Extracorporeal Photopheresis

Nurse Education Session

Monday April 2, 2012
Objectives

- The original Photopheresis concept?
- What is Photopheresis?
- How might it work?
- Chronic Graft vs Host Disease and Photopheresis
  - When?
  - Results
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Photopheresis - the concept?

- Transferable autoimmune disease in mice caused by autoreactive clones of T cells
- Infusion of killed autoreactive T cells blocks development of autoimmune disease, when further active autoreactive T cells are administered
- Hypothesis, could infusion of lethally damaged T cells in humans block T cell mediated disease?

1. Autoreactive T cells → Disease
2. Killed Autoreactive T cells → No Disease
Human Application

- Edelson, Yale - in early 1980’s
- CTCL - partial response to skin applied PUVA
Why Psoralen??

Blocks unwinding of DNA on exposure to UVA
Cutaneous T cell lymphoma

- Using UVA / Psoralen as source of CELL KILL
- Attempt to treat Sezary patients (CTCL with circulating malignant cells in the peripheral blood) with UVA to circulating lymphs
- Leucapheresis + methoxypsoralen + UVA light + reinfusion
- First series of 37 patients with stage III / IVa CTCL suggested benefit > direct cell (skin improvement)

Edelson et al NEJM, 1987, 316, 297-303
What is Extracorporeal Photopheresis?

The UVAR XTS Instrument draws blood from the patient.

Blood is separated by centrifugation and red blood cells are returned.

White blood cells are treated with methoxsalen and exposed to UVA light.

Photoactivation with UVA light.

Methoxsalen

The photoactivated white blood cells are returned to the patient.

UVA = ultraviolet A radiation.

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Photopheresis

Cell separator

Photoceptor
Comparison of White cell counts and differential Peripherally vs Buffy Coat post
25 Cases - Rotherham ECP Unit

- 50% ↑ WBC
- x2 ↑ Lymphs
- x10 ↑ Mono's
What is an effective cell dose?

Leucocyte numbers in collections of 1st day treatments, Steroid usage group
ECP - Patients perspective

- 2-3 hour treatment, 2 consecutive days

Patient information -- www.photopheresis.co.uk
ECP - How does it work?

- Apoptosis - cell kill
- ‘Programmed cell death’ or ‘cellular suicide’
Initial focus on apoptosis as mechanism of action for photopheresis

"Extracorporeal photopheresis induces apoptosis in the lymphocytes of cutaneous T-cell lymphoma and graft-versus-host disease patients"

*British Journal of Haematology, 1999, 107, 707–711*
What are the effects on apoptosis?

Extracorporeal photopheresis in cutaneous T-cell lymphoma and graft-versus-host disease induces both immediate and progressive apoptotic processes.

J. Bladon and P. C. Taylor
Department of Haematology, Rotherham General Hospital, Moorgate Road, Rotherham, South Yorkshire S60 2UD, U.K.
ECP Mechanisms

- Immune tolerance
- Immune processing of apoptotic cells
- T regulatory cell mediated downregulation of the immune system
Cytokines

- Cytokines are soluble proteins or glycoproteins produced by cells.
- Cytokines act as chemical communicators between cells.
- ECP alters cytokine expression and T-helper subsets.
ECP influence on cellular cytokine production; direct and distal

Linked apoptosis work with cytokine production by monocytes

Non-apoptotic distal effects – Monocyte pro-inflammatory cytokine production diminished in *untreated* monocytes exposed to ECP treated cells;

Lymphocytes treated by extracorporeal photopheresis can down-regulate cytokine production in untreated monocytes
Tolerance

- Decreased pro-inflammatory cytokines
- Increased anti-inflammatory cytokines
- Reduced stimulation of T cell response
- Delete CD8 (T cell) effectors
- Induces T regulatory cells
- REDUCES IMMUNE RESPONSE

Peritt D  Biol Blood Marrow Transplant. 2006 Jan;12(1 Suppl 2):7-12
**T regulatory cells**

- T regulatory cells maintain order in the immune system.
- They enforce a negative regulation on other immune cells.
T regulatory cells - clues?

- Absence of T reg control of Th1 & Th17 cells causes GvHD  
  Chen Blood 2007 110, 3804
- Apoptotic cell infusions generate T regulatory cells  
  Mahnke Blood 2003
- T regs upregulated following ECP in cGvhD  
- Deletion of CD4\(^+\) / CD 25\(^+\) (T regulatory) cells reduces the ECP effect in murine model  
  Maeda J Immunol 2005
- ECP reverses experimental GVHD via T regs  
  Gatza Blood 2008, 112, 1515
Mechanisms of Action - overall effect

- Interaction between apoptotic cells and host immune system
- Leads to immunomodulation
  - Cytokine changes, effective reduction in inflammation
  - T helper profile changes
  - Increased T regulatory cells
  - Reduced B cell activating factor
- Reduced GVHD with preservation of GVD
- No increased risk of opportunistic infections.
- No increased risk of disease relapse
Mechanism of Action of ECP

Methoxalen
UV radiation

Cross-linked

Apoptosis

Phagocytosis

Receptor-mediated signaling

Tolerogenic DC/APC

Anti-inflammatory cytokines (eg, IL-10, TGF-β)

Proinflammatory cytokines (eg, IL-12, IFNγ)

Stimulation
Teffector cells

Treg

Deletion of T cells

Proinflammatory cytokines (eg, IL-12, IFNγ)

Stimulation
Teffector cells

Receptor-mediated signaling

Cross-linked DNA

Leukocytes

Apoptosis

Phagocytosis

Tolerogenic DC/APC

Anti-inflammatory cytokines (eg, IL-10, TGF-β)
Chronic Graft vs Host Disease

“Leading cause of non relapse mortality more than 2 yrs after transplantation”
Chronic graft vs Host Disease

- Diagnosis
- Staging / Scoring
- Management
  - First line
  - Second line
- Photopheresis
- Future..
# cGvHD - Diagnosis

NIH Consensus Development project 2005

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic</th>
<th>Distinctive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>Poikiloderma</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Lichen planus like</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sclerosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morphea like</td>
<td></td>
</tr>
<tr>
<td><strong>Mouth</strong></td>
<td>Lichenoid</td>
<td>Mucocele</td>
</tr>
<tr>
<td></td>
<td>Oral sclerosis</td>
<td>Ulcers</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>BO - biopsy</td>
<td>BO – radiology/PFT’s</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>New onset dry/painful eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cicatricial conjunctivitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kerato-conj sicca</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis cGvHD = 1 Diagnostic or 1 Distinctive + biopsy.
### cGvHD - Site Scoring

<table>
<thead>
<tr>
<th>Site</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>&lt;20% BSA No sclerosis</td>
<td>20-50% BSA Superficial sclerosis</td>
<td>&gt;50% BSA Deep Sclerosis Ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mouth</strong></td>
<td>Oral intake satis</td>
<td>Partial impairment oral intake</td>
<td>Marked impairment of oral intake</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>&lt; t.d.s. drops/day</td>
<td>&gt;t.d.s. drops/day</td>
<td>&gt;t.d.s. + Impairs work</td>
</tr>
<tr>
<td><strong>Gut</strong></td>
<td>GI symptoms &lt;5% weight loss</td>
<td>GI symptoms 5-15% weight loss</td>
<td>GI symptoms &gt;15% weight loss</td>
</tr>
<tr>
<td><strong>Lung (LFS)</strong></td>
<td>&lt;70%</td>
<td>40-70%</td>
<td>&lt;40%</td>
</tr>
</tbody>
</table>
cGvHD – Global Scoring

- **Mild GVHD**
  - 1-2 organ sites
  - Max score of 1 at any organ site
  - No lung involvement

- **Moderate GVHD**
  - 1 organ site with significant disability (max score 2)
  - 3 or more organ sites, score 1 - no disability
  - Lung score 1

- **Severe GVHD**
  - Site score 3
  - Lung score 2
cGvHD - First Line Management

- Mild - Topical/Local

<table>
<thead>
<tr>
<th>SITE</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>PUVA / UVB</td>
</tr>
<tr>
<td></td>
<td>Topical tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Topical steroids</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>Topical triamcinolone</td>
</tr>
<tr>
<td></td>
<td>Topical CNI’s</td>
</tr>
<tr>
<td>Ocular</td>
<td>Artificial tears/lubricants</td>
</tr>
<tr>
<td></td>
<td>Tear duct occlusion</td>
</tr>
<tr>
<td></td>
<td>Autologous serum</td>
</tr>
<tr>
<td>Vulvo-vaginal mucosa</td>
<td>Topical steroids</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
</tr>
</tbody>
</table>
cGvHD - First Line Management

- Moderate/Severe GVHD
  - 30-70% require systemic therapy
  - Prednisolone 1mg/kg/day – established role
  - Prednisolone + Cyclosporin
    - Pred + cyclosporin + low platelets
      - 26% vs 51% 5yr survival (Sullivan 1981)
    - Pred + cyclosporin + normal risk
      - pred only arm increased progression free survival (Koc 202)
cGvHD – Alternative additional therapies?

Second line - lowest toxicity
• No benefit from 3 agents in first line therapy

Use of agents tailored to side effects and patient circumstances
• Cyclosporin / Tacrolimus ? Steroid sparing
• MMF -limited disease  Martin, Blood 2009
• Thalidomide - increased response rate in children
• Koc, Blood 2000  - limited efficacy, high toxicity
• ECP safety profile, single RCT- Flowers, Blood 2008
cGvHD – Further options

- Third and later line therapies
  - mTOR inhibitor - sirolimus (increase T regs – toxicity TAM)
  - Sclerodermatous GvH  Jedlickova Z, Biol Blood Marrow Transplant 2010
  - Rituximab
  - Thrombocytopenia
    - Ratanatharanthorn, Ann Inter Med 2000
    - Zifa BMT 2007
  - Dose?  Von Bonin  Transplantation 2008
  - Imatinib – anti-fibrotic (PDGF / TGFβ)
    - Olivieri, Blood 2009
cGvHD –
What about when systemic therapy is insufficient?

Indications for ECP?

- Progression on pred 1mg/kg/day for 2 weeks
- Stable disease on >0.5mg/kg/day for 6-8 weeks
- Requires >0.5 mg/kg/day to maintain disease control

Wolff, Biol Blood Marrow Transplant, 2010
Indications?

- CTCL – FDA approved since 1988
- GvHD
  - Chronic
  - Acute
  - Prevention
- Transplant rejection
  - Cardiac – treatment / prevention
  - Renal
- Other
  - Nephrogenic fibrosing dermopathy (post renal transplant)
  - Many autoimmune / inflammatory diseases
Successful treatment of chronic graft-versus-host disease with extracorporeal photopheresis

M. Owsianowski¹, H. Gollnick¹, W. Siegert², R. Schwerdtfeger² & C.E. Orfanos¹

¹Department of Dermatology, University Medical Center Benjamin Franklin and ²Department of Hematology and Oncology, University Medical Center Rudolf Virchow, The Free University of Berlin, Berlin, Germany

- Owsianowski  *Bone Marrow Transplantation* 1994, **14**: 845-848
  - Allo sib BMT 1986 for CML
  - 2 yrs progressive cGvHD despite steroids / cyclosporin / PUVA
  - Paired treatments 4 weekly
  - Healing of ulcers by 24 weeks
Photopheresis - ECP assessment

- Baseline NIH assessment
  - Global score of 2 or more require systemic therapy
  - Quality of life assessment
- Involvement of skin, oral mucosa, gut, liver
- Steroid refractory / independent
  - Progressive GvHD despite high dose steroids / calcineurin inhibitor (>1mg/kg)
  - Progressive / stable GvHD and unable to taper steroids < 10mg/d for 4 weeks
  - Clinical picture of taper / flare
- Refer before there is significant loss of function
## ECP schedule - baseline assessments

<table>
<thead>
<tr>
<th>Category</th>
<th>Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Skin score (NIH consensus)</td>
</tr>
<tr>
<td></td>
<td>Photography</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>Severity score</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Severity score, drop usage</td>
</tr>
<tr>
<td></td>
<td>Schirmers*</td>
</tr>
<tr>
<td>Gut</td>
<td>Severity score, Stool volume*</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Function testing FEV1 &amp; incl Kco</td>
</tr>
<tr>
<td>Joint</td>
<td>Goniometry / grip strength</td>
</tr>
<tr>
<td>Mobility</td>
<td>QoL survey</td>
</tr>
</tbody>
</table>
ECP Eligibility – UK Perspective

- Cutaneous, mucosal, hepatic cGvHD
- Steroid refractory/resistant/intolerant cGvHD
- Extensive cGvHD - Seattle
- Biopsy – compatible with GVHD

* Respiratory, gastro-intestinal, ophthalmic
ECP Exclusion – UK Perspective

- No age limits
- Weight > 40kg (manufacturers licence)
- Hct >0.35 with transfusion if necessary
- Platelets > 20x10⁹/l (manufacturers licence)
- NO sensitivity to 8 methoxypsoralen
- Venous access – ACF / Apheresis line
Chronic Graft vs Host Disease
Chronic GvHD – affected sites

- Skin: 90
- Mucous Membrane (M): 75
- Eyes: 45
- Joints: 30
- Resp: 25
- Gut: 25
- Liver: 20

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Number of sites affected in patients with cGvHD treated by ECP

Number of sites affected

1 2 3 4 5 6

0 50

13 25

13 38

13 50
Chronic GvHD prior therapy

- Prednisolone
- Cyclosporin
- Tacrolimus
- MMF
- Thalidomide
- Azathioprine
### Chronic GvHD Demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>15-70 yrs</td>
<td>37 yrs</td>
</tr>
<tr>
<td>Transplant to cGvHD</td>
<td>1 – 30 mths</td>
<td>6 mths</td>
</tr>
<tr>
<td>cGvHD to ECP</td>
<td>1 – 177 mths</td>
<td>11 mths</td>
</tr>
<tr>
<td>ECP Duration</td>
<td>1 – 94 mths</td>
<td>9 mths</td>
</tr>
<tr>
<td>ECP Duration post 14wks</td>
<td>0 – 72 mths</td>
<td>12 mths</td>
</tr>
<tr>
<td>Type of transplant (DLI)</td>
<td>Unrelated 81 (15)</td>
<td>Related 32 (5)</td>
</tr>
<tr>
<td>Baseline assessments</td>
<td>2 weekly paired treatments 14 weeks</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Evidence of GvHD progression</td>
<td>STOP</td>
<td></td>
</tr>
<tr>
<td>Intolerance of ECP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to receive regular treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To 14 wks for primary endpoints</td>
<td>STOP if non-responder</td>
<td></td>
</tr>
<tr>
<td>Steroid &gt;50% reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin score &gt;25% reduction</td>
<td>RESPONDER &gt;14 weeks</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Continue paired ECP 4 weekly</td>
<td></td>
</tr>
<tr>
<td>Improvement in GvHD site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review every 12 wks</td>
<td>Continue to max response in GvHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunosuppression STOP</td>
<td></td>
</tr>
<tr>
<td>Max Response - ECP taper 6,8,12 wks</td>
<td>Maintain assessments</td>
<td></td>
</tr>
</tbody>
</table>
ECP and cGvHD - duration of therapy
Skin Score Response to ECP at 3 mths

64 patients assessed with skin cGvHD as primary endpoint

- 36% Worsened
- 0-25% Poss Resp
- 25-50% 16%
- >50% 16%

37 / 64 (58%) responders
Skin Score Response to ECP at 6 mths

58 patients assessed with skin cGvHD as primary endpoint

42 / 58 (72%) responders
Effect of ECP on skin scores in steroid refractory cGvHD

n = 46

Skin Score

Start 14 weeks 28 weeks 56 weeks

1 Feb 2007

p = 0.002
p = 0.002
p = 0.002

±Std. Dev. ±Std. Err. Mean
Time to maximum skin response to ECP
(n = 37)
Steroid dose reduction at 14 weeks
(n=75)

48/75 (64%)  Responder @ 3 mths
Steroid Response to ECP at 6 months

79% responder at 6 months
Effects of ECP on prednisolone dose in steroid refractory cGvHD

n = 56

p = <0.001

1 Feb 2007
Time to steroid STOP with ECP

- Total: 49%
- 20% STOP
- 14 wks, 28 wks, 56 wks, 112 wks
## Serious Adverse Events - Relapse

<table>
<thead>
<tr>
<th>Primary Diagnosis/Relapse</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>4</td>
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<tr>
<td>Hodgkins</td>
<td>2</td>
</tr>
<tr>
<td>CML</td>
<td>2</td>
</tr>
<tr>
<td>NHL</td>
<td>2</td>
</tr>
<tr>
<td>MDS</td>
<td>2</td>
</tr>
<tr>
<td>Myeloma</td>
<td>2</td>
</tr>
<tr>
<td>CLL</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>15 (13%)</strong></td>
</tr>
</tbody>
</table>

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### Serious Adverse Events – Mortality

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>18</td>
</tr>
<tr>
<td>Relapse primary disease</td>
<td>12</td>
</tr>
<tr>
<td>Progressive GvHD</td>
<td>7</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>TTP</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>41 (36%)</strong></td>
</tr>
</tbody>
</table>
# Infection risk in ECP treated cGVHD

<table>
<thead>
<tr>
<th></th>
<th>14 wks</th>
<th>28 wks</th>
<th>56wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>72</td>
<td>59</td>
<td>41</td>
</tr>
<tr>
<td>Patients with infection</td>
<td>48</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Infective episodes</td>
<td>107</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Infections/pt/month</td>
<td><strong>0.52</strong></td>
<td><strong>0.33</strong></td>
<td><strong>0.24</strong></td>
</tr>
<tr>
<td>Oral Antibiotic/patient/month</td>
<td>0.31</td>
<td>0.21</td>
<td>0.15</td>
</tr>
<tr>
<td>IV Antibiotic/patient/month</td>
<td>0.21</td>
<td>0.12</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Quality of Life Assessment (EORTC 30)
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Response @ 14 wks n= 68

Response @ 28wks n=7

P = <0.0001

Non-responder n=45

P = <0.001
So… what have we learnt?

- Assessment of response, using standardised tools, is essential to monitor role of ECP
- Steroid reduction (64% to 81%) and elimination (20%)
- Skin score reduction (56% to 77%)
- Responses durable
- Responses ongoing up to 2 years
- Responders have significant survival advantage -65% vs 30% 5yrOS
- Relapse in GvHD is rare
- Side effects are minor
Photopheresis Unit - Acknowledgements

- **Nursing**
  - M Foster
  - T Maher
  - R Goodgrove
  - C Swift

- **Scientific**
  - Mr R Whittle
  - Dr H Denney
  - Dr J Baldon

- **Data Management**
  - F Hammerton

**Referring Centres** (alphabetical)
- Christie Hospital, Manchester
- Edinburgh Royal Infirmary
- Heartlands, Birmingham
- Leeds Teaching Hospitals
- Leicester Royal Infirmary
- Liverpool Childrens Hospital
- Manchester Childrens Hospital
- Manchester Royal Infirmary
- Nottingham City Hospital
- Royal Hallamshire, Sheffield
- RVI, Newcastle
- University Hospitals, Birmingham
- Weston Park Hospital, Sheffield

**Sponsors:**
- Rotherham Foundation Trust
- Haematology and Leukaemia Trust
cGvHD costs

- Dignan 2011
  - 96/196 allo BMT patients developed cGvHD
  - Readmission rate 87%
    - 33% within 100 days
    - 83% within 1 yr
  - 31% required critical care support
    - Median stay 6 days
  - Overall survival 43% at 2 yrs
  - Total costs for post transplant care - €3m
  - Average ~ €30,000 per cGvHD case
Photopheresis - costs

- Three months - 7 visits for paired treatments
  - Initial assessment period
  - ~30% will not proceed
    - 14 treatments ~ €18,000

- Average of 9 months of 4 weekly paired treatments
  - Continue to maximum response
  - ~80% of those that proceed beyond three months will complete a further 9 months
    - 18 treatments ~ €22,000

- Approx 5% of all allo BMT
GVHD morbidity

- Percentage of subjects with poor or fair general health according to time since HCT and cGVHD status. *P* values are for comparison between active and no cGVHD groups and active and resolved cGVHD groups.

Prevalence of HCT survivors with adverse health outcomes by cGVHD status

Long term performance in Allo BMT survivors

- Norm-based SF-36 scores in allogeneic HSCT survivors with cGVHD
- [Bone Marrow Transplant.](https://doi.org/10.1097/BMT.0b013e3181c98f50) 2010 Apr;45(4):762-9
Functional capacity partially mediates the relationship between cGVHD symptom bother and functional performance, controlling for intensity of immunosuppression. Numbers outside parentheses represent the raw partial coefficient \( b \); numbers in parentheses represent the standard error of the raw partial coefficient \( b \).

Bone Marrow Transplant. 2010 Apr;45(4):762-9
Factors affecting GvHD morbidity

- Six variables explained 56% of the variance in functional performance:
  - time since cGVHD diagnosis,
  - cGVHD severity,
  - intensity of immunosuppression,
  - comorbidity,
  - functional capacity - distance walked in 2 min/ grip strength
  - cGVHD symptom bother (P<0.001).

- Significant independent predictors of impaired performance were:
  - intensive systemic immunosuppression,
  - reduced capacity for ambulation, and
  - greater cGVHD symptom bother (P<0.05)