Current State and Advances in Chronic GVHD

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Overview

• Current status:
  • Primary treatment
  • Second line agents

• What drug and when?

• Long-term Impact of chronic GVHD
Chronic GVHD incidence and limited treatment options

- Chronic GVHD commonly affects 30-50% of allogeneic HCT recipients
- Less than 20% will achieve a CR or PR without requiring secondary therapy within 1 YR of diagnosis
- Most patients will require years of treatment; average 2-3 years
- 3 FDA approved agents available for second line treatment of chronic GVHD
  - Ibrutinib, Ruxolitinib, Belumosudil
- Morbidity and mortality in patients needing second or further lines of therapy remains high
- Patients with with sclerosis and lung involvement are difficult to treat and associated with worse outcomes
- Development of novel agents to treat chronic GVHD remains an unmet medical need
Atypical Chronic GVHD Organs and Manifestations

- **CNS**
  - Cognitive Deficits,
  - Meningoencephalitis,
  - Demyelinating diseases,
  - CNS vasculitis*

- **PNS**
  - Neuropathy,
  - Myasthenia gravis

- **LUNGS**
  - COP²,
  - Non-specific Interstitial Pneumonia³,
  - PPFE⁴

- **SERO/SISIS**
  - Pericardial effusion*,
  - Pleural effusion*,
  - Ascites*

- **RENAL**
  - Proteinuria*,
  - Nephrotic Syndrome*,
  - Tubular, Glomerular,
  - or Interstitial disease*,
  - Vascular disease*

- **MSK**
  - Edema,
  - Muscle cramps,
  - Arthralgia,
  - Arthritis,
  - Myositis

- **IMMUNE MEDIATED CYTOPENIAS**
  - AIHA, ITP, AIN

NIH Defined Chronic GVHD Target Organs and Manifestations

- **EYES**
  - Dry eyes,
  - Keratoconjunctivitis sicca,
  - Punctate Keratopathy

- **MOUTH**
  - Lichen Planus-Like Features
  - Ulcers, Xerostomia

- **LUNGS**
  - Bronchiolitis Obliterans
  - Bronchiolitis Obliterans Syndrome

- **GI**
  - Esophageal web,
  - Stricture or stenosis

- **GU**
  - Lichen Planus or Lichen Sclerosus-Like Features
    - Females: Vaginal Scarring or Clitoral/Labial Agglutination
    - Males: Phimosis or Urethral/Meatus Scarring or Stenosis

- **SKIN**
  - Poikiloderma, Sclerotic Features, Lichen-Planus, Morphea,
  - or Lichen-Sclerosus-like Features
  - Depigmentation, Papulosquamous Lesions

- **MSK**
  - Fasciitis, Joint Stiffness, or Contractures due to fasciitis or sclerosis

Goals of Treatment for Chronic GVHD

<table>
<thead>
<tr>
<th>Goal</th>
<th>Clinical considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control current signs and symptoms</td>
<td>How bothersome are symptoms?</td>
</tr>
</tbody>
</table>

tox = toxicity; Rx = Treatment.
First Line Treatment

Corticosteroids

- Textbook starting dose 1 mg/kg/day
- No significant benefit to add additional agents up front
- Only 40-50% response rate
- > 50% require second-line therapy within 2 years
- Broadly immunosuppressive
- Abundant side effects: Infection, myopathy, edema, cataracts, hyperglycemia, bone density loss, avascular necrosis, sleep/mood disturbances

- Prednisone only – 411 (55%)
- Prednisone + other – 194 (27%)
  - Of those on prednisone ~55% on doses > 0.74 mg/kg/d
- Non-prednisone – 137 (18%)
## NCCN Guidelines: Steroid-Refractory Chronic GVHD

### Recommendations

Those in **bold** are FDA approved for ages ≥12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib (category 1)</td>
<td>Ibrutinib [approved ages ≥1]</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Interleukin-2 (IL-2)</td>
</tr>
<tr>
<td><strong>Belumosudil</strong></td>
<td>Low-dose methotrexate</td>
</tr>
<tr>
<td>Calcineurin inhibitors (eg, tacrolimus, cyclosporine)</td>
<td>mTOR inhibitors (eg, sirolimus)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Extracorporeal Photopheresis (ECP)</td>
<td>Pentostatin</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Rituximab</td>
</tr>
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All recommendations cat 2A unless indicated otherwise. 
FDA Approved Agents

All approved for steroid refractory cGVHD

- Ibrutinib
- Ruxolitinib
- Belumosudil
Ibrutinib for SR-cGvHD: *Phase 1b/2 Design*

Patients with steroid-dependent/refractory cGvHD
- > 25% BSA "erythematous rash" or
- > 4 total mouth score
- N = 42

Ibrutinib 420 mg until cGvHD progression or unacceptable toxicity

Primary Endpoint:
cGvHD Response per NIH 2005 Consensus Response Criteria

BSA, body surface area.
Ibrutinib for SR-cGVHD

• Ibrutinib: TKI targeting and impeding activation of B and T cells (binds and inhibits Btk and Itk)
• Phase 1b/2 open-label multi-center study of ibrutinib in steroid-refractory cGVHD who failed ≥1 therapy, leading to FDA approval of ibrutinib

REACH 3: Ruxolitinib vs BAT

- Ruxolitinib: JAK1/2 inhibitor; JAK/STAT system is downstream of 50+ cytokine receptors
- Phase 3 open-label randomized trial, in steroid-refractory or dependent cGVHD who failed ≥1 therapy

**ORR at 24 weeks**

<table>
<thead>
<tr>
<th></th>
<th>RUX (n=165)</th>
<th>BAT (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR PR</td>
<td>43.0</td>
<td>25.6</td>
</tr>
<tr>
<td>OR</td>
<td>2.99 (95% CI, 1.86-4.80)</td>
<td>2.62 (95% CI, 1.42-4.82)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>0.0011</td>
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**Improvement in Lee Symptom Scale**

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<tbody>
<tr>
<td>OR</td>
<td>24.2</td>
<td>11.0</td>
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Zeiser R et al. NEJM. 2021
Rux vs BAT: Failure-free Survival

Zeiser et al. NEJM. 2021
ROCKstar: Pivotal Trial of Belumosudil (KD025) in cGVHD

- Phase 2 open-label, in steroid-refractory or dependent cGVHD who failed 2-5 lines of therapy

**ORR**

<table>
<thead>
<tr>
<th>KD025 200 mg QD (n=66)</th>
<th>KD025 200 mg BID (n=66)</th>
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<tr>
<td>73% (95% CI: 60%, 83%)</td>
<td>77% (95% CI: 65%, 87%)</td>
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**Median duration of response** = 50 weeks

Cutler et al. Blood. 2021
What Drug and When?

- Current strategies typically rely on availability of clinical trials and physician preference (trial and error)
- All steroid refractory cGVHD is not the same
- Ideal state
  - Biologically driven selection
  - Consideration for toxicity profile
  - Biomarkers may help better define clinical and biologic phenotype
What else do I need to worry about when treating GVHD?

**QOL and Function**
- Physical health
- Functional status
- Social wellbeing
- GVHD specific symptoms
- Overall QOL

**Psychological Distress**
- Screening for psychological distress
- Depression
- Anxiety
- Post-traumatic stress
- Prognostic uncertainty
- Existential distress
- Demoralization

**Maximal Supportive Care**
- Multidisciplinary management
- Maximal topical therapy to alleviate GVHD symptoms
- Infection prophylaxis
- Vaccinations

GvHD
Treatment-Induced Damage

- Immune deficiency
- Cataracts
- Chronic kidney injury
- Steroid-induced diabetes
- Dyslipidemia
- Steroid myopathy
- Adrenal insufficiency
- Osteoporosis
- Neuropathy
- Poor wound healing
- Second malignancies/PTLD

Questions?