



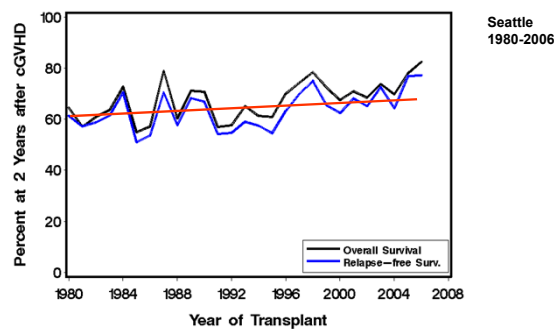
Phase II: CR/PR after 6 mos
Phase III: Complete resolution of all GVHD after 2 yrs

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

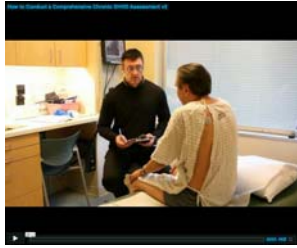
- Chronic GVHD diagnosis requires at least one diagnostic manifestation OR one distinctive finding plus biopsy/test confirmation
- Scoring criteria (0-3) are available to record chronic GVHD severity in 8 organ systems
- Overall mild, moderate and severe categories
 - Are calculated from severity scoring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



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



Recommended post-transplant care
<http://www.marlow.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.
 Blood. 2011; 118:2679-87.

Ancillary and Supportive Care

Biology of Blood and Marrow Transplantation 12 (2006) 375-376 (2006)
 © 2006 American Society for Blood and Marrow Transplantation
 1503-1634/06/1206-375\$12.00
 doi:10.1016/j.bbmt.2006.05.008



BBMT 2006; 12:375

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: V. Ancillary Therapy and Supportive Care Working Group Report

David Cutler,¹ Paul A. Carpenter,² Corey Cutler,³ Javier Blasco-Mendez,⁴ Nathaniel S. Pinner,⁵ Juan Luis Hernandez,⁶ Paul Dillingham,⁷ Steven J. Lee,⁸ David Akin,⁹ Alan C. Brubaker,¹⁰ James W. Clancy,¹¹ Peter Neumann,¹² Sandeep Mohil,¹³ Karen Sordahl,¹⁴ Corinne K. Meunier,¹⁵ Jack Altman,¹⁶ Jyoti Lakshminarayanan,¹⁷ Ann Sargent,¹⁸ John Gentry,¹⁹ Karen Schaefer,²⁰ Alexandra M. Filipowicz,²¹ Daniel W. Blazer,²² Karl M. Uhlir,²³ Howard Shapiro,²⁴ Kara Schaefer,²⁵ Barbara Brumback,²⁶ James Harkin,²⁷ George H. Vogelsang,²⁸ Paul J. Martin,²⁹ Stephen J. Lee,³⁰ Mary E. D. Hickey³¹

<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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