Chronic Graft-versus-Host Disease: Contemporary Strategies for Surveillance and Organ-Directed Supportive Care

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Chronic Graft-versus Host Disease

A multi-system chronic alloimmune and autoimmune disorder that occurs later after allogeneic hematopoietic stem cell transplantation, featured by immunosuppression, immune dysregulation, decreased organ function and impaired survival.
Chronic Graft-Versus-Host Disease (GVHD)

- Chronic GVHD affects 33%-80% of individuals who survive more than 100 days after allogeneic stem cell transplant
- Disease of immune dysregulation
- Immunosuppressive agent(s), together with good supportive management, are the mainstays of treatment
- Course is variable:
  - May persist, requiring immunosuppression for up to 20+ years following transplantation
  - In some instances GVHD appears to dissipate gradually and immunosuppression can be tapered to discontinuation
- Lower relapse rate, presumably because of a graft-versus-tumor effect
- Chronic GVHD (and its treatment) is a leading cause of non-relapse mortality and serious morbidity
Increasing Incidence of cGVHD

- Older recipient age
- Peripheral blood
- Unrelated donors
- DLIs
- Lower TRM

Incidence - about 4000 new cases in North America
Unknown number live with the diagnosis of chronic GVHD
Ocular sicca

Oral ulcers

Nail dystrophy

Skin sclerosis

Deep sclerosis

Bronchiolitis obliterans

Loss of bile ducts

Fasciitis

Skin ulcers
Functional and Symptomatic Consequences of Chronic GVHD and Its Treatment

- Infections
- Pulmonary impairment
- Endocrinopathies
- Arthralgias/myalgias/fasciitis/contractures
- Oral/dental complications
- Nutritional compromise
- Side effects of chronic immunosuppression
- Functional disability
- Distressing symptoms
- Body image changes
- Psychosocial distress
- Adjustment difficulties associated with chronicity
Predictive Factors for cGVHD

- Consistently reported
  - Prior acute GVHD
  - Recipient age
  - HLA disparity
  - Female donor to male
  - Peripheral blood stem cell source
  - Donor lymphocyte infusion (DLI)

- Shown in some studies
  - CD34 dose
  - Faster donor chimerism
  - CMV+ or infection
  - CML or AA
  - Steroids for prophylaxis
  - UCB (lower incidence)
1. **Diagnosis and staging**
   - Filipovich et al., BBMT 11:945, 2005
   - Jagasia et al., BBMT, 21, 2015

2. **Histopathology**
   - Shulman et al., BBMT 12:31, 2006
   - Shulman et al., BBMT, 21, 2015

3. **Biomarkers**
   - Schultz. et al., BBMT 12:126, 2006
   - Paczesny et al., BBMT, 21, 2015

4. **Response criteria**
   - Pavletic et al, BBMT 12: 252, 2006
   - Lee et al, BBMT; 21, 2015

5. **Ancillary and supportive care**
   - Couriel et al, BBMT 12: 375, 2006
   - Carpenter et al. BBMT 21: 1167-1187

6. **Clinical trials design**
   - Martin et al., BBMT 12: 491, 2006
   - Martin et al., BBMT; 21; 2015

Co-chairs: S. Pavletic, NCI
G. Vogelsang, Johns Hopkins

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Is this chronic GVHD? How severe it is? What is prognosis? Does it need systemic treatment? Did the patient respond to therapy?
Diagnosis of Chronic GVHD

I. Distinction from acute GVHD

II. Presence of at least one diagnostic clinical manifestation OR at least one distinct manifestation confirmed by pertinent biopsy or other relevant tests

III. Exclusion of other possible diagnosis for the clinical manifestation (i.e., infection, drug effect, others)

Filipovich et al, BBMT, 2005
Diagnostic signs of chronic GVHD

- **Skin**
  - Poikiloderma
  - Lichen planus-like
  - Sclerotic features
  - Morphea-like
  - Lichen sclerosus-like

- **Mouth**
  - Lichen-type
  - Hyperkeratotic
  - Restriction of mouth opening from sclerosis

- **Genitalia**
  - Lichen-planus like
  - Vaginal scarring or stenosis

- **Gastrointestinal**
  - Esophageal web
  - Esophageal strictures

- **Lung**
  - BO by biopsy
  - BO by PFT and CT criteria

- **Muscle fascia, joints**
  - Joint stiffness or contractures from sclerosis
Diagnostic signs of cGvHD
Poikiloderma
Diagnostic Signs of cGVHD
Lichen Sclerosus
Diagnostic Signs of cGVHD
Lichen planus-like

LICHEN PLANUS-LIKE: Violaceous papules which may coalesce into annular (ring-like) small plaques. Closely resemble the dermatologic disease lichen planus.
Diagnostic Signs of cGvHD
Morphea-Like Sclerosis
Diagnostic signs of cGvHD
Subcutaneous Sclerosis
Rippling-Diagnostic

Subcutaneous sclerosis/fasciitis
Diagnostic Signs of cGVHD
Early fasciitis
Lichenoid Hyperkeratosis – Diagnostic Feature of cGVHD

Lichenoid Hyperkeratosis

(“Diagnostic” Feature)

Lichenoid Hyperkeratosis

(Ulcerations-”Distinct” Feature)
Diagnostic – restriction of mouth opening from sclerosis
Additional Features of cGVHD

- **Skin**
  - Depigmentation
- **Nails**
  - Dystrophy
  - Ridging, splitting
  - Onycholysis
  - Pterygium unguis
  - Nail loss
- **Scalp and body hair**
  - New onset of scarring or non-scarring alopecia after recovery from chemoradiotherapy
  - Scaling, papulosquamous lesions

- **Mouth**
  - Xerostomia
  - Mucoceles
  - Mucosal atrophy
  - Pseudomembranes
  - Ulcers
- **Eyes**
  - Dry, gritty or painful eyes
  - Cicatricial conjunctivitis
  - Kertoconjunctivitis sicca
  - Punctate keratopathy
- **Genitalia**
  - Erosions, fissures, ulcers
- **Lung**
  - Bronchiolitis Obliterans Syndrome by PFTs and inspirator/expiratory CT scans
- **Muscles, fascia, joints**
  - Myositis or polymyositis
Other features that can be acknowledged as part of chronic GVHD if diagnosis is established

- **Skin**
  - Sweat impairment
  - Keratosis pilaris
  - Hypopigmentation
  - Hyperpigmentation
- **Scalp and body hair**
  - Thinning hair
  - Premature gray hair
- **Eyes**
  - Photophobia
- **GI**
  - Exocrine pancreatic insufficiency
- **Muscles, fascia, joints**
  - Edema, cramps
  - Arthralgia, arthritis
- **Other**
  - Thrombocytopenia
  - Eosinophilia
  - Lymphopenia
  - Hypo or hyper gammaglobulinemia
  - Autoantibodies
  - Effusions, ascites
  - Peripheral neuropathy
  - Nephrotic syndrome
  - Myasthenia gravis
  - Cardiac conduction abnormalities or cardiomyopathy
Not all is cGvHD…?

Patel et al, BBMT 2009
Principles of Chronic GVHD Management

- Early diagnosis; index of suspicion during tapering of IS, after DLI
- Primary therapy – steroids
- Secondary therapy – no standard but options include ECP, rituximab, imatinib, sirolimus, tacrolimus, cyclosporine, MMF, low dose methotrexate, etanercept, or participation in a clinical trial (strongly recommended)
- Topical/local therapy for mouth, eyes, genitalia, skin, GI tract
- Meticulous supportive care
- Multidisciplinary management
- Regular periodic long-term follow up
<table>
<thead>
<tr>
<th>Immediate</th>
<th>Delayed</th>
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<tr>
<td>Glucose intolerance</td>
<td>Avascular necrosis</td>
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<tr>
<td>Hypertension</td>
<td>Osteoporosis</td>
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<tr>
<td>Emotional lability</td>
<td>Cataracts</td>
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<tr>
<td>Sleep disturbance</td>
<td>Growth disturbance (pediatrics)</td>
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<tr>
<th>Early</th>
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<tr>
<td>Infections</td>
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<td>Weight gain /cushionoid features</td>
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<td>Myopathy</td>
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Ancillary and Supportive Care – Mainstay of cGVHD therapy!

- Optimize nutrition, exercise, symptom management, drug interactions, infection prophylaxis, health maintenance including disease prevention and management of comorbidities (e.g., diabetes, osteoporosis, dyslipidemia)
- Patient education and care coordination
- Organ system approach
  - Skin and appendages
  - Mouth and oral cavity
  - Eyes
  - Musculoskeletal
  - GI and liver
  - Lungs
  - Hematopoietic
  - Neurologic
  - Gynecologic

Carpenter et al, BBMT 2015
Supportive Care Management: Ocular GVHD

- Signs and symptoms: erythema, conjunctival ejection, dryness, irritation, itchiness, grittiness, foreign body sensation, burning, epiphora (excessive tearing), photophobia, pain, and blurred vision

- Surveillance:
  - Baseline ophthalmology evaluation pre-transplant and at day +100; annually thereafter for surveillance
  - Schirmer’s tear testing in clinic for surveillance for onset of ocular cGVHD
  - Close follow-up by ophthalmology to optimize treatment and prompt detection of AE (infectious keratitis, cataracts, and elevated IOP)
Supportive Care Management: Ocular GVHD

- Preservative-free tears (single use) as needed during the day and lacrilube at night
- Lid scrubs (e.g. Systane, Occusoft) for blepharitis
- Steroid eye drops, steroid ointment
- CSA eye drops: either standard formulation (.05%) or compounded 1%, 2% or 4% (storing eye drops in refrigerator and pre-treatment with steroid eye drops for two weeks may reduce burning sensation)
- Control of evaporation (wrap around eyewear, partial tarsorrhaphy)
- Control of drainage (punctal plugs, punctal occlusion)
- Scleral lenses
- Autologous serum eye drops
Supportive Care Management: Genital GVHD

• Signs and symptoms:
  – Incidence is 20-50% in women; less is known about prevalence in men
  – Dysuria, dryness, tenderness to touch, vulvodynia, dyspareunia, erythema, lichen-planus like lesions, clitoral and labial agglutination, vaginal adhesions, ulcers and vestibular tenderness (women)
  – Lichen-planus like lesions, phimosis, and contracture secondary to Peyronie’s disease (men)

• Surveillance:
  – Screen through review of systems during history taking
  – Annual gynecologic evaluation, including PAP and HPV testing
Supportive Care Management: Genital GVHD

- **Men:** treatment of lesions with topical calcineurin-inhibitors or high-potency topical steroids

- **Women:**
  - Topical clindamycin, ultra-high potency steroid cream/ointment, calcineurin suppositories or ointment/cream
  - Sclerotic features including synechiae managed with topical steroids or calcineurin-inhibitors and dilators. In advanced cases, surgery may be needed.
  - Management of estrogen deficiency and vaginal atrophy (topical estrogen, Estring)
  - Management of concurrent infection (HPV, HSV, yeast, bacteria and other gynecologic pathogens)
Supportive Care Management: GVHD of the Lung (Bronchiolitis Obliterans Syndrome or BOS)

• Signs and symptoms:
  – Shortness of breath (with exercise, with talking, or at rest), dry cough, wheezing
  – Onset of BOS may be subclinical (asymptomatic): air trapping on chest CT; obstructive changes on PFTs FEV-1 decline of >10%; decline in FVC and FEV-1/FVC < .70; RV/TLC > 125%

• Surveillance:
  – Frequent monitoring of PFTs (or at least spirometry) every 3 months for at least 1-2 years or longer, especially in high risk patients (frequent sinopulmonary infections) or during times of high risk (DLI, tapering)
  – Inspiratory and expiratory sequences during high-resolution chest CT to identify air trapping, bronchiectasis, and small airway thickening
  – 6 minute walk to characterize physical performance and identify patients who need supplemental oxygen
Supportive Care Management: GVHD of the Lung (Bronchiolitis Obliterans Syndrome or BOS)

- Systemic immunosuppression (steroids are mainstay, but ECP, rituximab and imatinib may also be helpful)
- Inhaled corticosteroids and bronchodilators
- Fluticasone, low dose azithromycin (250 mg daily), and montelukast (10 mg daily) are immunomodulatory: **FAM**
- Optimize protein and calorie intake
- Pulmonary rehabilitation including aquatic exercise
- Close follow-up with pulmonary for prompt pre-emptive management
- Supplementary oxygen as needed
Supportive Care Management: GVHD of the Lung (Bronchiolitis Obliterans Syndrome or BOS)

- Respiratory infections may aggravate respiratory impairment; BAL as warranted to investigate for infection
  - Prophylaxis for PCP, encapsulated organisms
  - Surveillance for CMV
  - IVIG for Ig G levels <400 and frequent sinopulmonary infection
  - Vaccination: pneumococcus, seasonal influenza
  - Patient education about prevention of transmission of respiratory infections
  - Referral to ENT for management of sinusitis
  - Inhaled amphotericin, inhaled tobramycin and rotating antibiotics have not been tested in GVHD but were pioneers in lung transplantation and may be considered

- Tobacco use cessation; avoidance of marijuana smoking or inhaled pulmonary toxins
Infection Prophylaxis and Surveillance

- Antibacterials PCN or azithromycin (encapsulated organisms especially pneumococcus, H. influenzae)
- Pneumocystis prophylaxis (PCP)
- Topical/systemic antifungals and surveillance for fungal infection with periodic chest/sinus CT
- Antivirals (HSV) especially in patients on dense/prolonged immunosuppression
- Frequent CMV antigenemia monitoring for reactivation
- IVIG for IgG< 400; especially if frequent sinopulmonary infection
- Vaccinations (inactivated polio, DT, HiB, influenza, pneumococcus)
