Symptoms, Functional Status and Altered Immunity in Survivors of Allogeneic Hematopoietic Stem Cell Transplantation with Chronic Graft-Versus-Host Disease (GVHD)

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Strengthening the Evidence Base for Cancer Rehabilitation and Survivorship Care

- Identify new knowledge that improves rehabilitation outcomes
- Disseminate that knowledge to healthcare professionals, patients, advocacy groups, and policy makers
- Develop and test interventions to improve self-management in stem cell transplant survivors with chronic GVHD
Chronic Graft-Versus-Host Disease (GVHD)

- Chronic GVHD affects 33%-80% of individuals who survive more than 100 days after allogeneic stem cell transplant
- Disease of immune dysregulation
- Immunosuppressive agent(s), together with good supportive management, are the mainstays of treatment
- Course is variable:
  - May persist, requiring immunosuppression for up to 20+ years following transplantation
  - In some instances GVHD appears to dissipate gradually and immunosuppression can be tapered to discontinuation
- Lower relapse rate, presumably because of a graft-versus-tumor effect
- Chronic GVHD is a leading cause of non-relapse mortality and serious morbidity
Spectrum of Manifestations of Chronic GVHD

- Ocular sicca
- Oral ulcers
- Nail dystrophy
- Skin sclerosis
- Deep sclerosis
- Bronchiolitis obliterans
- Loss of bile ducts
- Fasciitis
- Skin ulcers
Functional and Symptomatic Co-Morbidities of Chronic GVHD

- Infections
- Pulmonary impairment
- Endocrinopathies
- Arthralgias/myalgias/fasciitis/contractures
- Oral/dental complications
- Nutritional compromise
- Side effects of chronic immunosuppression
- Functional disability
- Distressing symptoms
- Body image changes
- Psychosocial distress
- Adjustment difficulties associated with chronicity
Strengthening the Evidence Base for Survivorship Care

Challenges in Studying Chronic GVHD:

- Challenges in studying chronic GVHD:
  - Heterogeneous, multi-system manifestations
  - Multi-morbidity
  - Management is complex, chronically ill with acute exacerbations
Symptoms and Functional Status in Chronic GVHD- State of the Knowledge

- No prior studies have characterized the symptom experience and functional consequences in a cohort comprised *exclusively* of allogeneic HSCT survivors experiencing chronic GVHD.

- General studies of late effects following allogeneic stem cell transplantation suggest chronic GVHD may have deleterious effects on:
  - Symptoms
  - Function
  - Quality of Life

- Distinct pro-inflammatory biologic profiles have been associated with chronic GVHD; prior studies have not examined their association with symptoms.
Symptoms, Functional Status and Altered Immunity in Allogeneic HSCT Survivors with Chronic GVHD

- Characterize chronic GVHD symptom bother and functional performance
- Explore the determinants of functional performance
- Derive symptom bother subgroups through latent profile analysis
- Determine if distinct chronic GVHD symptom profiles are also distinguished by unique patterns of cytokine expression
Design and Methods

- Cross-sectional, descriptive/correlational study
- Sample (n=100)
  - Older than 18
  - Literate in English or Spanish
  - At least 100 days status post allogeneic HSCT
  - Diagnosis of chronic GVHD established through clinical signs and/or tissue biopsy of one or more organ systems
Measures

• **Symptom Bother**
  ▫ Lee Chronic GVHD Symptom Scale

• **Functional Performance**
  ▫ Medical Outcomes Study Short Form-36 (SF-36 v.2)

• **Functional Capacity**
  ▫ 2 Minute Walk Distance, Grip Strength, Range of Motion

• **Immunological Parameters**
  ▫ Plasma cytokine expression by sandwich ELISA
  ▫ Lymphocyte subsets by flow cytometry

• **Demographic and Clinical Characteristics**
Results
Sample Characteristics (N=100)

- Median age of 47 years (range 20-66 years)
- 42% working or attending school full-time
- 3.5 years post-transplant
- Living with chronic GVHD for mean of 3 years (range of 1 month to 16 years)
- 75% on moderate or high levels of immunosuppression
- Median of two comorbidities:
  - osteoporosis (48%)
  - depression (39%)
  - peripheral neuropathy (34%)
  - GERD (21%)
Functional Performance

Normed SF-36 Scores (Mean and SD)

- Physical Component Summary Score: 36.8
- Physical Function: 38.8
- Role Physical: 37.9
- Bodily Pain: 43.8
- General Health: 36.2
- Vitality: 45.6
- Social Function: 40.2
- Role Emotional: 45.2
- Mental Health: 48.5
## Predictors of Functional Performance

<table>
<thead>
<tr>
<th>Block</th>
<th>Variables in the model</th>
<th>β</th>
<th>Adj. R²</th>
<th>R²Δ</th>
<th>F Δ</th>
<th>t</th>
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<tbody>
<tr>
<td>1</td>
<td>Demographic</td>
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<td>0.01</td>
<td>0.1</td>
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<td>Age</td>
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<td></td>
<td></td>
<td>0.1</td>
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<tr>
<td></td>
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<td></td>
<td>-0.2</td>
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<tr>
<td>2</td>
<td>Treatment</td>
<td></td>
<td>0.2</td>
<td>0.3</td>
<td>10.2**</td>
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<tr>
<td></td>
<td>cGVHD severity</td>
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<td></td>
<td>-1.6</td>
<td></td>
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<tr>
<td></td>
<td>Intensity immunosupp.</td>
<td>-0.2</td>
<td></td>
<td></td>
<td>-2.2*</td>
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<tr>
<td></td>
<td>Time since cGVHD Dx</td>
<td>0.1</td>
<td></td>
<td></td>
<td>0.7</td>
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<tr>
<td>3</td>
<td>Comorbidity</td>
<td>-0.1</td>
<td>0.3</td>
<td>0.1</td>
<td>14.0**</td>
<td>-1.6</td>
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<tr>
<td>4</td>
<td>Functional capacity</td>
<td>0.5</td>
<td>0.1</td>
<td></td>
<td>5.7**</td>
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<td></td>
<td>Dist. walked in 2 min</td>
<td>0.4</td>
<td></td>
<td></td>
<td>4.6**</td>
<td></td>
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<td></td>
<td>Grip strength</td>
<td>0.01</td>
<td></td>
<td></td>
<td>0.1</td>
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<td></td>
<td>Upper body ROM</td>
<td>-0.1</td>
<td></td>
<td></td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower body ROM</td>
<td>0.1</td>
<td></td>
<td></td>
<td>0.4</td>
<td></td>
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<tr>
<td>5</td>
<td>Symptom bother</td>
<td>-0.4</td>
<td>0.55</td>
<td>0.1</td>
<td>17.2**</td>
<td>-4.1**</td>
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</tbody>
</table>

Model adjusted $R^2 = 0.55$; $F = 10.72$; $p < .001$

** $p < .01$  * $p < .05$
Intensity of Immunosuppression

Functional Capacity (2 min walk)

Symptom Bother (Lee Symptom Scale)

Functional Performance (PCS)

Mitchell et al. Determinants of Functional Performance in Long-Term Survivors of Allogeneic Hematopoietic Stem Cell Transplantation with Chronic Graft-Versus-Host Disease. Submitted to *Bone Marrow Transplantation*. 
Functional Capacity Partially Mediates the Relationship Between Chronic GVHD Symptom Bother and Functional Performance

Intensity of Immunosuppression

Adjusted $R^2=0.09$

$F=5.5$

$p<.01$

-3.3 $^{a} (0.99)^{b}$

Functional Capacity (2 min walk)

Symptom Bother (Lee Symptom Scale)

Adjusted $R^2=0.55$

$F=37.66$

$p<.001$

0.04 $^{a} (0.006)^{b}$

Adjusted $R^2=0.38$

$F=30.2$

$p<.001$

-0.45 $^{a} (0.06)^{b}$

Functional Performance (PCS)

$^{a}$ Raw coefficient ($\beta$)

$^{b}$ Standard error of raw coefficient ($\beta$)
Chronic GVHD Symptom Prevalence and Bother

Prevalence

Bother

- Use Eye Drops Frequently: 64
- Dry Eyes: 54
- Thickened Skin: 53
- Avoid Foods Due to Mouth Pain: 49
- Weak Muscles: 46
- Loss of Energy: 45
- Joint and Muscle Aches: 44
- Difficulty Seeing Clearly: 43
- Abnormal Skin Color: 43
- Short of Breath with Exercise: 41

Chronic GVHD Symptom Bother (Percent)
# Chronic GVHD Symptom Bother

<table>
<thead>
<tr>
<th>Clinician Rated Severity of cGVHD</th>
<th>Number of Highly Bothersome Symptoms Median (Range)</th>
<th>cGVHD Symptom Bother (linearly transformed to 0-100 scale) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild cGVHD</td>
<td>4 (0-12)</td>
<td>27.84 (12.23)</td>
</tr>
<tr>
<td>Moderate cGVHD</td>
<td>5 (0-13)</td>
<td>25.73 (12.42)</td>
</tr>
<tr>
<td>Severe cGVHD</td>
<td>6 (0-18)</td>
<td>33.75 (14.63)</td>
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</table>

<table>
<thead>
<tr>
<th>Intensity of Immunosuppression</th>
<th>Number of Highly Bothersome Symptoms Median (Range)</th>
<th>cGVHD Symptom Bother (linearly transformed to 0-100 scale) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4 (0-12)</td>
<td>26.20 (14.11)</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (1-9)</td>
<td>25.15 (5.15)</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (0-18)</td>
<td>29.52 (13.43)</td>
</tr>
<tr>
<td>High</td>
<td>4.5 (0-17)</td>
<td>29.41 (14.80)</td>
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</table>

<table>
<thead>
<tr>
<th>Comorbid Conditions</th>
<th>Number of Highly Bothersome Symptoms Median (Range)</th>
<th>cGVHD Symptom Bother (linearly transformed to 0-100 scale) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4 (0-4)</td>
<td>18.49 (9.70)</td>
</tr>
<tr>
<td>1-2</td>
<td>5 (0-14)</td>
<td>25.32 (10.87)</td>
</tr>
<tr>
<td>3-4</td>
<td>5.5 (0-17)</td>
<td>31.26 (15.39)</td>
</tr>
<tr>
<td>5 or more</td>
<td>9 (0-18)**</td>
<td>37.36 (12.57) **</td>
</tr>
</tbody>
</table>

**p < .01 or *p < .05 after Bonferroni correction for multiple comparisons**
Knowledge of symptoms clustering together can inform symptom management

Latent class analysis uses mixture modeling with maximum likelihood estimation algorithms to identify groups of individuals who are similar

Discern homogeneous subgroups within a heterogeneous population
### Latent Class Analysis

<table>
<thead>
<tr>
<th>Number of Classes</th>
<th>-2 Log Likelihood</th>
<th>No. of Parameters</th>
<th>BIC</th>
<th>aBIC</th>
<th>Entropy</th>
<th>VLMR-LRTp</th>
<th>aLRTp</th>
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<tr>
<td>1</td>
<td>-1121.597</td>
<td>8</td>
<td>2280</td>
<td>2255</td>
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<td>2</td>
<td>-1061.530</td>
<td>17</td>
<td>2201</td>
<td>2148</td>
<td>0.814</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<td>3</td>
<td>-1026.592</td>
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<td>2173</td>
<td>2091</td>
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<td>-1004.544</td>
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<td>2170</td>
<td>2060</td>
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<td>.137</td>
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<tr>
<td>5</td>
<td>-988.273</td>
<td>44</td>
<td>2179</td>
<td>2040</td>
<td>0.873</td>
<td>.284</td>
<td>.323</td>
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</table>

Mitchell et al. Symptom Bother in Adult Survivors of Hematopoietic Stem Cell Transplantation with Chronic Graft-versus-Host Disease (GVHD): A Latent Class Analysis. Submitted to *Journal of Cancer Survivorship*
Low on all symptoms

Prominent oral and upper GI symptoms

Prominent eye, muscle/joint, fatigue and mood symptoms

BIC = 2168, aBIC = 2074, Entropy = .906, VLMR-LRT p = .006, aLRT p = .008
**Symptom Profiles and Cytokine Expression**

- Profile 1: Low on all symptoms
- Profile 2: Prominent oral and GI symptoms
- Profile 3: Prominent eye, muscle/joint, fatigue and mood symptoms

<table>
<thead>
<tr>
<th></th>
<th>Symptom Profile 1 vs. Symptom Profile 2</th>
<th>Symptom Profile 1 vs. Symptom Profile 3</th>
<th>Symptom Profile 2 vs. Symptom Profile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>IL-1β</td>
<td>1.59 (0.30-8.45)</td>
<td>0.92 (0.32-2.60)</td>
<td>0.58 (0.10-3.32)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.27 (0.09-0.79)*</td>
<td>1.15 (0.52-2.52)</td>
<td>4.26 (1.32-13.82)*</td>
</tr>
<tr>
<td>IL-1 RA</td>
<td>0.69 (0.22-2.14)</td>
<td>0.55 (0.29-1.07)</td>
<td>0.81 (0.26-2.48)</td>
</tr>
<tr>
<td>sIL-6R</td>
<td>0.50 (0.12-2.13)</td>
<td>1.78 (0.54-5.90)</td>
<td>3.53 (0.83-15.13)</td>
</tr>
<tr>
<td>sTNF-RII</td>
<td>0.29 (0.04-2.42)</td>
<td>0.28 (0.08-0.99)*</td>
<td>0.95 (0.12-7.59)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>8.70 (1.46-51.66)*</td>
<td>0.40 (0.11-1.40)</td>
<td>0.05 (0.01-0.36)**</td>
</tr>
<tr>
<td>MIG</td>
<td>1.33 (0.73-2.44)</td>
<td>1.02 (0.63-1.65)</td>
<td>0.77 (0.42-1.39)</td>
</tr>
<tr>
<td>sBAFF</td>
<td>0.40 (0.13-1.30)</td>
<td>1.86 (0.88-3.93)</td>
<td>4.61 (1.39-15.31)**</td>
</tr>
</tbody>
</table>

**p < .01 or * p < .05; multinomial logistic regression**

‡ values were log normal transformed prior to analysis

Mitchell et al. Proinflammatory Serum Cytokines and BAFF Levels Distinguish Allogeneic HSCT Survivors with Differing Chronic GVHD Symptom Profiles. Presented at American Society of Blood and Marrow Transplantation, February 2009, Tampa, FL
Estimated marginal means for sBAFF:

Low on all symptoms
Prominent mouth, upper GI and weight loss symptoms
Prominent eye, muscle/joint, fatigue and mood symptoms

Estimated marginal means for IL-6:

Low on all symptoms
Prominent mouth, upper GI and weight loss symptoms
Prominent eye, muscle/joint, fatigue and mood symptoms

Estimated marginal means for MCP-1:

Low on all symptoms
Prominent mouth, upper GI and weight loss symptoms
Prominent eye, muscle/joint, fatigue and mood symptoms

Estimated marginal means for sTNF-RII:

Low on all symptoms
Prominent mouth, upper GI and weight loss symptoms
Prominent eye, muscle/joint, fatigue and mood symptoms

p = 0.01
p = 0.02
p = 0.05
p = 0.02
p = 0.003

Prominent mouth, upper GI and weight loss symptoms
Prominent eye, muscle/joint, fatigue and mood symptoms
Implications for Survivorship Care

• Anticipate symptoms that are most prevalent and bothersome in patients with chronic GVHD
• Symptom profiles can be used to tailor evaluation and treatment:
  ▫ Profile with eye, muscle/joint, fatigue and mood symptoms
    • Manage pain and fatigue
    • Improve physical functioning
    • Psychological support
  ▫ Profile with oral and gastrointestinal symptoms
    • Nutritional counseling
    • Improve oral mucosal integrity and dysphagia
• Target younger individuals and those with more comorbid conditions for aggressive symptom management
Implications for Survivorship Care

- Functional status is markedly impaired in this group of survivors
  - Periodic evaluation of both capacity and performance
  - Preventive and restorative rehabilitation measures
- Survivors receiving intensive immunosuppression are at particular risk for impairments in functional performance
  - Early preventive interventions
- Two-fold opportunity to improve functional performance:
  - Improve functional capacity (e.g., muscle strength, ambulation)
  - Reduce chronic GVHD symptom
Measuring Functional Outcomes

- Two dimensions are required to capture the complexity of functional outcomes in chronic GVHD
- Results support inclusion of differing dimensions of function and contrasting methodologic approaches
Implications for Research

- Extend our findings through a longitudinal multi-site observational study designed to model the trajectory of symptoms and functional status from the time of early diagnosis of chronic GVHD.

- Develop and test supportive care interventions:
  - Management of specific symptoms (e.g., muscle/joint pain, weight loss).
  - Multi-component rehabilitative interventions shown in other chronically ill populations to reduce symptoms and improve functional capacity and self-management.

- Pharmacologic approaches that target TNF-R-II and MCP-1 could be studied in phase I/II trials with symptoms and functional status as primary outcomes.
Strengthening the Evidence Base for Survivorship Care

Guidelines available at: www.marrow.org

Webcast available at: www.nbmtlink.org
A debt of gratitude is also owed to our research participants for their willingness to participate in these studies, so that into the future, we may improve our care for individuals with chronic GVHD.
Symptoms and Functional Status: Improving Rehabilitation Outcomes in Cancer Survivors

Sandra A. Mitchell, PhD, CRNP AOCN