Treatment of Bronchiolitis Obliterans (BOS) after HCT

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Blood and Marrow Transplantation and Cellular Immunotherapy

H. Lee Moffitt Cancer Center and Research Institute
Disclosure

• This continuing education activity contains discussion of published and/or investigational uses that are not indicated by the FDA

• No relevant Conflicts of Interest
Learning Objectives

• Review current criteria for diagnosis, severity staging, and treatment response assessment for bronchiolitis obliterans (BOS)

• Explain current first-line therapy for BOS

• Discuss options for therapy of advanced BOS
Outline

• Chronic GVHD
  — Introduction

• Bronchiolitis obliterans
  — Diagnosis
  — Primary therapy
  — Response assessment
  — Secondary therapy
  — Supportive care
  — Lung transplantation
Chronic GVHD
Chronic GVHD

- Commonly occurring late IMD after HCT
- Responsible for
  - Mortality
  - Morbidity, disability, impaired QOL
  - Prolonged IS therapy
- NIH Consensus guidelines
  - Diagnosis and severity scoring
  - Assessment of treatment response
## Current Estimates of Late Immune-mediated Disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>N</th>
<th>2yr CI % (95%CI)</th>
<th>Median time to onset (months)</th>
<th>NRM at 2yr after onset (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late acute GVHD</td>
<td>92</td>
<td>10 (8-12)</td>
<td>5.5 (0.9-24)</td>
<td>23 (15-35)</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>428</td>
<td>47 (44-51)</td>
<td>7.4 (0.8-45.1)</td>
<td>12 (9-16)</td>
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<tr>
<td>BOS</td>
<td>30</td>
<td>3 (2-5)</td>
<td>12.2 (2.8-24.3)</td>
<td>32 (18-57)</td>
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<tr>
<td>Cutaneous sclerosis</td>
<td>68</td>
<td>8 (6-10)</td>
<td>14.0 (4-36.9)</td>
<td>20 (10-39)</td>
</tr>
</tbody>
</table>

- Chronic GVHD Consortium longitudinal study of IMD
- Prospective cohort (N=911)
Chronic GVHD Causes Late HCT Mortality

<table>
<thead>
<tr>
<th></th>
<th>NRM</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td>severe</td>
<td>32%</td>
<td>62%</td>
</tr>
<tr>
<td>moderate</td>
<td>9%</td>
<td>86%</td>
</tr>
<tr>
<td>mild</td>
<td>3%</td>
<td>97%</td>
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</table>


NRM: non-relapse mortality
OS: overall survival
Chronic GVHD Impairs QOL

<table>
<thead>
<tr>
<th>Disease</th>
<th>PCS</th>
<th>MCS</th>
</tr>
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<tbody>
<tr>
<td>Normal Population</td>
<td></td>
<td></td>
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<tr>
<td>cGVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cGVHD from NIH severity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate cGVHD from NIH severity score</td>
<td></td>
<td></td>
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<tr>
<td>Severe cGVHD from NIH severity score</td>
<td></td>
<td></td>
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<tr>
<td>Multiple Sclerosis</td>
<td></td>
<td></td>
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<tr>
<td>Systemic Sclerosis and Active Alveolitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergies</td>
<td></td>
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<td>Dermatitis</td>
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<td>Arthritis</td>
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<tr>
<td>Sciatica</td>
<td></td>
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<tr>
<td>Hearing impairment</td>
<td></td>
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<tr>
<td>Vision impairment</td>
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<tr>
<td>Limitation in the use of an arm(s) or leg(s)</td>
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<tr>
<td>Cancer (except skin cancer)</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Chronic lung disease</td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
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<td>Angina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
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<tr>
<td>Congestive heart failure</td>
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</table>

PCS: physical component score, MCS: mental component score

Limited ISD after Chronic GVHD

- Chronic GVHD cohort (n=250)
  - Median 5.6 years
    - 32% successfully off IST
    - Others: on IST, death/relapse

ISD: immunosuppression therapy discontinuation
Chronic GVHD Diagnosis

- Major proposed changes in diagnosis, classification, and severity grading following 2005 NIH Consensus Conference
- Distinction of acute and chronic
- Definitions of classic vs. overlap chronic
- Individual organ severity grading, summarized in global composite score of mild, moderate, severe
Diagnostic Manifestations

**SKIN**
- Poikiloderma
- Lichen-planus
- Sclerosis
- Morphea
- Lichen sclerosis

**MOUTH**
- Lichen-planus

**Lung**
- Bronchiolitis obliterans

**GI**
- Esophageal web, stricture

**Joint/Fascia**
- Fasciitis
- Contractures or joint stiffness

**Genital**
- Lichen planus
- Lichen sclerosis
- Vaginal scarring
- (male – phimosis, or urethral/meatus stenosis)

## NIH Overall Severity

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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</thead>
<tbody>
<tr>
<td>Mild</td>
<td>• 1 or 2 organs or sites (except lung) with score 1</td>
</tr>
<tr>
<td>Moderate</td>
<td>• 3 or more organs with score 1&lt;br&gt;• At least 1 organ or site with score 2&lt;br&gt;• Lung score of 1</td>
</tr>
<tr>
<td>Severe</td>
<td>• At least 1 organ or site with score 3&lt;br&gt;• Lung score 2</td>
</tr>
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</table>
Chronic GVHD: Primary Treatment

- First-line treatment
  - 1mg/kg/day prednisone
  - CNI – spare steroids
  - Combination therapy (prednisone + other IST agents) – no benefit
Chronic GVHD: Secondary Treatment

- Second-line therapy
  - Many IS agents used
  - Frequent failure
  - Multiple lines of therapy

Bronchiolitis Obliterans (BOS)

Diagnosis
Bronchiolitis Obliterans (BOS)

• **BOS**
  - Most common late non-infectious pulmonary complication after HCT

• **Expected incidence**
  - 5-6%, and 13% in those with chronic GVHD

• **Presentation**
  - Asymptomatic (detected by PFT)
  - Dyspnea, cough (concurrent chronic GVHD)
  - Late (median of 12 months post-HCT) onset
  - Presenting FEV1 of 46% (trial) to 53% (cohort) predicted values

• **Pathogenesis**
  - Immune attack of small airways
  - Fibrotic occlusion, obliteration

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PFT: pulmonary function test
FEV1: forced expiratory volume in 1 second
BOS diagnostic criteria

- FEV1/FVC < 0.7*
- FEV1 < 75% predicted value*
  - With ≥ 10% decline within 2 years
- Absence of lung infection*
- 1 of the 2 following criteria:
  - CT chest findings
    - Air trapping
    - Small airway thickening or bronchiectasis
  - RV > 120% predicted value

*first 3 criteria sufficient for BOS diagnosis if presence of cGVHD based on other organ involvement

FVC: Forced Vital Capacity, RV: Residual Volume, CT: computed tomography
Pulmonary Function Testing

A. Spirogram

- Normal
- Bronchiolitis obliterans
- Scleroderma and obstructive lung disease

B. Flow-volume curve

- Normal
- Bronchiolitis obliterans

Lung volume, L

Expiration

FEV₁

FVC

TLC

SVC

TLC

RV

Inspiration

Flow, L/s

Lung volume, L

FVC

FVC

RV

RV

Time, s
Bronchiolitis Obliterans (BOS)

Primary Therapy
Initial Therapy of BOS

- **FAM + prednisone**
  - Phase II, single-arm, cGVHD Consortium trial
  - N=36 subjects with BOS (within 6 months of diagnosis)
  - Primary endpoint
    - Treatment failure
      - ≥ 10% decline in FEV1 by 3 months
    - Historical benchmark
      - Expected 40% failure

FAM: fluticasone, azithromycin, monteleukast

Study Therapy

**Fluticasone**
- 440 mcg IHL BID (subjects >12 yrs)
- 220 mcg IHL BID (subjects 6-12 yrs)

**Azithromycin**
- 250 mg PO 3x week (subjects >18 yrs)
- 5mg/kg PO 3x week (subjects 6-18 yrs)

**Montelukast**
- 10mg PO QHS (subjects >14 yrs)
- 5mg PO QHS (subjects 6-14 yrs)

**Corticosteroids**
- 1mg/kg/day PO x 2weeks
- 0.25mg/kg/day PO taper weekly
  - target 0.25mg/kg/day PO

6 months total therapy

Stop therapy for:
- Treatment Failure (evaluated by PFT’s at Months 1-3) or
- ≥ Grade 3 Toxicity unresolved within 14 days
- Grade 4 Toxicity
FAM/Prednisone Treatment Failure

- 3 months
  — 2/36 (6%, 95%CI 1-19%)
  — p < 0.001

- 6 months
  — 13/36 (36%, 95%CI 21-54%)
FAM + Prednisone Outcome

- Prednisone dose reduction
  - 48% had ≥ 50% reduction by 3 months

- Overall survival
  - 97% (95%CI 84-100%) at 6 months

- PRO improved from baseline
  - SF36: SF, MCS
  - FACT: EWB
  - Lee scale: lung, skin, mouth, overall
ALLOZITHRO: Azithromycin for BOS Prevention

- RCT (stratified by FEV1/FVC ratio, age)
  - HCT for hematologic malignancy
  - Study therapy x 2 years
    - Azithromycin (n=243) 250mg TIW
    - Placebo (n=237)
  - Primary endpoint
    - Airflow decline-free survival at 2 years
  - Secondary
    - OS, BOS incidence at 2 years

- DSMB halted trial due to excess relapse

- N=465 included in modified ITT analysis

Azithromycin for BOS Prevention

Azithromycin for BOS Prevention

$P = .08$ (Gray test)

Cumulative incidence of Bronchiolitis Obliterans Syndrome

Months After Randomization

234 221 194 163 150 133 119 90 53

231 210 194 174 158 153 141 111 73

Azithromycin for BOS Prevention

Azithromycin for BOS Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relapse or Subsequent Neoplasm</th>
<th>Relapse</th>
<th>Subsequent Neoplasm</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
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<tr>
<td>AZM exposure</td>
<td>1.51 (0.90-2.55)</td>
<td>.12</td>
<td>0.82 (0.37-1.83)</td>
</tr>
<tr>
<td>TBI</td>
<td>1.17 (0.62-2.23)</td>
<td>.62</td>
<td>0.55 (0.22-1.40)</td>
</tr>
<tr>
<td>DRI</td>
<td>1.64 (1.20-2.24)</td>
<td>.002</td>
<td>2.07 (1.35-3.16)</td>
</tr>
<tr>
<td>cGVHD-t</td>
<td>0.86 (0.34-2.15)</td>
<td>.74</td>
<td>1.28 (0.37-4.41)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.98-1.02)</td>
<td>.91</td>
<td>0.99 (0.96-1.02)</td>
</tr>
<tr>
<td>Sex/male</td>
<td>1.07 (0.64-1.79)</td>
<td>.79</td>
<td>1.06 (0.46-2.46)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1.28 (0.74-2.23)</td>
<td>.38</td>
<td>1.45 (0.64-3.33)</td>
</tr>
<tr>
<td>Prior autologous HCT</td>
<td>1.99 (1.03-3.87)</td>
<td>.041</td>
<td>4.24 (1.61-11.1)</td>
</tr>
<tr>
<td>AZM exposure before BOS</td>
<td>0.59 (0.30-1.17)</td>
<td>.13</td>
<td>0.85 (0.31-2.36)</td>
</tr>
</tbody>
</table>

- Multi-center study, N=316 BOS
- BOS: median 16.8 months post-HCT
- Azithromycin exposed N=227, not N=89
Bronchiolitis Obliterans (BOS)

Response Assessment
## NIH 2014: Organ Responses

<table>
<thead>
<tr>
<th>Organ</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>NIH Skin Score 0 after previous involvement</td>
<td>Decrease in NIH Skin Score by 1 or more points</td>
<td>Increase in NIH Skin Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Eyes</td>
<td>NIH Eye Score 0 after previous involvement</td>
<td>Decrease in NIH Eye Score by 1 or more points</td>
<td>Increase in NIH Eye Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Mouth</td>
<td>NIH Modified OMRS 0 after previous involvement</td>
<td>Decrease in NIH Modified OMRS by 2 or more points</td>
<td>Increase in NIH Modified OMRS by 2 or more points</td>
</tr>
<tr>
<td>Esophagus</td>
<td>NIH Esophagus Score 0 after previous involvement</td>
<td>Decrease in NIH Esophagus Score by 1 or more points</td>
<td>Increase in NIH Esophagus Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Upper Gl</td>
<td>NIH Upper Gl Score 0 after previous involvement</td>
<td>Decrease in NIH Upper Gl Score by 1 or more points</td>
<td>Increase in NIH Upper Gl Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Lower Gl</td>
<td>NIH Lower Gl Score 0 after previous involvement</td>
<td>Decrease in NIH Lower Gl Score by 1 or more points</td>
<td>Increase in NIH Lower Gl Score by 1 or more points, except from 0 to 1</td>
</tr>
<tr>
<td>Liver</td>
<td>Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more</td>
<td>Decrease by 50%</td>
<td>Increase by 2 × ULN</td>
</tr>
<tr>
<td>Lungs</td>
<td>- Normal %FEV1 after previous involvement</td>
<td>- Increase by 10% predicted absolute value of %FEV1</td>
<td>- Decrease by 10% predicted absolute value of %FEV1</td>
</tr>
<tr>
<td></td>
<td>- If PFTs not available, NIH Lung Symptom Score 0 after previous involvement</td>
<td>- If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points</td>
<td>- If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1</td>
</tr>
<tr>
<td>Joints and fascia</td>
<td>Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure</td>
<td>Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site</td>
<td>Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site</td>
</tr>
<tr>
<td>Global</td>
<td>Clinician overall severity score 0</td>
<td>Clinician overall severity score decreases by 2 or more points on a 0-10 scale</td>
<td>Clinician overall severity score increases by 2 or more points on a 0-10 scale</td>
</tr>
</tbody>
</table>
2014 Response Criteria: Lungs

- FEV1 decline by ≥ 10%
  —Associated with mortality

- Symptom-based NIH 0-3 lung score (not LFS-based)
  —Associated with OS and NRM
  - Enrollment, change score

NRM: non-relapse mortality, OS: overall survival, LFS: lung function score

### NIH 2014: Overall response

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td><strong>CR</strong> (complete response)</td>
<td>Complete resolution in all involved organ sites</td>
</tr>
<tr>
<td><strong>PR</strong> (partial response)</td>
<td>Improvement in ≥ 1 organ site without progression in others</td>
</tr>
<tr>
<td><strong>Lack of response</strong></td>
<td></td>
</tr>
<tr>
<td>- Unchanged</td>
<td>No change in any site</td>
</tr>
<tr>
<td>- Mixed response</td>
<td>CR/PR in 1 organ, yet progression in another</td>
</tr>
<tr>
<td>- progression</td>
<td>Progression in ≥ 1 organ site</td>
</tr>
</tbody>
</table>

Bronchiolitis Obliterans (BOS)

Secondary Therapy
BOS Second-line Therapy

• General principles
  — Serial PFT monitoring for assessing response
  — Supportive care (Pulmonary, ID)
  — Therapy is often directed at multiple sites (concurrent cGVHD in other organs)
  — Numerous agents possible in second-line (and beyond), yet comparative data lacking
  — Should consider risk/benefit profile of any intervention
  — Lung transplant referral potentially indicated
Agents Used in Advanced Chronic GVHD

- *Ibrutinib
- Ruxolitinib
- Pulse steroids
- Calcineurin inhibitors
- ECP
- MMF
- mTOR inhibitors (sirolimus, everolimus)
- Thalidomide
- Hydroxychloroquine
- Azathioprine
- Etretinate/isotretinoin

- Campath
- Rituximab
- Alefacept
- Etanercept, Infliximab
- Imatinib
- Pentostatin
- Low-dose MTX
- Cyclophosphamide
- Clofazimine
- Thoracoabdominal irradiation
ECP for BOS Therapy

- ECP
  - Larger body of evidence in BOS therapy
  - Spans both post-HCT BOS and post-lung transplant BOS
  - Aggregate of largely smaller retrospective series
  - Appears promising overall
  - Good safety profile
ECP for BOS Post-lung Transplant

• Retrospective series
  — Suggest stabilization of FEV1 decline

• Prospective trial
  — ECP (CNI/MMF/steroid) vs. no ECP (CNI/MMF/steroid)
  — ECP arm: n=51
    • 61% response rate (31% stable FEV1, 30% improved FEV1)
    • Sustained responses through 6 months
    • ECP: Improved survival
    • Earlier BO onset: better ECP response

Jaksch P. J Heart Lung Transplant. 2012;31(9):950-7

MMF: mycophenolate mofetil
ECP for BOS after HCT

• Retrospective series
  — Suggest ~2/3 stabilize FEV1

• Matched cohort study
  — N=74 with BOS
    • N=26 with ECP within 1 year of BO diagnosis
    • N=26 matched non-ECP treated
  — No significant difference in FEV1 change
  — Multivariate analysis of OS
    • ECP (HR 0.1, 95%CI .01-0.3, p = 0.001)
    • MRD HCT, slower rate of FEV1 decline before ECP/index date
Etanercept for BOS Therapy

- Subacute lung disease
  - N=34 total, n=25 with obstructive lung disease (OLD)
- OLD group
  - FEV1/FVC < 75% predicted
  - FEV1 < 80% predicted
  - >15% decline in FEV1 from pre-HCT value
- Etanercept
  - 0.4mg/kg/dose SC twice weekly (x 4 or 12 weeks)
- OLD response
  - ≥ 10% increase in FEV1 among evaluable subjects (at week 4 or week 12)

Etanercept for BOS Therapy

- Overall response — 10/31 (32%)
- OLD sub-group response — 7/22 (32%)
- Response across — Severity, duration
- 5 year OS (OLD) — 67%

## European HCT Center Survey

<table>
<thead>
<tr>
<th>Agent</th>
<th>Frequently Used</th>
<th>Occasionally Used</th>
<th>Infrequently Used</th>
<th>Not Used but Regarded as Treatment Option</th>
<th>Not Regarded as Treatment Option</th>
<th>No Report on the Use</th>
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<tbody>
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<td>Cyclosporine</td>
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<td>7</td>
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<td>Tacrolimus</td>
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<td>8</td>
<td>5</td>
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<td>Photopheresis</td>
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<td>5</td>
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<td>Mycophenol Mofetil</td>
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<td>Mycophenolic acid</td>
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<td>8</td>
<td>11</td>
<td>8</td>
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<tr>
<td>Pulse of steroids</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>5</td>
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<td>Thalidomide</td>
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<td>4</td>
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<td>Azathioprine</td>
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<td>3</td>
<td>10</td>
<td>9</td>
<td>6</td>
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<tr>
<td>Retinoids (Acitretin/Isotretinoine)</td>
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<td>7/10</td>
<td>12/9</td>
<td>10/9</td>
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<tr>
<td>Alemtuzumab</td>
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<td>5</td>
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<td>Cyclophosphamide</td>
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<td>1</td>
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<td>Etanercept</td>
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<td>3</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Novel Agents for Chronic GVHD

**Phase 1**
Acute inflammation & Tissue injury
- Innate immunity
  - Cytokines
  - TLR agonists
  - Neutrophils
  - Platelets
  - Vascular inflammation

**Phase 2**
Chronic inflammation & dysregulated immunity
- Adaptive immunity
  - CD8+ T cell
  - B cell
  - CD4+ T cell
  - NK cell
- Thymic Injury and dysfunction
  - T cells
  - B cells
  - NK cells
  - Antigen presenting cells
  - Regulatory Cells
    - Treg, Breg
    - IL-10 producing regulatory T cells (Tr1)

**Phase 3**
Aberrant tissue repair & fibrosis
- Innate & adaptive
  - TGFβ
  - PDGFα
  - TNFα
  - IL-17
  - Macrophages
  - Fibroblasts


PDGFα: platelet-derived growth factor-alpha, TGFβ: transforming growth factor-beta, TNFα: tumor necrosis factor-alpha, IL-17: interleukin-17, TLR: toll-like receptor
Novel agents for chronic GVHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Target</th>
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<tbody>
<tr>
<td>Baricitinib</td>
<td>JAK1/2 inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Proteasome inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Proteasome inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>KD025</td>
<td>ROCK2 inhibitor</td>
<td>T-cell signaling</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA4-Ig fusion protein</td>
<td>T-cell costimulatory pathway</td>
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<tr>
<td>Ponesimod</td>
<td>S1P1 receptor modulator</td>
<td>T-cell homing</td>
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<tr>
<td>Brentuximab</td>
<td>CD30 antibody-drug conjugate</td>
<td>T-cell responses</td>
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<tr>
<td>Ibrutinib</td>
<td>BTK/ITK inhibitor</td>
<td>B cells</td>
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<td>Ofatumumab</td>
<td>Anti-CD20 antibody</td>
<td>B cells</td>
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<tr>
<td>Fostamatinib</td>
<td>Syk inhibitor</td>
<td>B cells</td>
</tr>
<tr>
<td>Entospletinib</td>
<td>Syk inhibitor</td>
<td>B cells</td>
</tr>
<tr>
<td>Dose escalated IL-2</td>
<td>Induction of T-regs</td>
<td>T-regs</td>
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<tr>
<td>IL-2+T-regs</td>
<td>Induction of T-regs</td>
<td>T-regs and Cellular therapies</td>
</tr>
<tr>
<td>Autologous MSCs</td>
<td>Suppressive population</td>
<td>Cellular therapies</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Suppressive population</td>
<td>Cellular therapies</td>
</tr>
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<td>AZD9668</td>
<td>Neutrophil elastase inhibitor</td>
<td>Non-lymphocyte target</td>
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<tr>
<td>Vismodegib</td>
<td>Hedgehog inhibitor</td>
<td>Non-lymphocyte target</td>
</tr>
<tr>
<td>LDE225</td>
<td>Hedgehog inhibitor</td>
<td>Non-lymphocyte target</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Multiple</td>
<td>Non-lymphocyte target</td>
</tr>
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</table>
**Limited BOS on Ibrutinib Trial**

<table>
<thead>
<tr>
<th>Steroid dependence of cGVHD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Steroid-dependent cGVHD</td>
<td>28 (67)</td>
</tr>
<tr>
<td>Steroid-refractory cGVHD</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Both</td>
<td>8 (19)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of involved organs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (14)</td>
</tr>
<tr>
<td>2</td>
<td>24 (57)</td>
</tr>
<tr>
<td>3</td>
<td>9 (21)</td>
</tr>
<tr>
<td>≥4</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Involved organ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Skin</td>
<td>34 (81)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Liver</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Lungs</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Current BOS Trials

- Ruxolitinib [NCT03674047]
- Interferon gamma 1b [NCT01639261]
- Nintedanib [NCT03805477]
- Pirfenidone [NCT03315741]
- Alvelestat [NCT02669251]

- ECP [NCT02181257]
- Itacitinib [NCT03978637]
- Pirfenidone [NCT02262299]
- Inhaled cyclosporine [NCT03657342, NCT03656926]

BOS after HCT

BOS after lung transplant
Bronchiolitis Obliterans (BOS)

Supportive Care
Supportive Care

• Multi-disciplinary (BMT, Pulmonary, ID)
  — Infection prophylaxis
  — Treatment of recurrent infections
  — Influenza vaccination
  — Pulmonary rehabilitation
  — Supplemental oxygen
  — IVIG
  — GERD therapy
  — Psychosocial support
Bronchiolitis Obliterans (BOS)

Lung Transplantation
Lung Transplant for BOS

• Limited published literature
  — Supports that long-term survival possible

• Eligibility challenges (ISHLT guidelines)
  — Absolute contraindication
    • Malignancy within 2 (5) years
    • Chronic, poorly controlled infection
  — Relative contraindication
    • Colonization or infection with highly resistant or virulent infections
Acknowledgments

• Guang-Shing Cheng, MD
• Kirsten Williams, MD
• Jeanne Palmer, MD
• Stephanie J. Lee, MD, MPH
• Chronic GVHD Consortium
Additional Reading Suggestions

• Comprehensive BOS review

• Current NIH Consensus diagnosis and treatment response criteria

• Primary therapy trial with prednisone + FAM

• Early post-HCT spirometry association with subsequent BOS risk
  — Jamani. Biol Blood Marrow Transplant. 2019; (ePub)

• Current evidence regarding risk/benefit of azithromycin in BOS patients
  — Cheng. Biol Blood Marrow Transplant. 2019 (ePub)
Question #1:

— Which of the following regarding bronchiolitis obliterans are true?

a) Lung severity score of 1 per NIH global severity scoring would be diagnostic of mild cGVHD
b) Incidence of bronchiolitis obliterans occurs primarily early during post-transplant course
c) Diagnosis of bronchiolitis obliterans requires additional findings of air trapping on chest CT and/or evidence of air trapping by PFTs if no other evidence of cGVHD is present
d) Bronchiolitis obliterans is associated with better non-relapse mortality than late acute GVHD
Audience Response Questions

Question #2:

—The combination of prednisone and FAM (fluticasone, azithromycin, montelukast) represents a standard first-line therapy approach for BOS:

a) True
b) False
Audience Response Questions

Question # 3:

—Important components of advanced BOS management include which of the following:

a) Careful selection of therapeutic agents based on risk/benefit profile and patient-specific considerations
b) Prevention and treatment of infectious complications
c) Serial monitoring of pulmonary function
d) Referral for lung transplant consultation
e) All of the above