Allogeneic Transplant Going Beyond 180 days

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Leukemia, Transplant and Immunotherapy
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Estimated Annual Number of HCT Recipients in the US by Transplant Type

- Autologous HCT
- Allogeneic HCT

Number of Transplants


Values:
- Autologous HCT: 0, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 11000, 12000, 13000, 14000, 15000, 16000
- Allogeneic HCT: 0, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 11000, 12000, 13000, 14000, 15000, 16000
Risk Factors/Predisposing Factors for Chronic GVHD

- Prior Acute GVHD
  • Grades 3-4

- HLA disparity: incidence and severity \( \uparrow \) with \( \rightarrow \) disparity
  • HLA matched related donor
  • HLA matched unrelated donors
  • HLA mismatched related donors
  • HLA mismatched unrelated donors

- Stem cell source
  • Transplanted with peripheral blood stem cells \( > \) Bone Marrow

- Older patient age

- Older donor age

- Donor Infusion Lymphocytes (DLI)

- Sex mismatching- ie. male and received cells from a female

- Conditioning intensity
  • Myeloablative (MAC) \( > \) Reduced Intensity (RIC)/Non-Myeloablative (NMA)
Defining GVHD

• Donated Stem Cells that are transplanted also contain T-Cells from the donor
• Benefit of donor T-Cells
  • “Graft-versus-tumor effect”
• Graft attacks Host
Spectrum of manifestations in chronic GVHD

- Infections
- Disability
- Quality of life
- Endocrine
- Metabolism
- Nutrition
- Pain

- Ocular sicca
- Oral ulcers
- Nail dystrophy
- Skin sclerosis
- Deep sclerosis
- Bronchiolitis obliterans
- Loss of bile ducts
- Fasciitis
- Skin ulcers
How to Measure Outcomes When Survival or Remission are Not Adequate Endpoints?

Disease

Death $\iff$ Symptoms $\rightarrow$ Remission $\rightarrow$ Cure

Lungs
Eyes
Skin

Function $\leftrightarrow$ Quality of life
Despite commendable progress, the algorithm for the selection of the appropriate systemic therapy for cGVHD has remained unchanged since the 1980s.

Systemic treatments for cGVHD still suffer from some major limitations. There is an urgent need to develop frontline treatment regimens that involve minimal or no use of corticosteroids.

Working Group 4 reviewed highly morbid forms of cGVHD, such as lung, skin sclerosis, and ocular disease, that pose a special challenge due to their rare and uncooperative nature.
**Staging (Grading)/ Classification**

<table>
<thead>
<tr>
<th>PERFORMANCE</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCORE:</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>KPS</strong></td>
<td>ECOG 100%</td>
<td>ECOG 70%</td>
<td>ECOG 50%</td>
<td>ECOG 30%</td>
</tr>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SCORE % BSA</strong></td>
<td>0%</td>
<td>1-18% BSA</td>
<td>19-50% BSA</td>
<td>&gt;50% BSA</td>
</tr>
<tr>
<td><strong>Check all that apply:</strong></td>
<td>Maculopapular rash/erythema</td>
<td>Lichen planus-like features</td>
<td>Sclerotic features</td>
<td>Pemphigus lesions or ichthyosis</td>
</tr>
<tr>
<td><strong>SKIN FEATURES</strong></td>
<td>No sclerotic features</td>
<td>Superficial sclerotic features</td>
<td>“not hidebound” (able to pinch)</td>
<td>Deep sclerotic features</td>
</tr>
<tr>
<td><strong>SCORE:</strong></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Other skin GvHD features (NOT scored by BSA):</strong></td>
<td>Hyperpigmentation</td>
<td>Hyperpigmentation</td>
<td>Severe or generalized pruritus</td>
<td>Hair involvement</td>
</tr>
</tbody>
</table>

**Abnormality present but explained entirely by non-GvHD documented cause (specify):**

**EYES**
- No symptoms
- Mild dry eye symptoms
- Moderate dry eye symptoms partially affecting ADL
- Severe dry eye symptoms significantly affecting ADL (specail eyecare to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS

**Eyes Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:**
- Yes
- No
- Not examined

**GI Tract**
- No symptoms
- Symptoms without significant weight loss
- Symptoms associated with moderate diarrhea
- Symptoms associated with significant weight loss

**Check all that apply:**
- Esophageal web/ proximal stricture or ring
- Dysphagia
- Anorexia
- Nausea
- Vomiting
- Diarrhea

**Diarrhea**
- Weight loss ≥5%
- Failure to thrive

**LIVER**
- Normal total bilirubin and ALT or AP < 3 x ULN
- Elevated total bilirubin and ALT > 5 ULN

**Lungs**
- No symptoms
- Mild symptoms (shortness of breath after climbing one flight of steps)
- Moderate symptoms (shortness of breath at rest; requiring O2)

**Lung Score:**
- FEV1 ≥80%
- FEV1 60-79%
- FEV1 40-59%
- FEV1 ≤39%

**Pulmonary function tests**
- Not performed

**Abnormality present but explained entirely by non-GvHD documented cause (specify):**
# Staging (Grading)/Classification

<table>
<thead>
<tr>
<th>JOINTS AND FASCIA</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-ROM score</td>
<td>No symptoms</td>
<td>Mild tightness of arms or legs, normal or mild decreased range of motion (ROM)</td>
<td>Tightness of arms or legs OR joint contractures, asthenia thought due to fascitis, moderate decrease in ROM AND mild to moderate limitation of ADL</td>
<td>Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, put on pants, dress self etc.)</td>
</tr>
<tr>
<td>(Include below)</td>
<td></td>
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</tr>
<tr>
<td>Shoulder (1-7):</td>
<td></td>
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<tr>
<td>Elbow (1-7):</td>
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<tr>
<td>Wrist/finger (1-7):</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ankle (1-4)*</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Abnormality present but explained entirely by non-GVHD documented cause (specify):**

<table>
<thead>
<tr>
<th>GENTIAL TRACT</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signs</td>
<td>Mild signs and females with or without discomfort on exam</td>
<td>Moderate signs and may have symptoms with discomfort on exam</td>
<td>Severe signs with or without symptoms</td>
<td></td>
</tr>
</tbody>
</table>

*Not examined*
| Currently sexually active | Yes | No |

**Abnormality present but explained entirely by non-GVHD documented cause (specify):**

## Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity 0-3 based on functional impact where applicable none - 0, mild - 1, moderate - 2, severe - 3)

<table>
<thead>
<tr>
<th>Asches (serositis)</th>
<th>Myalgia</th>
<th>Gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial Effusion</td>
<td>Peripheral Neuropathy</td>
<td>Eosinophilia &gt; 500/μL</td>
</tr>
<tr>
<td>Pulmonary Effusion</td>
<td>Polymyositis</td>
<td>Platelets &lt; 100,000/μL</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Weight loss &gt; 5%* without GI symptoms</td>
<td>Others (specify)</td>
</tr>
</tbody>
</table>

## Overall GVHD Severity

| Decision of the evaluator | None (GVHD) | Mild | Moderate | Severe |

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*Photographic Range of Motion (P-ROM)*

† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months

** Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status), BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

† To be completed by specialist or trained medical providers (see Supplemental Figure).
### NIH Clinical and Global Scoring System for cGVHD

<table>
<thead>
<tr>
<th>Severity of cGVHD</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Mild cGVHD**    | • Involves only 1 or 2 organs/sites (EXCEPT lung)  
• no clinically significant functional impairment  
• maximum score of 1 in all affected organs/sites |
| **Moderate cGVHD** | • Involves at least 1 organ/site  
• with clinically significant but no major disability  
• maximum score of 2 in any affected organ/site OR  
• 3 or more organs/sites  
• with no clinically significant functional impairment  
• maximum score of 1 in all affected organs or sites  
• A lung score of 1 will also be considered moderate cGVHD |
| **Severe cGVHD**  | • Indicates major disability caused by cGVHD - score of 3 in any organ or site.  
• A lung score of $\geq 2$ will also be considered severe cGVHD |

- Skin: higher of 2 scores (BSA and skin features) used  
- Lung: FEV1 is used instead of clinical score

LUNG: Bronchiolitis Obliterans Syndrome (BOS)

- **Incidence**: 10-15% - most common late non-infectious pulmonary complication after HCT
- **Onset**: insidious rather than abrupt
- **Presenting symptoms**: nonproductive cough, dyspnea, and wheezing
  - Fever uncommon
- **Image**: CXR -> commonly normal
  - High-resolution CT -> demonstrates evidence of air trapping and bronchial dilatation
- **Pathogenesis (manner of disease development)**
  - Immune attack of small airways
  - Fibrotic occlusion, destruction of lung tissue
- **Diagnosis**: persistent airflow obstruction on simple spirometry and exclusion of other causes (e.g., viral bronchiolitis, asthma).
  - BAL: broncheoalveolar washing
  - Early Detection is the key for successful treatment
Patients with pulmonary GVHD often do not have symptoms until the disease has progressed. Periodic pulmonary function tests are the best way to catch lung GVHD and begin treatment early, before the symptoms become severe.
BOS Treatment Options

- Systemic Steroids
- Calcineurin Inhibitors (tacrolimus, cyclosporine)
- FAM+LABA
  - Fluticasone/Budesonide (inhaled corticosteroid)
  - Azithromycin
  - Montelukast (singular®)
  - LABA: long-acting beta-agonist
- Extracorporal Photopheresis
- Rituximab weekly x4 then once every 12 weeks
Supportive Care for BOS

• Multi-Disciplinary Care Team: (BMT, Pulmonary, ID)
  • Infection Prophylaxis
  • Treatment of recurrent respiratory/sinus infections
  • Vaccinations
  • Pulmonary rehabilitation
  • Supplemental oxygen
  • IVIG
  • GERD therapy
  • Psychosocial support
Ocular GVHD

- **Incidence:** Approximately 40% to 60% of patients with systemic chronic GVHD will develop ocular disease
- **Onset:** Typically within first 2 years of transplant
- **Presenting Symptoms:**
  - Dry eye disease is a hallmark sign
  - Gritty or painful eyes
  - Blurred vision
  - Photophobia
  - Redness
  - Burning sensation
  - Mucoid secretions
  - Excessive tearing
  - Foreign body sensation
- **Pathogenesis (manner of disease development):**
  - Immune attack from donor cells on conjunctiva
  - Conjunctiva is the thin, clear membrane that covers the eye
  - Tear glands located in lacrimal glands are attacked
- **Diagnosis:**
  - Complete ocular history
  - Medication history
  - Schirmer testing
  - Co-managed with Ophthalmologist (r/o cataracts)
Ocular GVHD Treatment
Topical Treatment

Lubricants
  ● Artificial tears/ointment
    ● Refresh PM/Systane nighttime/Genteal ointment or gel
  ● Preservative-free when utilizing >QID

Corticosteroids
  ● Lotemax, Flurometholone, dexamethasone/trobradex (antibiotic)
  ● Start QID for 3-4 weeks followed by slow taper
  ● provide high ocular surface drug concentrations and are able to promote lymphocyte apoptosis and suppress cell mediated inflammation
  ● Monitor closely for increased intra-ocular pressure, cataract, corneal thinning, and infectious keratitis

Cyclosporine A
  ● Restasis 0.05%, Compounded 1%
  ● Dosed two (or more) times daily (Restasis: 4-8x, Cyclo 1%: 4x)
  ● Reduces inflammation, via inhibition of T-cell activation and down-regulation of inflammatory cytokines in the conjunctiva and lacrimal gland → allow enhanced tear production

Lifitegrast 5% (Xiidra)
  ● Dosed twice daily
  ● Reduces inflammation via blocking the binding of surface proteins lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1)
Ocular GVHD Treatment continued

Serum tears

- 50% - 100% serum
- Dosed 4-8 times daily
- Serum contains several anti-inflammatory factors that have the capability to inhibit soluble mediators of the ocular surface inflammatory cascade of dry eye

Tacrolimus (Protopic™)

- Available in 0.03% and 0.1% ointment (applied externally to eyelids) and compounded drops and systemically
- Inhibits T and B lymphocyte activation
- Also suppresses immune response by inhibiting the release of other cytokines
Ocular GVHD Treatment continued

• Punctal occlusion
  • Collagen or Silicone / Cauterization
  • Use of anti-inflammatory prior to occlusion
Ocular GVHD Treatment continued

- Prosthetic lens custom designed and fabricated
- Supports and protects the ocular surface system
- Creates a smooth optical surface over the irregular, damaged or diseased cornea
- Expanded artificial tear reservoir provides constant lubrication while maintain necessary oxygen supply
Skin Chronic GVHD

- **Incidence:** 80% of patients who develop chronic GVHD have some skin involvement

- **Onset:**

- **Presenting Symptoms:**
  - Epidermis - rash, hyperpigmentation, redness
  - Dermis - sweat glands, hair follicles, nail beds
  - Subcutaneous layer - deeper layers, scar tissue, skin tightening, fibrotic
  - Joint

- **Pathogenesis (manner of disease development):**

- **Diagnosis:**
  - Assessment of body surface area
  - Skin biopsy
  - Range of motion
Skin GVHD Treatment- Localized Topical Therapy

- Topical Steroids
  - Hydrocortisone 1% cream/ointment: face – Low potency
  - Clobetasol 0.5 cream-moderate potency
  - Triamcinolone 0.1% cream/ointment: body- high potency
- Emollients after steroids
- Tacrolimus/pimecrolimus cream-lips/genitals
- Phototherapy
  - UVA or UVB
- Message and Physical Therapy
- Extracorporeal Photopheresis- ECP
Skin GVHD Treatment - Beyond Topicals

- Systemic Steroids
- Calcineurin Inhibitors (tacrolimus, cyclosporine)
Second-Third Line Chronic GVHD Treatments

- After corticosteroid failure, no current consensus on optimal second-line treatment choice
- FDA Approved Drugs for second/third line
  - Ibrutinib- Imbruvica™
  - Belumosodil- Rezurock™
  - Ruxolinib- Jakafi™
- Many retrospective and prospective studies suggest high response rates with other second-line treatment options
  - Results are hard to interpret, often because of suboptimal study designs ie Small sample size
- Treatment choices are based on:
  - Physician experience, ease of use, need for monitoring, risk of toxicity
Ibrutinib: Phase II Trial in Chronic GVHD After Failure of Corticosteroids

- **Primary endpoint:** chronic GVHD response per NIH 2005 response criteria
- **ORR:** 67%

Patients with steroid-dependent/refractory chronic GVHD (> 25% BSA “erythematous rash” or > 4 total mouth score) (N = 42)

Ibrutinib 420 mg

Until chronic GVHD progression or unacceptable toxicity

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
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<tr>
<td>60</td>
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<tr>
<td>40</td>
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<tr>
<td>20</td>
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<tr>
<td>0</td>
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</tbody>
</table>

Best Chronic GVHD Response (N = 42)

Ibrutinib: Phase II Trial in Chronic GVHD After Failure of Corticosteroids

Study 1129
IMBRUVICA® 420 mg (N=42)
Median duration of exposure: 4.4 months

<table>
<thead>
<tr>
<th>Treatment-emergent hematologic laboratory abnormalities in the 1129 cGVHD trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Platelets decreased</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
</tr>
</tbody>
</table>

The ability to dose modify may help manage adverse events
If an AR listed below occurs, the IMBRUVICA® dose should be modified:
- Grade 3 or 4 non-hematologic toxicities, Grade 3 or 4 neutropenia with infection or fever, or Grade 4 hematologic toxicities

START at approved dose

CGVHD 420 mg

1ST OCCURRENCE
Interrupt until improvement to Grade 1 or baseline
RESUME 1 at starting dose 420 mg

2ND OCCURRENCE
Interrupt until improvement to Grade 1 or baseline
RESTART 2 at 280 mg

3RD OCCURRENCE
Interrupt until improvement to Grade 1 or baseline
RESTART 3 at 140 mg

4TH OCCURRENCE
DISCONTINUE
If adverse reaction persists or reoccurs following 2 dose reductions

For use with CYP3A inhibitors and inducers, and in patients with hepatic impairment, please see the full Prescribing Information. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

AR=Adverse reaction, cGVHD=chronic graft versus host disease, CYP3A=Cytochrome P450, Family 3, Subfamily A.
REACH3 Was a Randomized, Open-label, Multicenter, Phase 3 Study of Jakafi® (ruxolitinib) vs BAT in Patients With Steroid-Refractory cGVHD

**REACH3 Study Design**

- Steroid-Refractory cGVHD
  - N = 329

**Inclusion Criteria**

- Age 12 and older
- Allogeneic stem cell transplant from any donor source and donor type
- Steroid-refractory/dependent cGVHD per NIH consensus criteria (moderate or severe)
- Evident myeloid and platelet engraftment

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REACH3 was a randomized, open-label, multicenter, Phase 3 study of Jakafi® (ruxolitinib) vs BAT in patients with steroid-refractory cGVHD.


**REACH3 Subgroup Analysis: ORR by Baseline Disease Severity at Week 24**

- **Moderate**: OR = 3.05 (95% CI: 1.59, 5.84)
  - Jakafi: 59.5% (47/79)
  - BAT: 10.1% (8/79)
  - CR: 49.4% (39/80)
  - PR: 3.8% (3/80)

- **Severe**: OR = 2.92 (95% CI: 1.46, 5.84)
  - Jakafi: 40.7% (39/96)
  - BAT: 19.0% (16/94)
  - CR: 37.2% (35/96)
  - PR: 3.5% (3/86)

**59.5% of patients with moderate cGVHD at baseline had an overall response with Jakafi at Week 24 vs 32.5% with BAT.**
Belumosudil-Rezurock™ in Chronic GVHD patients after failure of ≥ 2 prior lines of systemic therapy

**Eligibility criteria**
- Aged ≥12 years
- Underwent an HCT
- Had active cGVHD
- Received 2 to 5 prior lines of systemic therapy for cGVHD
- Systemic therapy for cGVHD was indicated

**Stratification factors**
- Prior ibrutinib (Y/N)
- Severe cGVHD (Y/N)

**Open label**

- **ARM A:** REZUROCK 200 mg once daily (n=66)
- **ARM B:** REZUROCK 200 mg BID (n=66)

**Primary end point**
- Best ORR at any time, according to the 2014 NIH cGVHD Consensus Criteria

**Key secondary end points**
- Safety
- DOR
- TTR
- LSS summary score
- CS and CNI doses
- FFS
- OS

Treat to clinically significant progression or unacceptable toxicity
Belumosudil-Rezurock™ in Chronic GVHD patients after failure of ≥ 2 prior lines of systemic therapy

Other Second Line Agents Worth Mentioning

Extracorporeal Photopheresis - ECP

- ORRs of 50 to 65 percent (approximately 30 to 35 percent complete)
- 25 to 35 percent of patients were able to significantly taper steroid use.
- Responses were less likely in patients with more extensive disease, those with a history of acute GVHD, and patients with thrombocytopenia
- Contraindicated in patients with severe cardiovascular or renal impairment
Other Second Line Agents Worth Mentioning

- **Rituximab-Rituxan™**
  - Administered weekly for 4 weeks
  - SE: Hepatitis B reactivation
  - Appears to be especially beneficial for skin, oral and musculoskeletal involvement
  - Rituximab is FDA approved for treatment of rheumatoid arthritis.

- Clinical responses were reported in 86 percent of 37 patients with SR-cGVHD
  - Most responses were maintained at one year
  - Reductions of glucocorticoid dose in 57 percent of patients.

Invitation:
Dr Noa Holtzman from the National Institute of Health will present in another webinar on “The Importance of New GVHD Treatments” in January of 2022, date to be determined. Visit nbmtlink.org (see home page) for more info soon.