Update on Graft versus Host Disease

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Bone Marrow Transplantation

• Indications for allogeneic BMT:
  – Malignancy
    – Leukemias, lymphoma
  – Non-malignant
    – Aplastic anemia

• Pre-transplant conditioning:
  – Myeloablative
  – Reduced intensity

• Source of donor stem cells:
  – Bone marrow, peripheral blood, umbilical cord

GVHD: Overview

• Traditionally: based on time after BMT
  – Acute: before 100 days
  – Chronic: after 100 days

• New classification: based on clinical manifestations
  – Acute:
    • Classic acute (before 100 days)
    • Persistent/late onset acute (after 100 days)
      – Often after withdraw immunosuppression
  – Chronic:
    • Classic chronic
    • Overlap syndrome
Acute GVHD: Clinical Manifestations

- Skin:
  - maculopapular rash
  - ulcerative dermatitis
- Gastrointestinal:
  - Secretory diarrhea
  - GI bleed, from patchy mucosal ulcerations
- Liver:
  - Elevated bilirubin, alkaline phosphatase, transaminase
- Occasionally: eye and oral mucosa involvement

Acute ocular GVHD

- Stage 1: hyperemia alone
- Stage 2: hyperemia with serosanguinous chemosis
- Stage 3: pseudomembranous conjunctivitis
- Stage 4: pseudomembranous conjunctivitis + corneal epithelial sloughing

Chronic GVHD

- Features mimic autoimmune disease:
  - Scleroderma
  - Sjogren’s syndrome
  - Primary Biliary Cirrhosis
  - Bronchiolitis obliterans
  - Immune cytopenias
  - Chronic immunodeficiency
- Presentation:
  - Usually within 3 years of BMT
  - Often in patients with prior acute GVHD
  - Single or multiple organs

### Site | Diagnostic | Distinctive | Other Features
--- | --- | --- | ---
Eyes | New onset dry, gritty, or painful eyes* | Cicatricial conjunctivitis Keratoconjunctivitis sicca* Confluent areas of punctate keratopathy | Photophobia Periorbital hyperpigmentation Blepharitis

* Requires Schirmer ≤ 5 mm
Eyes: NIH Working Group

- New ocular sicca
  - Schirmer ≤ 5mm at 5 minutes
- New KCS
  - Schirmer 6-10mm at 5 minutes
  - Slit lamp evidence of KCS
- Sufficient for diagnosis of chronic GVHD:
  - New ocular sicca/KCS with distinctive manifestations from one other organ

<table>
<thead>
<tr>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
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<tbody>
<tr>
<td>EYES</td>
<td>No symptoms</td>
<td>Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3x per day)</td>
<td>Moderate dry eye symptoms partially affecting ADL (requiring drops &gt; 3x per day or punctual plugs), WITHOUT vision impairment</td>
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<tr>
<td>Mean tear test (mm):</td>
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<tr>
<td>□ &gt; 10</td>
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<td>□ 6-10</td>
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<td>□ ≤ 5</td>
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<tr>
<td>□ Not done</td>
<td>Asymptomatic signs of KCS</td>
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Staging of cicatricial conjunctivitis

<table>
<thead>
<tr>
<th>GRADE 1</th>
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<tr>
<td>Hyperemia</td>
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Other findings

- Meibomian gland dysfunction
- Keratinization
- SLK
- Episcleritis
- Trichiasis (from cicatricial conjunctivitis)
- Corneal infection
- Rarely involves posterior segment
  - Retinal heme probably due to anemia
Ocular GVHD: Local treatment

- **Acute:**
  - Topical corticosteroids
  - Removal of pseudomembranes

- **Chronic:**
  - Lubrication
  - Punctal plugs/cauterization
  - Topical corticosteroids?
  - All trans retinoic acid

Topical 0.05% Cyclosporine A

- Case series (n=8 patients):
  - Improved burning in 7/8
  - Improved Schirmer (7.2 → 11.3)
  - Improved TBUT (3.4 → 6.6)

- Case series (n=16 patients):
  - Improved dry eye symptoms in 10/16
  - Improved corneal staining in 16/16

- Non-randomized comparative case series
  - 81 patients given CSA 1 month before BMT
  - 24 patients given CSA ≥ 6 months after BMT
  - At 1 year, early CSA group had better Schirmer (9.5 vs 5.2) and dry eye score.

Topical 0.03% Tacrolimus

- Case report
  - 1 child with conjunctivitis, cicatrical changes, and corneal epithelial breakdown
  - Improved conjunctivitis and healed corneal epithelium after 1 week of topical tacrolimus

Tranilast

- Prepared from leaves of nandina plant
- Used in Japan and South Korea for allergic disease
- Inhibits TGF-β

- Non-randomized comparative case series:
  - 8 patients treated with tranilast
  - 10 patients treated with tears, retinoic acid
  - Tranilast group had better Schirmer (13.0 vs 9.0) and corneal staining at 3 months
Autologous serum tears

- Case reports (n=2)
  - 2 weeks of hourly serum tears improved symptoms, corneal staining, and corneal epithelial defect in 1 patient
  - 10 months of hourly serum tears improved corneal staining, hyperemia, and filaments in 1 patient
- Case series (n=14 patients)
  - 1 month of hourly serum tears improved:
    - Symptom score (33 → 23)
    - Corneal staining score (5.6 → 2.2)
    - Conjunctival staining score (5.2 → 3.1)
    - TBUT (2.8 → 5.8)
  - 7/14 patients had sustained improvement

Cornea 2007; 26:861  Bone Marrow Transplant 2003; 31:579

Scleral Contact Lenses

- Boston Scleral Lens
  - Customized
  - Case series (n=9 patients with KCS/GVHD)
    - Dry eye symptoms score improved in all patients
    - 1 patient had difficulty inserting lens
- Jupiter Scleral Lens
  - Standard or customized
  - Case series (n=5 patients with KCS/GVHD)
    - All patients had symptomatic improvement
    - 7/10 eyes had improved vision
    - 6/10 eyes could be fit with standard trial lenses


Conclusions

- Several staging systems for ocular GVHD
- Lubrication and punctal cautery are mainstays of treatment
- Anti-inflammatory agents may be helpful
- Scleral contact lenses may provide symptomatic improvement
- No randomized clinical trials for this uncommon disease