



NIH Chronic Graft versus Host Disease Research

Kristin Baird, MD
AOES Seminar October 24, 2011

Kristin Baird, MD

Disclosures

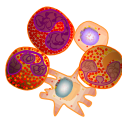
No Relevant Financial Relationships with Commercial Interest

List of Non-FDA Approved uses
All treatments discussed for cGVHD

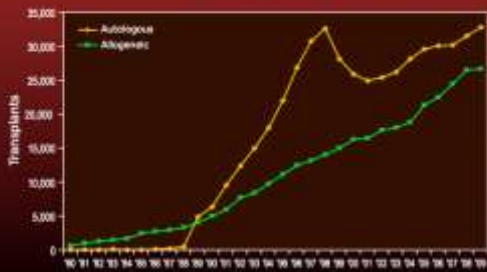
Objective:
Review cGVHD etiology and manifestations and discuss unique approaches to studying and treating a rare disease at the NIH.

Introduction

- Transplant as a treatment option
- Brief review of acute GVHD
- Chronic GVHD
 - Risk Factors, incidence, manifestations
 - Prevention
 - Standard Treatment
- cGVHD Research at NIH
- Limitations in cGVHD Research
- Future directions

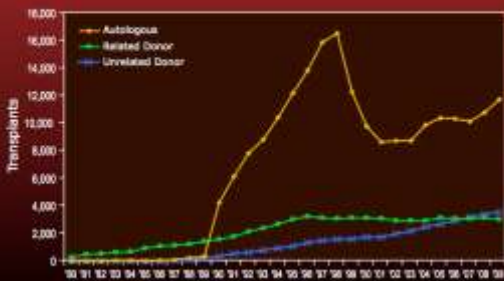


Transplant activity worldwide 1980-2009



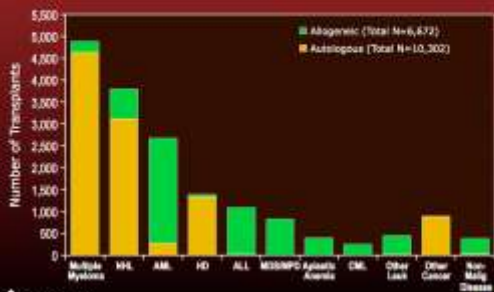
Slide 3

Transplant activity in the U.S. 1980-2009



Slide 4

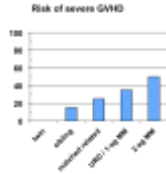
Indications for hematopoietic stem cell transplant in North America 2008



Slide 5

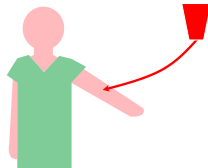
Choosing a donor

- Autologous = Patient's stored cells
 - No GVHD
- Syngeneic = Identical twin
 - No (significant) GVHD
- Allogeneic = Another person
 - Related HLA identical match (Genotypic match)
 - Unrelated HLA match (Phenotypic match)
 - Haploidentical +/- phenotypic matching (parent)
 - Mild to severe GVHD

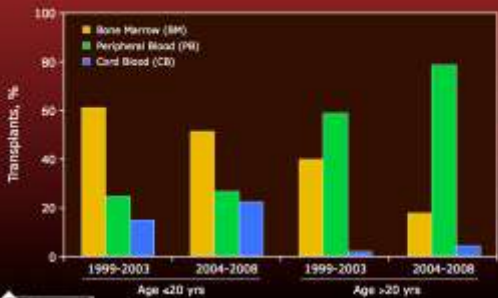


Stem cell sources

- Bone Marrow
- Peripheral Blood Stem Cells
 - Highest rates of GVHD
 - BUT, they engraft better than cord blood
- Cord Blood
 - More common in children
 - Lowest rates of GVHD

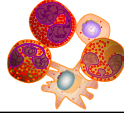


Allogeneic stem cell sources, by recipient age 1999-2008

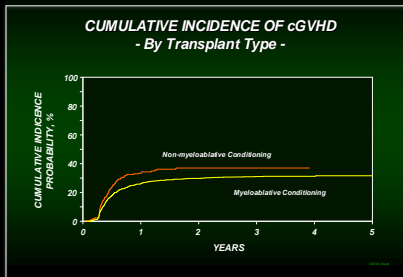


Preparation or conditioning for transplant

- Destroy malignant cells
- “Turn off” the immune system to promote engraftment
- Provide milieu for normal cells to grow
- Conditioning regimen depends on patient
 - Myeloablative
 - Non-myeloablative or RIST



Myeloablative versus Non-myeloablative



CIBMTR

Transplant as a treatment option

Relapse Free Survival Leukemia Patients

- a) Patients with good risk cGVHD – low relapse rates (8-9%) with higher survival (approximately 80% relapse free survival), best outcome.**
- b) Patients with intermediate risk cGVHD lower relapse, high mortality.**
- c) Patients with worst risk group cGVHD lowest relapse, but highest mortality (<20% survival).**
- d) Patients with no cGVHD –highest relapse rates (>30%).**

Lee et al. BLOOD 100:406-414, 2002

Prevention of GVHD

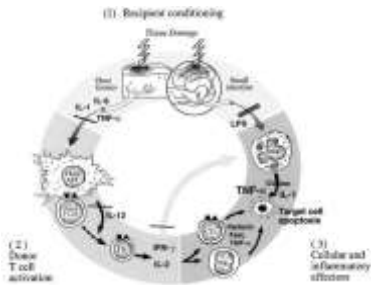
- Medications given to prevent GVHD
 - Prednisone
 - Cyclosporine
 - Cytoxan
 - Antithymocyte Globulin (ATG)
 - Methotrexate
 - Tacrolimus (FK506)
 - Mycophenolate mofetil (MMF)



Categories of Acute and Chronic GVHD

- **Classic Acute**
≤ 100 days Acute features
- **Persistent , Recurrent or Late Acute**
>100 days Acute features
- **Acute/Chronic Overlap**
No time limit Acute and chronic features
- **Chronic**
No time limit Chronic features

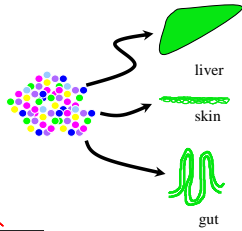
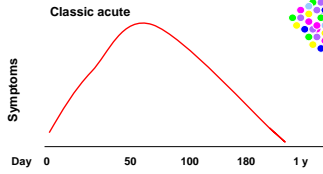
Acute GVHD Immunopathology



Blood 2000;95:2754–2759.

Development of GVHD after transplant

Acute GVHD: Skin, GI tract, liver



Development of GVHD after transplant

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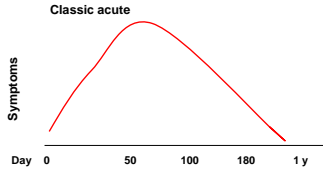
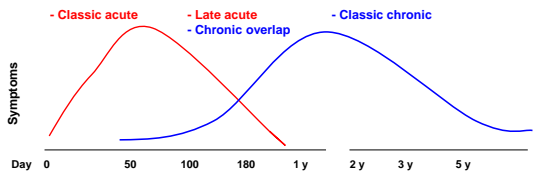


Figure 1. Acute GVHD of the skin. (a) Acute GVHD of the skin. (b) Acute GVHD of the gut. Lancet 2000; 373: 1550-61

Development of GVHD after transplant

Acute GVHD: Skin, GI tract, liver

Chronic GVHD: skin, eyes, mouth, GI liver, musculoskeletal, lungs, GU



Acute GVHD

- Grade II-IV aGVHD occur in 30-50% matched related donor recipients and up to 70% of unrelated donor recipients
- Prevention
 - High resolution typing
 - Preparative regimen, graft manipulation, chemoprevention/immunosuppression
 - MTX, CSA, ATG, prednisone, Cya

Acute GVHD

Stage	Skin	Liver	Gut
I	Maculopapular rash <25% BSA	Bili 2-3.5mg/dl	Diarrhea < 1,000 ml/d (10-15ml/kg)
II	Maculopapular rash <25 - 50% BSA	Bili 3.5-8mg/dl	Diarrhea 1,000-1,500 ml/d (15-20ml/kg)
III	Generalized erythroderma	Bili 8-15 mg/dl	Diarrhea >1,500 ml/d (20-25ml/kg)
IV	Desquamation and bullae	Bili > 15 mg/dl	2,500 ml/d or ileus (>25ml/kg)

Acute GVHD

Grade	Skin Stage	Liver Stage	Gut Stage
1	1-2	0	0
2	1-3	1	1
2o	0	1	1
2s	4	0	0
3	2-4	2-4 &/or	2-4
4	3-4	2-4	2-4

Acute GVHD

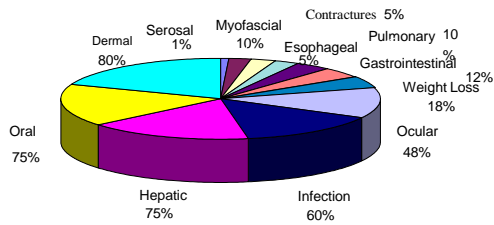
- Standard frontline therapy - steroids (prednisolone equivalent 2mg/kg/d)
 - 50% overall response rate.
 - RR 63-95% grade II, 17-39% grade III, and 0-6% for grade IV
- 100 day survival
 - 78-90% grade I, 66-92% grade II, 29-62% grade III and 23-25% for grade IV

Chronic Graft-Versus Host Disease (cGVHD)

- A multi-system chronic alloimmune and autoimmune disorder which develops within three years after allo-HSCT
 - Features resemble autoimmune diseases and immunodeficiency, immune dysregulation
 - Can result in significant morbidity decreased organ function
- Major cause of late non-relapse mortality
 - Increased risk of life-threatening infections
 - Leading cause of non-relapse mortality > 2 years after BMT



Complications of cGVHD

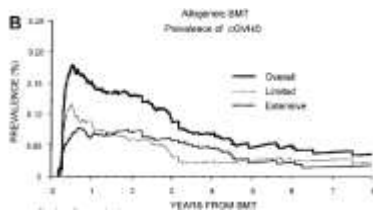


Not mutually exclusive

Sullivan K. (1994) Graft Vs Host Disease. In S.J. Forman, K.G. Blume, E.D. Thomas (Eds) Bone Marrow Transplantation, pp. 339-362/Blackwell Scientific Publications, Boston.

Chronic Graft-Versus Host Disease (cGVHD)

- Major cause of late non-relapse mortality



Zecca et al, Blood, 2002

Diagnosis and Staging of cGVHD

Definition

- Onset
 - Quiescent - aGVHD resolved (intermediate prognosis)
 - Progressive - aGVHD not resolved (worst prognosis)
 - De novo - no aGVHD (best prognosis)
- Grade – Seattle Criteria
 - Limited - localized skin or hepatic
 - Extensive - generalized skin or localized skin or hepatic with 2nd involved organ system

Diagnosis and Staging of cGvHD

- Grade - NIH Consensus Criteria
 - **Mild** - 1 or 2 organs or sites (except lung) with no clinically significant functional impairment
 - **Moderate** -
 - i) at least one organ or site with clinically significant but no major disability, or
 - ii) three or more organs or sites with no clinically significant functional impairment. A lung score of 1 will also be considered moderate chronic GVHD.
 - **Severe** - major disability caused by chronic GVHD. A lung score of 2 or greater will also be considered severe chronic GVHD.

NIH cGVHD Organ Score

Signs	<input type="checkbox"/> No symptoms	<input type="checkbox"/> <10% BSA with disease signs but NO sclerotic features	<input type="checkbox"/> 10-50% BSA OR involvement with superficial sclerotic features "not indurated" (able to pinch)	<input type="checkbox"/> >50% BSA OR deep sclerotic features "indurated" (unable to pinch) OR impaired mobility, alteration of serous cavities
<input type="checkbox"/> Clinical features:				
<input type="checkbox"/> Microepidermal ink				
<input type="checkbox"/> Lichen planus-like features				
<input type="checkbox"/> Papulosquamous lesions or ichthyosis				
<input type="checkbox"/> Hypopigmentation				
<input type="checkbox"/> Hyperpigmentation				
<input type="checkbox"/> Keratosis pilaris				
<input type="checkbox"/> Erythema				
<input type="checkbox"/> Erythroderma				
<input type="checkbox"/> Anikidemia				
<input type="checkbox"/> Sclerotic features				
<input type="checkbox"/> Pruritus				
<input type="checkbox"/> Hair involvement				
<input type="checkbox"/> Nail involvement				
% BSA involved <input type="text"/>				

Increasing Incidence of cGVHD

- Older recipient age
- Peripheral blood
- Unrelated donors
- DLIs
- Lower RR mortality
- Treatment of infections

cGVHD Risk Factors

	Patient	Donor/Graft	Transplant
Known Risk Factors	<ul style="list-style-type: none"> • Older age 	<ul style="list-style-type: none"> • Female donor to male patient • Mismatched • Unrelated • PBSCs • DLI's • T-cell replete graft 	<ul style="list-style-type: none"> • Acute GVHD
Possible Risk Factors	<ul style="list-style-type: none"> • CMV + • CMV reactivation • Splenectomy 	<ul style="list-style-type: none"> • Older age • High CD 34+ count (GCSF?) PBSCs • Ethnic difference • ↓ Cord blood 	<ul style="list-style-type: none"> • Steroid prophylaxis for aGVHD • No MTX prophylaxis • Non-myeloablative

cGVHD Pathogenesis

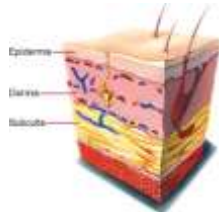
- Poorly understood
- Theories
 - Alloreactive T-cells, aberrant thymopoiesis
 - Altered APC function
 - T-cell imbalance
 - Th2 cells in murine models, Th1/Th2 imbalance
 - ↑TREGs in donor/recipient early = ↓cGVHD
 - Cytokine dysregulation
 - High IL1- β , IL-6, INF γ , TNF- α , TGF- β
 - Low IL-10
 - Antibody mediated

cGVHD Poor Prognostic Factors

- Thrombocytopenia (platelets < 100k)
- Progressive onset
- Generalized skin involvement
- Hyperbilirubinemia, cirrhosis
- Low Karnofsky score
- Recurrent infections
- GI involvement (diarrhea, weight loss)
- Steroid refractory disease

Cutaneous cGVHD: A Polymorphous Disorder

- Epidermis
 - Papular
 - Lichen planus-like
 - Papulosquamous
 - Poikiloderma
 - Keratosis pilaris-like
- Dermis
 - Lichen-sclerosus-like
 - Dermal sclerosis
- Subcutaneous
 - Subcutaneous sclerosis
 - Fasciitis



www.cellagon.de

Marie L. Turner, MD - Edward W. Cowen, MD
Dermatology Branch - NCI/NIH



PAPULAR cGVHD (A) – Discrete to confluent erythematous 3-4 mm papules more often associated with acute GVHD but also seen beyond the acute stage, particularly following donor lymphocyte infusions; **(B)** finer, morbilliform eruption, 7 months post-transplant.

Marie L. Turner, MD - Edward W. Cowen, MD
Dermatology Branch - NCI/NIH

LICHEN PLANUS-LIKE
Hyperpigmented/purple papules which may coalesce into annular (ring-like) small plaques. These lesions closely resemble the dermatologic disease lichen planus.



POIKILODERMA – Combination of reticulated pattern, epidermal atrophy (cigarette-paper wrinkling of skin surface), erythema and brown pigment forming the borders of skin-colored or depigmented skin.

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Dermatology Branch - NCI/NIH



KERATOSIS PILARIS-LIKE cGVHD– Skin-colored to erythematous perifollicular papules with spiny keratotic plugs within the follicular openings.

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PAPULO-SQUAMOUS cGVHD – Papules and small scaly plaques.



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Subcutaneous skin changes



Lower extremity sclerosis



Moveable sclerosis



Hidebound sclerosis

Lower extremity sclerosis



Moveable sclerosis



Hidebound sclerosis

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Dermatology Branch - NCI/NIH

Ulceration

- Full thickness loss of skin (not erosion)
- Largest ulcer
- Record longest diameter



Merla L. Turner, MD - Edward W. Cowan, MD
Dermatology Branch - NCI/NIH

Schirmer's Test

- Measurement of tear function (in mm)
 - Without anesthetic: measures both reflex and basal tear function
 - With anesthetic: measures basal tear function



Stella K. Kim, MD
MD Anderson Cancer Center

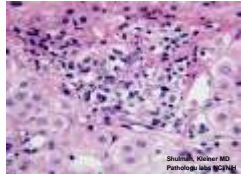
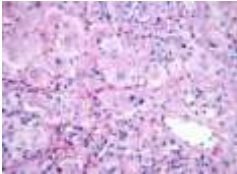
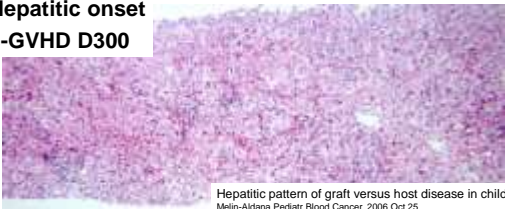
Photos Courtesy of Dr. M. Robinson

Chronic Oral GVHD



Truster BBMF, (11)721-731 200

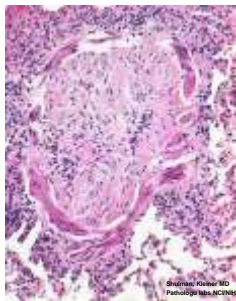
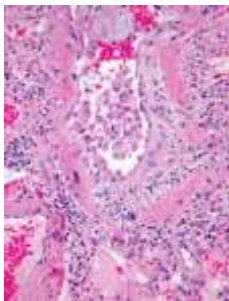
**Hepatic onset
c-GVHD D300**



Obliterative bronchiolitis

Early Constrictive

Late Obliterative



Infections

- Immune function recovery is variable and depends on several factors; stem cell source, GVHD, and immunosuppression.
- Patients are considered functionally asplenic and should be on penicillin prophylaxis.
- Immunosuppressed from disease and medication.
- Many patients have barrier breakdown from mucosal involvement.
- (Re)vaccination schedules are variable and relying on a generalized schedule for immunization is not practical. Guidelines can be found: CDC website, <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm>.

cGVHD treatment

- “Standard therapy” of steroid and calcineurin inhibitor have responses rates of approximately 70%
- Toxicity profiles of standard therapies
 - bone health, growth and development
 - organ damage
 - hormone balance
 - neurologic and psychosocial effects
 - immunity

cGVHD Systemic Therapy

- **Steroids**
- **Calcineurin inhibitors (cyclosporine, tacrolimus)**
- Mycophenolate Mofetil (MMF)
- Sirolimus (Rapamycin)
- Pentostatin
- Thalidomide
- Hydroxychloroquine
- Extracorporeal Photopheresis
- Rituximab (anti-CD20), Etanercept (TNF α blockade), Infliximab (anti-TNF α), Daclizumab (anti-IL2R/CD25)



cGVHD Local Therapy

- Skin: Psoralen-UVA, topical steroids, topical tacrolimus, photoprotection
- Oral: Topical dexamethasone, tacrolimus
- Eye: Ophthalmic steroids, cyclosporine eye drops, punctal plugs, scleral lens
- GI: Ursodiol, oral budesonide
- Joints and fascia: Physical therapy

2003: NIH Chronic GVHD Study Group

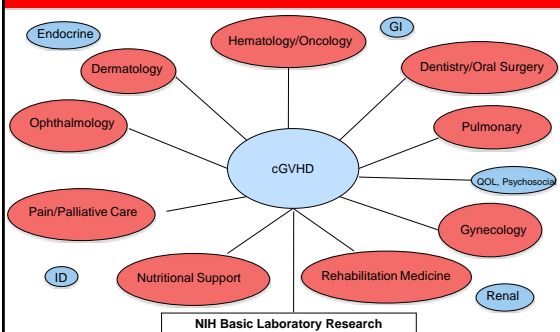
"Create a high quality multidisciplinary clinical and research program to address challenges that can be uniquely addressed at the NIH"

- Establishing clinical infrastructure
- Studies of chronic GVHD biology
- Development of new treatments
- Leadership in the field
- 04-C-0281
 - Natural History Study of Clinical and Biological Factors in Patients With Chronic Graft-Versus-Host Disease After Prior AlloHSCT

Current cGVHD Studies

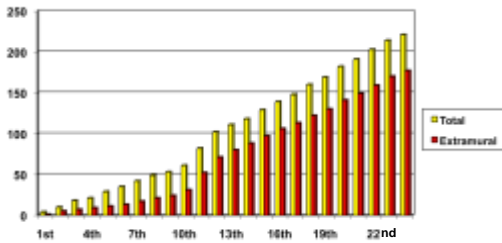
- cGVHD Natural History Study
- Montelukast Study for cGVHD Bronchiolitis Obliterans
- Cyclosporine Inhalation Solution (CIS) in Lung Transplant and HSCT Recipients for the Treatment of BO
- Imatinib Mesylate for ScGVHD
- Development of a Pediatric Symptom Scale in cGVHD
- Pilot Study of Topical Dexamethasone 0.01% Solution for Prevention of Oral cGVHD

NIH cGVHD Natural History Study



04-C-0281 NCI Chronic GVHD Natural History Protocol - Cumulative Accrual/Quarter

Accrual to Date 250



October 2004-September 2010

NIH cGVHD Scores

NIH Clinical Domain	N (%)
1 = mild	2 (1)
2 = moderate	62 (25)
3 = severe	328 (94)

NIH Organ System	N (%)
Skin	
0 = none	42 (22)
1 = mild	58 (30)
2 = moderate	48 (25)
3 = severe	75 (39)
Mouth	
0 = none	19 (11)
1 = mild	184 (95)
2 = moderate	22 (12)
3 = severe	3 (1.5)
Eyes	
0 = none	33 (17)
1 = mild	68 (35)
2 = moderate	68 (35)
3 = severe	25 (13)
GI Tract	
0 = none	197 (100)
1 = mild	62 (32)
2 = moderate	14 (7)
3 = severe	6 (3)

Organ	N (%)
Liver	
0 = none	81 (49)
1 = mild	68 (34)
2 = moderate	10 (5)
3 = severe	0
Lungs	
0 = none	45 (24)
1 = mild	79 (42)
2 = moderate	42 (22)
3 = severe	23 (12)
Adoles and Female	
0 = none	11 (6)
1 = mild	40 (21)
2 = moderate	51 (29)
3 = severe	39 (20)
Genital (female only - N=)	
0 = none	46 (51)
1 = mild	15 (14)
2 = moderate	13 (14)
3 = severe	18 (18)

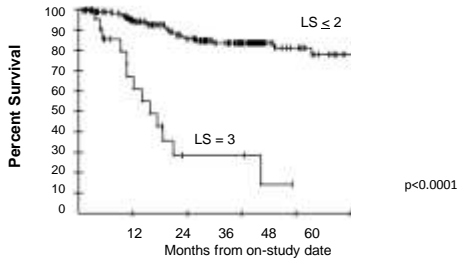
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NIH Lung Score

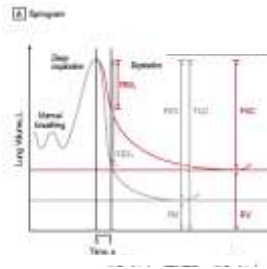


Montelukast BOS Phase II Trial Design

- Stable cGVHD rx regimen for > 3 months
- Montelukast added QHS at approved doses
- Primary Endpoint (6 month):
 - Absolute change of FEV1 % predicted (> 15 %)
 - FEV1 slope change (from baseline)
- Secondary Endpoints:
 - functional, patient reported outcomes
 - cGVHD evaluations
 - 2 year overall survival

BOS Diagnosis- Modified NIH Consensus Criteria

- FEV1 < 75% and patient decline in FEV1 > 10% per year
- Absence of infection
- Presence of another cGVHD manifestation
- Evidence of obstruction:
 - FEV1/VC < 0.7
 - RV > 120 or RV/TLC > 120% and air trapping on expiratory CT



Summary of Patient and Response (n=20)

Subject & Symptom

- Age
 - Median 48
 - Range (15-63)¹ pediatric
- Gender
 - Women/Men (12/8)
- Ethnicity:
 - 2 AA, 2 H, 1 A, 15 C
- Lung Symptom Score:
 - Mild (0,1): 8
 - Moderate (2): 7
 - Severe (3): 4 (1NE)

Lung Disease

- BASELINE: FEV1 % predicted
 - Median 45% (24-73)
 - 12/20 patients < 50%
- 6 month PRIMARY ENDPOINT:
 - 16/16 met criteria for success (< 15% decline in absolute FEV1 % predicted)
 - 31% FEV1 \geq 5% increase
 - 38% stable
 - 31% \geq 5% decline

Preliminary Conclusions

- Montelukast is safe and well-tolerated in patients with BOS (after HSCT)
- Montelukast stabilizes majority of patients with BOS at 6 months: (14/16) by slope, 16/16 by FEV1 change.
- Montelukast may improve survival of patients with BOS
- Leukotrienes may be involved in the pathogenesis of BOS after HSCT

Inhaled Cyclosporine (CIS)

- Phase II open label study
- To evaluate whether CIS can improve or stabilize lung function and QOL in individuals with BO.
- >10 yrs of age – 80 yrs
- Evaluation q 3 weeks to minimum of 18 weeks
- Newly opened

cGVHD symptom scale for children

System	Signs and Symptoms	Grading	Signs and Symptoms	Grading
Skin	Maculopapular rash	0-3	Pruritus	0-3
	Chronic dry skin	0-3	Chronic dry skin	0-3
	Chronic dry skin	0-3	Chronic dry skin	0-3
	Chronic dry skin	0-3	Chronic dry skin	0-3
Mucous Membranes	Oral leukoplakia	0-3	Oral leukoplakia	0-3
	Oral leukoplakia	0-3	Oral leukoplakia	0-3
	Oral leukoplakia	0-3	Oral leukoplakia	0-3
	Oral leukoplakia	0-3	Oral leukoplakia	0-3
GI	Chronic diarrhea	0-3	Chronic diarrhea	0-3
	Chronic diarrhea	0-3	Chronic diarrhea	0-3
	Chronic diarrhea	0-3	Chronic diarrhea	0-3
	Chronic diarrhea	0-3	Chronic diarrhea	0-3
Respiratory	Chronic cough	0-3	Chronic cough	0-3
	Chronic cough	0-3	Chronic cough	0-3
	Chronic cough	0-3	Chronic cough	0-3
	Chronic cough	0-3	Chronic cough	0-3
Ocular	Chronic dry eye	0-3	Chronic dry eye	0-3
	Chronic dry eye	0-3	Chronic dry eye	0-3
	Chronic dry eye	0-3	Chronic dry eye	0-3
	Chronic dry eye	0-3	Chronic dry eye	0-3

cGVHD symptom scale for children

System	Signs and Symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Maculopapular rash	0-3	0-3	0-3	0-3
	Chronic dry skin	0-3	0-3	0-3	0-3
	Chronic dry skin	0-3	0-3	0-3	0-3
	Chronic dry skin	0-3	0-3	0-3	0-3
Mucous Membranes	Oral leukoplakia	0-3	0-3	0-3	0-3
	Oral leukoplakia	0-3	0-3	0-3	0-3
	Oral leukoplakia	0-3	0-3	0-3	0-3
	Oral leukoplakia	0-3	0-3	0-3	0-3
GI	Chronic diarrhea	0-3	0-3	0-3	0-3
	Chronic diarrhea	0-3	0-3	0-3	0-3
	Chronic diarrhea	0-3	0-3	0-3	0-3
	Chronic diarrhea	0-3	0-3	0-3	0-3
Respiratory	Chronic cough	0-3	0-3	0-3	0-3
	Chronic cough	0-3	0-3	0-3	0-3
	Chronic cough	0-3	0-3	0-3	0-3
	Chronic cough	0-3	0-3	0-3	0-3
Ocular	Chronic dry eye	0-3	0-3	0-3	0-3
	Chronic dry eye	0-3	0-3	0-3	0-3
	Chronic dry eye	0-3	0-3	0-3	0-3
	Chronic dry eye	0-3	0-3	0-3	0-3

Dexamethasone Oral Rinse Trial

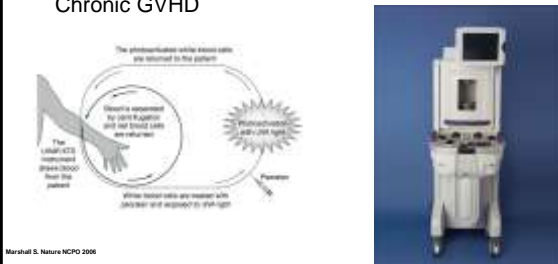
- Primary Endpoint: determine if dexamethasone mouth rinse reduces risk of developing oral cGVHD.
 - Eligibility: >12 yrs within 70 - 90 days of transplant.
 - Patients rinse with dexamethasone or placebo TID x 3 mos.
- Visits prior to treatment, 1, 2 and 3 mos
- Exams include: photographs; oral biopsy; saliva collection; QOL questionnaires; oral symptom questionnaires

Future Directions

- ECP in Children with cGVHD (POB)
- Autologous Serum Eye Drops – M. Datiles (NEI)
- Phase II - Development of a Pediatric Symptom Scale in cGVHD – L. Weiner (POB)
- Natural History and Pathophysiology of Gastrointestinal Graft-versus-Host Disease (NIDDK)
- Cyclosporin gel injection for ocular cGVHD (NEI)
- Mesenchymal Stem Cells for cGVHD (ETIB)

Future Directions

- A Phase I-II Study of Continuous Flow Extracorporeal Photopheresis in Children with Chronic GVHD



Limitations in cGVHD Research

- Heavily pre-treated
- Polypharmacy
- Underlying organ dysfunction
- Altered immunity
- Recurrent Infections
- Pain
- Depression

NCI and NIH Chronic GVHD Study Group



Patients and Families
