Update On
Acute Graft-Versus-Host Disease

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Disclosures

• Therakos- Advisory Board
• Bristol-Myers Squibb- Advisory Board

• I will be discussing the off-label use of medications in the treatment of acute GVHD
Objectives

• Review the clinical presentation of acute graft-versus-host disease (GVHD)

• Demonstrate the challenges associated w/ diagnosis of acute GVHD

• Review emerging diagnostic tools for acute GVHD

• Discuss new treatment options for acute GVHD
Causes of Death after transplant 2009-2010

Unrelated Donor
- Primary Disease (37%)
- New Malignancy (1%)
- Other (18%)
- Organ Failure (8%)
- Infection (18%)

HLA-matched Sibling
- Primary Disease (49%)
- GVHD (16%)
- Other (16%)
- Infection (13%)
- New Malignancy (1%)
- Organ Failure (5%)
- Other (16%)
Balancing GVHD and Graft versus malignancy (GVM)

<table>
<thead>
<tr>
<th></th>
<th>(-) Immunosuppression (+)</th>
<th>No GVHD</th>
<th></th>
<th>(+) DLI (-)</th>
<th>No GVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD</td>
<td></td>
<td></td>
<td>GVM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Balancing GVHD and Graft versus malignancy (GVM)

- No GVHD
  - (-) Immunosuppression (+)

- No GVM
  - (+) DLI (-)

- GVHD
  - (-) Immunosuppression (+)

- GVM
  - (+) DLI (-)
Mechanism of Acute GVHD

### Definitions of Acute and Chronic GVHD

**NIH 2004-2005**

<table>
<thead>
<tr>
<th></th>
<th>Symptoms post HSCT or DLI</th>
<th>Presence of acute features</th>
<th>Presence of chronic features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute</td>
<td>≤ 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, Recurrent, Late-onset acute</td>
<td>&gt; 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Sources of Stem Cells

  
  1) No difference in acute GVHD incidence, overall mortality

  2) Reduced risk of graft failure with PBSC

  3) BM reduces risk of chronic GVHD
Clinical features of acute GVHD
## Clinical Grading of Acute GVHD

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SKIN</th>
<th>LIVER</th>
<th>GUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rash</td>
<td>Total Bilirubin 2.0-2.9 mg/dL</td>
<td>Diarrhea 0.5-1 L/day or Persistent nausea/emesis with +gut biopsy</td>
</tr>
<tr>
<td></td>
<td>&lt; 25% BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Rash</td>
<td>Total Bilirubin 3.0-5.8 mg/dL</td>
<td>Diarrhea 1-1.5 L/day</td>
</tr>
<tr>
<td></td>
<td>25-50% BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Rash</td>
<td>Total Bilirubin 5.9-14.9 mg/dL</td>
<td>Diarrhea &gt; 1.5 L/day</td>
</tr>
<tr>
<td></td>
<td>&gt; 50% BSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythema with bullae and/or desquamation</td>
<td>Total Bilirubin &gt; 14.9 mg/dL</td>
<td>Severe abdominal pain or ileus</td>
</tr>
</tbody>
</table>
Clinical Grade of Acute GVHD

<table>
<thead>
<tr>
<th>GRADE</th>
<th>SKIN STAGE</th>
<th>LIVER STAGE</th>
<th>GUT STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Mild)</td>
<td>1-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II (Moderate)</td>
<td>1-3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III (Severe)</td>
<td>2-3</td>
<td>2-4</td>
<td>2-3</td>
</tr>
<tr>
<td>IV (Life threatening)</td>
<td>3-4</td>
<td>2-4</td>
<td>2-4</td>
</tr>
</tbody>
</table>
Histologic Grading of Acute GVHD

- **Grade I**
  - Focal or diffuse vacuolar change
- **Grade II**
  - Grade I w/ dyskeratotic keratinocytes
- **Grade III**
  - Grade II w/ subepidermal cleft
- **Grade IV**
  - Complete loss of epidermis
Prognosis of Acute GVHD

100 day survival:

- Grade I: 90%
- Grade II/III: 60%
- Grade IV: 0-20%

3 year survival:

- Grade I: 74%
- Grade II: 64%
- Grade III: 37%
- Grade IV: 10%
Risk Factors for Acute GVHD

- Unrelated donor
- Histocompatibility antigen mismatch
- Older age of recipient
- CML
- Total body irradiation
- Sex mismatch (female donor - male recipient)
- Host exposure to previous blood products
- High T cell numbers in donor inoculum
- Low concentration of recipient immunosuppressive medications
Newly Recognized Risk Factors for Acute GVHD

- **Innate immunity:**
  - polymorphisms of NOD-2, TLR4

- **Inflammatory genes:**
  - polymorphisms of IL-10, TNFα
  - IL-1, IFN-γ, IL-6, IL-23R, VDR

- **Plasma proteins:**
  - polymorphisms of TNFα, IL-7, IL-6, CD40L, CD8, IL-2R, sBAFF
What do we know about viral infections and risk of acute GVHD?
Herpesviruses and GVHD

- Donor HSV seronegativity associated with higher incidence of acute GVHD

Broers et al. *Blood* 2000
- CMV seropositivity is risk factor for development of acute GVHD

Ngoma et al. *Int J Hematol* 2012
- Impaired reconstitution of Tregs may be associated with CMV viremia and acute GVHD

Akpek et al. *Biol Blood Marrow Transplant* 2013
- HSV viral ag (Pol) expressed in skin and CD34+ cells in blood of aGVHD pts
Herpesviruses post HSCT

- **Jaskula et al. Transplant Proceedings 2010**
- 102 HSCT pts- prospective blood PCR for CMV, EBV, HHV-6

- $\geq 100$ DNA copies/$10^5$ cells of CMV, EBV increased risk:
  - sepsis, hepatitis, encephalitis, cystitis, pneumonia, hemolytic anemia, disease relapse, marrow failure, **worse survival**
  - > Grade I acute GVHD

- Grade $\geq 1$ acute GVHD greatest risk with CMV reactivation

- Direct effect of herpesvirus reactivation or simply compromised immune function?
HHV-6

• HHV-6A
  – No known disease associations

• HHV-6B
  – Roseola infantum, exanthem subitum
  – 90% of population infected during first 2 years, latent

• Reactivates early after HSCT

• Integrates into host DNA, transmitted in germ line

• Bone-marrow suppression, delayed engraftment
HHV-6

- Encephalitis
- Diarrhea, fever, morbilliform eruption
- Diagnose with PCR of blood
HHV-6 and acute GVHD

Zerr et al. *Clin Infect Dis* 2005
- HHV-6 reactivation in 52/110 (47%) HSCT pts
- Grade III-IV acute GVHD

Hentrich et al. *Br J Haematol* 2005
- OR 5.31 for acute GVHD with HHV-6 infection

Dulery et al. *Biol Blood Marrow Transplant* 2012
- Risk with myeloablation for HHV-6 associated GVHD
HHV-6 following HSCT

Dulery et al. Biol Blood Marrow Transplant 2012
HHV-6

- Treatment- foscarnet, ganciclovir, cidofovir but resistant to acyclovir
- Data lacking on prophylactic treatment
- Cause of acute GVHD or consequence?
What about non-herpesviruses and acute GVHD?
## Other Viruses as Triggers of Acute GVHD

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>African American</td>
<td>Hispanic</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Disease</td>
<td>Acute myelogenous leukaemia</td>
<td>Chronic myelogenous leukaemia</td>
<td>Pre-B-cell acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>Cutaneous acute GVHD grade prior to infection</td>
<td>Grade II</td>
<td>Grade I</td>
<td>Grade I</td>
</tr>
<tr>
<td>Days post-HSCT</td>
<td>78</td>
<td>148</td>
<td>116</td>
</tr>
<tr>
<td>Implicated virus</td>
<td><strong>Rhinovirus</strong></td>
<td><strong>BK virus, cytomegalovirus</strong></td>
<td><strong>Parainfluenza-2</strong></td>
</tr>
<tr>
<td>Cutaneous acute GVHD grade after infection</td>
<td>Grade IV</td>
<td>Grade IV</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Postinfection immunosuppression</td>
<td>Pulse MP, MMF 750 mg t.i.d., etanercept 50 mg b.i.w., tacrolimus 1·5 mg b.i.d., prednisone 10 mg q.d.</td>
<td>Rituximab, MMF, pulse MP, tacrolimus 1·5 mg b.i.d.</td>
<td>IVIg, etanercept 50 mg b.i.w., MMF 1000 mg b.i.d., prednisone 140 mg q.d., ECP b.i.w. every 2 weeks</td>
</tr>
<tr>
<td>Outcome</td>
<td>No active GVHD</td>
<td>Deceased day +170</td>
<td>Grade I acute cutaneous GVHD</td>
</tr>
</tbody>
</table>

*The number of days post-HSCT when viral symptoms were first experienced. MP, methylprednisolone; MMF, mycophenolate mofetil; t.i.d., three times per day; b.i.w., twice per week; b.i.d., twice per day; q.d., daily; IVIg, intravenous immunoglobulin; ECP, extracorporeal photopheresis.*
Rhinovirus

blood CMV, urine BK virus

Parainfluenza 2
Conclusion:

All viruses may contribute to acute GVHD via immune activation
The Challenge:

How to accurately diagnose acute GVHD and delineate from clinical & histologic mimickers?
Dermatology Consult

- 55yom with AML
- Day +8 s/p MUD HSCT
- Conditioning- Cy/TBI
- Febrile neutropenia
- ANC 200

- Cefepime, vancomycin, acyclovir
- Methotrexate, Cyclosporine

- Mild mucositis
- 1-2 episodes of diarrhea
- Total bilirubin normal
Exploring mimickers of acute GVHD to develop a differential diagnosis
Eruption of Lymphocyte Recovery (ELR)

- **Horn et al. 1989**

- Prospective study of leukemia patients over 2 months
- Skin biopsy of all rashes following induction tx
- Morbilliform rash correlated with fever, return of WBC count
- Histologically similar to Grade II acute GVHD
Eruption of Lymphocyte Recovery

- Non-specific morbilliform eruption within 3 weeks after chemotherapy
- Result of recovery of peripheral lymphocytes after myeloablative chemotherapy-induced nadir
- Fever
- Self-limited
- Incidence 50-60% after chemotherapy

Eruption of lymphocyte recovery

- Superficial perivascular mononuclear infiltrate
- +/- dyskeratotic keratinocytes

Eruption of Lymphocyte Recovery

Bauer, Hood, Horn 1993

• Is it possible to distinguish between ELR and GVHD on the basis of skin biopsy?

• Retrospective, blinded analysis of 38 skin biopsies given diagnosis of ELR or GVHD

Conclusion:
• ELR indistinguishable from acute GVHD
Engraftment syndrome

- Morbilliform eruption, fever
- Pulmonary edema/hemorrhage, pneumonitis
- Elevated total bilirubin, diarrhea
- Follows neutrophil recovery after HSCT (allogeneic or autologous)
- Histologically similar to acute GVHD
- Exclude infection
- Short course of high-dose steroids
- Increased mortality
  - Pulmonary complications
  - Multi-organ failure
Hyperacute GVHD

• Occurs within 14 days of HSCT
• Cutaneous involvement more common, more severe

• Risk factors:
  - mismatched related/matched unrelated donors
  - myeloablative conditioning
  - >5 previous chemo regimens
  - donor-recipient sex mismatch
Hyperacute GVHD

Saliba et al. 2007

• 27% of acute GVHD were hyperacute

• Associated with higher rate of nonrelapse mortality
Toxic Erythema of Chemotherapy

Courtesy of the Victor D. Newcomer, MD collection at UCLA and Logical Images, Inc.
Toxic Erythema of Chemotherapy
Bologna et al. 2008

• Overlap of reactions to chemotherapy

• Toxic effect on eccrine ducts, acrosyringium, epidermis

• Areas of involvement reflect high density of eccrine glands

• Shared histologic features
  – Eccrine squamous syringometaplasia
  – Keratinocyte dysmaturation, apoptosis, necrosis
  – Vacuolar degeneration

• Cytarabine, Anthracyclines, 5-FU, Capecitabine, Taxanes, Methotrexate

• May develop within 1 week post-transplant

Parker et al. Bone Marrow Transplantation (2013) 48, 646–650
Toxic Erythema of Chemotherapy

- AraC ears
- Burgdorf’s reaction
- Eccrine squamous syringometaplasia
- Intertriginous eruption associated with chemotherapy
- Flexural erythematous eruption
- Intertrigo dermatitis
- Neutrophilic eccrine hidradenitis
- Chemotherapy-induced hidradenitis
- Epidermal dysmaturation
- Chemotherapy-induced epidermal dystrophy

- Acral erythema
  - Acral erythrodysesthesia
  - Chemotherapy-induced acral erythema
  - Hand-foot syndrome
  - Palmar-plantar erythema
  - Palmar-plantar erythrodysesthesia
  - Toxic acral erythema
  - Toxic erythema of the palms and soles
Morbilliform Drug Eruption
Drug Eruption

• Medications for HSCT patients:

  – Conditioning chemotherapy
  – Tumor lysis prophylaxis
  – Febrile neutropenia - antibiotics, antifungals, antivirals
  – Antiemetics
  – Growth factors
  – PRN meds
  – Pre-existing medications
Viral Exanthem

- **Viruses**
  - Epstein- Barr
  - HHV-6
  - Cytomegalovirus
  - Parvovirus
  - Enteroviruses

- **Clinical presentation**
  - No unique distribution or morphology
  - Fevers, myalgias, headache

- **Diagnosis**
  - Serologies, serum DNA quantification, PCR

- **Treatment**
  - Supportive care, antivirals

- **Histopathology**
  - Non-specific
<table>
<thead>
<tr>
<th>Disease</th>
<th>Onset</th>
<th>Clinical Presentation</th>
<th>Histopathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eruption of Lymphocyte Recovery</td>
<td>Within 21 days after chemotherapy</td>
<td>Early- erythema hands/feet/face, Morbilliform</td>
<td>Vacuolar change, Necrotic keratinocytes</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Engraftment Syndrome</td>
<td>Within 14 days After HSCT</td>
<td>Diffuse erythema, morbilliform</td>
<td>Vacuolar change, necrotic keratinocytes</td>
<td>Systemic steroids</td>
</tr>
<tr>
<td>Hyperacute GVHD</td>
<td>Within 14 days after HSCT</td>
<td>Early- erythema hands/feet/face, Morbilliform</td>
<td>Vacuolar change, Necrotic keratinocytes</td>
<td>Systemic steroids</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>Variable within 1 month after HSCT</td>
<td>Early- erythema hands/feet/face, Morbilliform</td>
<td>Vacuolar change, Necrotic keratinocytes</td>
<td>Systemic steroids</td>
</tr>
<tr>
<td>Toxic Erythema of Chemotherapy</td>
<td>Pre-transplant-21 days after HSCT</td>
<td>hands/feet FACE Flexural</td>
<td>Vacuolar change, Necrotic keratinocytes, Eccrine squamous syringometaplasia</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Viral exanthem</td>
<td>Anytime</td>
<td>Morbilliform</td>
<td>Non-specific</td>
<td>Antivirals</td>
</tr>
<tr>
<td>Morbilliform drug eruption</td>
<td>Anytime</td>
<td>Morbilliform</td>
<td>Non-specific Eosinophils?</td>
<td>Withdraw inciting medication</td>
</tr>
</tbody>
</table>
Wait, there’s more...
- 42yom w/ hepatosplenic T cell lymphoma
- Day +15 s/p double UCB HSCT
- Fever, diarrhea, pulmonary edema, t bili 1.4
- Skin bx: interface change w/ necrotic keratinocytes
- Cleared with IV HC
- 35yof w/ AML
- Day +12 s/p double UCB HSCT
- Fever, diarrhea, elevated AST/ALT
- Skin bx: mild interface change
- Cleared with prednisone
- 25yof w/ peripheral T cell lymphoma
- Day +11 s/p double UCB HSCT
- Fever, diarrhea
- Skin bx: perivascular lymphocytic inflammation
- Cleared with prednisone
Peri/Pre-engraftment Syndrome

- Exclusive to UCB HSCT?
- Median onset 7-11 days
- Incidence 25-70%
- Prior to neutrophil engraftment
- Fever
- Skin eruption
- Pulmonary infiltrates
- Diarrhea
- Jaundice
- Weight gain
- Self-limited but IV steroids
- ? risk factor for grade II-IV aGVHD
Acute GVHD: diagnosis made simple?

- Acute MI - chest pain, EKG, serum troponin, catheterization

- GHVD - no gold standard
  - Limitations of tissue biopsy
  - Dilemma - overtreat vs. undertreat?

Firoz et al. 2006 Arch Dermatol. 2006 Feb;142(2):175-82
How to improve the clinical diagnosis of acute GVHD?

• Rash = acute GVHD?

• Are there clinical patterns of acute GVHD that differentiate it from mimickers?
Comparing clinical presentation of acute GVHD vs. drug eruptions


• 39 post-HSCT pts with morbilliform eruptions within 100 days

• Facial involvement more common in GVHD

• 36% of pts with GVHD had face/palms/soles, 0% in drug eruption cohort

• Diarrhea more common in GVHD

• Combination of diarrhea and elevated serum bilirubin only in GVHD group
Does lesion morphology and anatomic site at initial presentation of acute GVHD have significance?
Clinical features of acute cutaneous GVHD following allogeneic HSCT

- Retrospective review of all 1st time allogeneic HSCT pts done at Northwestern 2010-2011

- Evaluate acute GVHD patients:
  - Onset of skin lesions
  - Lesion morphology
  - Anatomic location of lesions
141 Allogeneic Hematopoetic Stem Cell Transplants from 2010 to 2011

93 Patients with Report of “Rash”

78 Patients Seen by Dermatology

42 Confirmed Acute GVHD (36/42 confirmed by skin biopsy)

3 Late Acute GVHD
14 Chronic GVHD
19 Other Diagnoses
Clinical Patterns of Acute GVHD

- Follicular
- Morbilliform
- Violaceous
- Reticulated
Clinical Patterns of Acute GVHD

Desquamative

Confluent

Erythrodermic
# Clinical Features of Acute Cutaneous GVHD

## Table 1. Characteristics of Cutaneous Eruptions in Patients with Acute GVHD (all grades; n=42)

<table>
<thead>
<tr>
<th>Morphologies:</th>
<th>Average Time from Transplant to Rash Onset</th>
<th>45 days (range 4 to 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform</td>
<td></td>
<td>23/42 (55%)</td>
</tr>
<tr>
<td>Patchy erythema</td>
<td></td>
<td>16/42 (38%)</td>
</tr>
<tr>
<td>Confluent</td>
<td></td>
<td>14/42 (33%)</td>
</tr>
<tr>
<td>Follicular accentuation</td>
<td></td>
<td>12/42 (29%)</td>
</tr>
<tr>
<td>Purpuric/Violaceous</td>
<td></td>
<td>10/42 (24%)</td>
</tr>
<tr>
<td>Desquamative</td>
<td></td>
<td>6/42 (14%)</td>
</tr>
<tr>
<td>Reticulated</td>
<td></td>
<td>4/42 (10%)</td>
</tr>
<tr>
<td>Bullous</td>
<td></td>
<td>2/42 (5%)</td>
</tr>
<tr>
<td>Erythodermic</td>
<td></td>
<td>2/42 (5%)</td>
</tr>
</tbody>
</table>

## Locations:

- **Trunk**: 29/42 (69%)
- **Arms/Legs**: 28/42 (67%)
- **Face**: 26/42 (62%)
- **Ears**: 16/42 (38%)
- **Palms**: 16/42 (38%)
- **Oral mucosa**: 9/42 (21%)
- **Soles**: 4/42 (10%)
- **Dorsal hands**: 3/42 (7%)
- **Genital**: 2/42 (5%)
- **Scalp**: 1/42 (2%)
- **Ocular**: 0/42 (0%)

## Table 2. Comparison of Characteristics of Cutaneous Eruptions in Patients with Clinical Grade I and Grade II aGVHD (n=37)

<table>
<thead>
<tr>
<th>Morphologies:</th>
<th>Grade I aGVHD (n=11)</th>
<th>Grade II aGVHD (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform</td>
<td>4/11 (36%)</td>
<td>0/26 (0%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Patchy erythema</td>
<td>8/11 (73%)</td>
<td>6/26 (23%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Purpuric/Violaceous</td>
<td>6/11 (55%)</td>
<td>4/26 (15%)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Morbilliform</td>
<td>4/11 (36%)</td>
<td>17/26 (65%)</td>
<td>0.151</td>
</tr>
<tr>
<td>Follicular accentuation</td>
<td>2/11 (18%)</td>
<td>9/26 (35%)</td>
<td>0.445</td>
</tr>
<tr>
<td>Confluent</td>
<td>3/11 (27%)</td>
<td>11/26 (42%)</td>
<td>0.477</td>
</tr>
<tr>
<td>Desquamative</td>
<td>0/11 (0%)</td>
<td>3/26 (12%)</td>
<td>0.540</td>
</tr>
<tr>
<td>Bullous</td>
<td>0/11 (0%)</td>
<td>1/26 (4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Erythodermic</td>
<td>0/11 (0%)</td>
<td>0/26 (0%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Locations:</th>
<th>Grade I aGVHD (n=11)</th>
<th>Grade II aGVHD (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk</td>
<td>4/11 (36%)</td>
<td>22/26 (85%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Arms/Legs</td>
<td>4/11 (36%)</td>
<td>20/26 (77%)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Face</td>
<td>5/11 (45%)</td>
<td>19/26 (73%)</td>
<td>0.143</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>3/11 (27%)</td>
<td>2/26 (8%)</td>
<td>0.144</td>
</tr>
<tr>
<td>Palms</td>
<td>2/11 (18%)</td>
<td>12/26 (42%)</td>
<td>0.150</td>
</tr>
<tr>
<td>Ears</td>
<td>3/11 (27%)</td>
<td>11/26 (42%)</td>
<td>0.477</td>
</tr>
<tr>
<td>Dorsal hands</td>
<td>1/11 (9%)</td>
<td>1/26 (4%)</td>
<td>0.512</td>
</tr>
<tr>
<td>Scalp</td>
<td>0/11 (0%)</td>
<td>1/26 (4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Soles</td>
<td>1/11 (9%)</td>
<td>2/26 (8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ocular</td>
<td>0/11 (0%)</td>
<td>0/26 (0%)</td>
<td></td>
</tr>
<tr>
<td>Genital</td>
<td>0/11 (0%)</td>
<td>0/26 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes statistically significant difference with p-value < 0.05
Limitations

- Retrospective
- Did not evaluate GVHD vs non-GVHD
- Not enough Grade III/IV
- How to account for >1 morphology, location?
What is the role of skin biopsy for diagnosis of acute GVHD?
Limitations of skin biopsy for diagnosis of acute GVHD

• Sale et al. 1977
  - 3 blinded dermatopathologists consensus < 1/3 of time

• Kohler et al. 1997
  - skin bx has little utility in early post-HSCT period to delineate GVHD from drug eruptions, viral exanthema

• Barksdale et al. 1998
  - 80% of rush skin biopsies to rule-out acute GVHD are interpreted as equivocal

• Zhou et al. 2000
  - 85% pts tx prior to bx performed or results available

• Kuykendall & Smoller 2003
  - No single case satisfied all histologic parameters,
    no skin bx 21d post-HSCT
What about eosinophilis?
Eosinophils in skin/blood following HSCT

- Massi et al. 1999
  - Eosinophils present in 3% of acute GVHD pts and 5% in those that did not develop GVHD

- Marra et al. 2004
  - 3 patients w/ diffuse morbilliform eruptions after HSCT coinciding w/ initiation of new medications
  - skin biopsies showed rich eosinophilic infiltrates, 2/3 patients died from GVHD

- Paralkar et al. 2008- Peripheral eosinophilia as a marker of acute GVHD

- Weaver and Bergfeld 2010 - Eosinophils in skin biopsies of acute GVHD patients
  16 eos/hpf= drug eruption
How else to diagnose acute GVHD and exclude mimickers?

- If there is no clinical distinction?
- If skin biopsies are not completely reliable?
- If eosinophils cannot be used as surrogate marker of drug allergy?
What about biopsy of other target organs?
Biopsy of other target organs

• Washington, K. and M. Jagasia *Pathology of graft-versus-host disease in the gastrointestinal tract*. Hum Pathol, 2009

Acute GVHD Biomarkers
Acute GVHD Biomarkers

- Diagnostic tool when clinical and histologic features cannot reliably determine diagnosis

  - **Advantage:**
    - Obviate need for invasive tests
    - Guide intensity and duration of GVHD tx to minimize toxicity
    - Predict development prior to onset of symptoms, lab abnormalities

  - **Limitations:**
    - How do we know for sure GVHD?
    - Widely available?
    - Single vs panel?
Elafin in Acute Cutaneous GVHD

- Anti-protease secreted in response to TNF-α and IL-1 by keratinocytes
- Differentiated drug allergy and acute GVHD in plasma and skin
- Stratification of low/high serum and GVHD severity for NRM

## Biomarkers for Acute GVHD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIL-2Ra</td>
<td>Systemic</td>
</tr>
<tr>
<td>IL-6</td>
<td>Systemic</td>
</tr>
<tr>
<td>IL-8</td>
<td>Systemic</td>
</tr>
<tr>
<td>IL-10</td>
<td>Systemic</td>
</tr>
<tr>
<td>IL-12</td>
<td>Systemic</td>
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<tr>
<td>IL-15</td>
<td>Systemic</td>
</tr>
<tr>
<td>IL-18</td>
<td>Systemic</td>
</tr>
<tr>
<td>CCL8</td>
<td>Systemic</td>
</tr>
<tr>
<td>CXCL10</td>
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</tr>
<tr>
<td>TNFa</td>
<td>Systemic</td>
</tr>
<tr>
<td>TNF-R1</td>
<td>Systemic</td>
</tr>
<tr>
<td>HGF</td>
<td>Systemic/GI tract</td>
</tr>
<tr>
<td>KRT18</td>
<td>GI tract</td>
</tr>
<tr>
<td>Elafin</td>
<td>Skin</td>
</tr>
<tr>
<td>REG3α</td>
<td>GI tract</td>
</tr>
<tr>
<td>CD30</td>
<td>Systemic, GI tract</td>
</tr>
</tbody>
</table>
Biomarker Panels for Acute GVHD
• Blood drawn on days: 0, +7, +14, +21, +28, +56, +100 and date of GVHD

• Combination of IL-2Ra, TNFR1, HGF, IL-8 predicted occurrence of acute GVHD

• Could discriminate GVHD from non-GVHD

• HGF could predict maximum Grade GVHD

Paczesny et al. Blood 2009
Biomarker Panels for Acute GVHD

**Paczesny et al ASH Blood. 2010;116(21):675.**

- IL-2Ra, TNFR1, elafin, REG3α at day +7 and +14 predicted acute GVHD
- Specificity 75%
- Sensitivity 57%

**August et al Bone Marrow Transplant. 2011;46(4):601-604.**

- Soluble CD8, IL-2Ra, CD40L, CD28, TNFR1 predicted severe acute GVHD by day+15

**Levine et al Blood. 2012;119(16):3854-3860.**

- IL-2Ra, TNFR1, HGF, IL-8, elafin, REG3α at GVHD tx day 0, +14, +28 predictive of acute GVHD response to treatment, 6 month mortality
• Suppression of tumorigenicity 2 (ST2)
• High levels at day +14 & initiation of acute GVHD tx:
  - 2.3 x as likely to be tx resistant
  - 3.7 x as likely to die at 6 mths
The future: diagnosis of acute GVHD

- Diagnosis on the basis of clinical, histologic features, biomarkers, genetic factors
- Preemptive tx based on GVHD risk stratification
- Intensity/duration of tx guided by GVHD stratification
- Need large-scale validation with dermatologist involvement
Treatment of Acute GVHD
Treatment of Acute GVHD

• **Prophylaxis**
  - Cyclosporine or Tacrolimus + Methotrexate
  - Cyclosporine or Tacrolimus + Mycophenolate mofetil
  - Antithymocyte globulin

• **1st line**
  - Methylprednisolone 1-2mg/kg
  - Durable complete response rate only 30-50%
  - Steroid-refractory acute GVHD 2-year survival 30%
  - No agent improves survival in steroid-refractory acute GVHD
Management of Acute GVHD

Acute GVHD

Grade I
- Optimize CSA, topical steroids

Grade II
- Restart CSA if off, systemic steroids 1mg/kg/qd

Grade III-IV
- IV methylprednisolone 2mg/kg/qd
Wet Wraps

• WET WRAP PROTOCOL:

1. Line the bed with blue chucks, blue side down.

2. Cover affected areas of the patient's skin on the back, trunk, arms, and legs with Triamcinolone 0.1% ointment – avoid use on the face, armpits and groin.

3. After the steroids have been applied, cover the patient (neck, front and back of the trunk, arms and legs) with cotton towels, soaked with room temperature saline.

4. Cover with Chucks, blue side out, then cover with blankets to keep patient warm, as needed.

5. Leave in place for 1.5 hours, remove dressings, and pat dry.


7. Repeat cycle BID.
Acute GVHD trials

- **BMT CTN 0302** - steroids +
  MMF, denileukin diftitox (dd), etanercept, pentostatin
- **BMT CTN 0802** - steroids + high-dose MMF

**Conclusions:**
- Many use systemic steroids for Grade I acute GVHD
- Addition of MMF does not improve outcome
Narrow-Band UVB

Feldstein et al. JAAD 2011

- 14 steroid-dependent or steroid-refractory pts
- 2-3 tx per week
- Stage I (1), Stage II (7), Stage III (6)
- Mean # sessions: 15
- 8/14 (57%) complete responders, 3(21%) partial response, 3 (21%) no response
- 10/13 (77%) able to reduce prednisone dose
Emerging acute GVHD treatments

- TNF-α inhibitors: infliximab, etanercept
- Mycophenolate mofetil
- Sirolimus
- Pentostatin (deoxycoformycin): nucleoside analog
- Thalidomide
- Extracorporeal photopheresis (ECP)
- Rituximab
- Antithymocyte globulin (ATG)
- Anti-CD 147 (ABX-CBL): on activated B/T cells, APCs
- Anti-CD3 (OKT3, visilizumab)
- Anti-CD5: on T cells
- Anti-CD52 (alemtuzumab): on B/T cells, monocytes, dendritic cells
- Anti-CD25 (daclizumab, inolimomab, basiliximab)
- Denileukin difitox: IL-2 w/ catalytic domains of diphtheria toxin
- nbUVB, broad-band UVB phototherapy
- Mesenchymal stem cells (MSC)
- T cell depletion
- Tregs
- Anti-IL-17
Mesenchymal stem cells (MSCs)

- Heterogeneous stromal stem cells from bone marrow, adipose tissue, placenta, cord blood
- CD $73^+$, CD $90^+$, CD $105^+$, adhere to plastic in vitro
- Suppress T/B cells, NK cells, dendritic cell function in vitro
- Promote angiogenesis, tissue repair, immune modulation via VEGF, IL-6, IL-11, M-CSF, stem cell factor
- Nearly 200 clinical trials IBD, cardiac ischemia, ALS, DM, MS, cirrhosis
Mesenchymal stem cells (MSCs)


- Le Blanc et al. *The Lancet* 2007- Phase II
  - 55pts w/ tx-refractory severe acute GVHD given MSCs
  - 30/55 complete response, 9/55 partial response- 39/55 (71%)
  - 2 year survival: complete responders 52%, partial/non responders 16%

- Unmatched allogeneic MSCs for steroid-resistant acute GVHD popular in Europe

- Multicenter Phase III trial (NCT00366145) in US failed primary endpoint in steroid-resistant acute GVHD patients in US
Mesenchymal stem cells (MSCs)

Future questions:

• Importance of HLA compatibility
• Source, volume
• Dose & Re-dose?
• Timing
• Cryopreservation
• Side effects and risk of disease relapse
The future: graft manipulation

• Goal: minimize GVHD and maximize graft versus malignancy
• Number of Tregs and effector T cells in graft
• Malignancy-specific alloreactive T cells in graft
• Virus-specific alloreactive T cells in graft
• T cell depleted graft with low-dose serial T cell infusions
Future Directions at Northwestern

• Prospective trial with serial evaluation of all allo-HSCT pts during first 60 days
• Apply clinical parameters of morphology & location of skin lesions to predict outcome
• Unique risk factors for acute GVHD
• Improve upon clinical description of acute GVHD mimickers (lymphocyte recovery, engraftment syndrome, pre-engraftment syndrome)
• Unique immunohistochemistry, biomarkers
• Additional histologic parameters
• Demonstrate therapeutic benefit (lower total steroid dose, less complications)
• Demonstrate mortality benefit
THANK YOU

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