Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Neurologic Diseases: Multiple Sclerosis and Stiff Person’s Syndrome

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George E. Georges, MD
Associate Member, Fred Hutchinson Cancer Research Center
Associate Professor, University of Washington
Objectives

- Review the autoimmune diseases utilizing hematopoietic stem cell transplantation (HSCT)
  - Multiple Sclerosis (MS)
  - Stiff Person Syndrome (SPS)
- Increase understanding of the rationale for transplanting autoimmune diseases
- Summarize the outcomes/ present data/ results
- Future directions
High-dose Immunosuppressive Therapy (HDIT) and Autologous HSCT

- Rapid reduction of ‘autoimmune’ effector cells
- Sustained immunomodulatory effect
- Reduced transplant related mortality (TRM) compared to allogeneic transplant
HSCT for Autoimmune Diseases

Allogeneic HSCT

- Replace the host immune system with donor cells
- Promote regulatory mechanisms that control autoimmune disease (e.g. mixed donor-host chimerism)
- Reduced intensity conditioning with less TRM
- Graft-versus-host disease remains a potential problem
Autologous HSCT is a Multi-Step Process

- Mobilize autologous PBSC: Cytokine or chemo. + cytokine
- Collect PBSC via apheresis
- (Optional) Select CD34+ cells (immuno-magnetic selection)
- Cryopreserve autologous PBSC/CD34+ cells
- High dose conditioning regimen (myeloablative / immunoablative chemotherapy/ TBI)
- Additional in vivo depletion of patient immune cells with anti-thymocyte globulin (ATG)
- Supportive care/ acute side effects of conditioning regimen
- Engraftment
- Immune reconstitution
- Assess response to disease
Renewal of the CD4$^+$ T cell compartment after autologous HSCT

Swart, J. F. et al. (2017) Haematopoietic stem cell transplantation for autoimmune diseases
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2017.7
Background: Multiple Sclerosis (MS)

- MS is an immune-mediated disease of the central nervous system (CNS, brain and spinal cord) causing multiple demyelinating lesions and neuronal/axonal loss.
- 300,000 cases in US
- Third leading cause of disability among young adults.
- High risk area: northern latitudes
- Gender: 2:1 female-to-male ratio

Clinical course:
- Relapsing-remitting (inflammatory)
- Secondary Progressive (inflammatory/degenerative)
Multiple Sclerosis: Clinical Course

- Relapsing-remitting
- Primary-progressive
- Secondary-progressive
- Relapsing-progressive

EDSS vs. time

Lublin & Reingold, Neurology 46:907, 1996
Multiple Sclerosis

Diagnostic Criteria

White matter lesions of the CNS disseminated in space and time.

Assessment

• Clinical
• Evoked potentials
• Brain MRI
• CSF (Oligoclonal bands)
Focal White Matter Lesions: T1, T2 and Gadolinium-Enhancing

Gd-enhancement on T1 scan with accompanying new T2 lesion

2 months post: no Gd-enhancement on T1 scan, but T2 lesion persists
Expanded Disability Status Scale

EDSS Score

**FDA approved disease modifying therapies (DMTs)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta 1a or 1b</td>
<td>cytokine (decreases inflammatory cells to CNS, decrease Th17 cells)</td>
<td>SC</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Random polymer of Glu, Lys, Ala, Tyr,</td>
<td>SC</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>Fungicide, NRF-2 activator, nicotinic acid R agonist.</td>
<td>PO</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>(FTY-720) sphingosine-1 phosphate R modulator.</td>
<td>PO</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Inhibits dihydroorotate dehydrogenase (de novo pyrimidine synthesis)</td>
<td>PO</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>mAb anti-α4 integrin (decrease lymphocyte migration to CNS)</td>
<td>IV</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>mAb anti-CD25 deplete high affinity IL-2R cells</td>
<td>SC</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>mAb anti-CD52 deplete T and B cells</td>
<td>IV</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>mAb anti CD20 deplete B cells</td>
<td>IV</td>
</tr>
</tbody>
</table>
Hypothesis: Intensive immunosuppressive therapy supported by autologous hematopoietic stem cell infusion will arrest disease activity in individuals with poor-risk MS.

Study design: Prospective, open-label, single-arm, multicenter Phase II clinical trial.

Primary Objective: To determine the 5-year durability of disease stabilization in MS subjects after HDIT and autologous HSCT.
Event-free survival during the 5 years after high-dose therapy.

**Composite endpoint** for event-free survival includes one or more of the following:

a) **Relapse**
   New neurological S/S persisting > 48 hr
b) **MRI abnormalities** (>12 months post-tx)
   ≥ 2 or more independent MS lesion
c) **Progression in disability** (> 6 months post-tx)
   ≥ 1.0 EDSS confirmed > 3 months later
d) **Mortality**

HALT MS: Primary Endpoint
HALT MS: Eligibility

1. Age: 18-60 years, inclusive.
2. Diagnosis of MS using McDonald Criteria.
3. MS duration < 15 yrs from diagnosis.
4. RRMS with cumulative disability.
5. EDSS 3.0 – 5.5
6. T2 abnormalities on MRI consistent with MS.
7. 2 or more relapses within 18 months on therapy with EDSS increase > 0.5
   or 1 relapse on therapy with EDSS increase > 1.0 and 1 separate event with gadolinium-enhancing lesions (brain or spinal cord) on MRI.
8. Approval by MS Review Panel.
## High-Dose Immunosuppressive Therapy (BEAM + ATG)

<table>
<thead>
<tr>
<th>HDIT</th>
<th>Day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-6</td>
<td>BCNU 300 mg/m² IV</td>
</tr>
<tr>
<td></td>
<td>-5</td>
<td>VP-16 100 mg/m² bid IV; Ara C 100 mg/m² bid IV</td>
</tr>
<tr>
<td></td>
<td>-4</td>
<td>VP-16 100 mg/m² bid IV; Ara C 100 mg/m² bid IV</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>VP-16 100 mg/m² bid IV; Ara C 100 mg/m² bid IV</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>VP-16 100 mg/m² bid IV; Ara C 100 mg/m² bid IV; rATG 2.5 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Melphalan 140 mg/m² IV; rATG 2.5 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>CD34+ HSC infusion</td>
</tr>
</tbody>
</table>

**Post-transplant**

- G-CSF from Day +5 until ANC >500/µL.
- Prednisone 0.5 mg/kg/day from Day +7-21 then taper over 2 weeks.
Primary Endpoint: Event-Free Survival

5 year EFS: 69.2% (90% CI: 50.2%, 82.1%)

<table>
<thead>
<tr>
<th>Number of Primary Endpoint Events</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS increase &gt; 0.5</td>
<td>2</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>3</td>
</tr>
<tr>
<td>MRI criteria</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

Nash RA et al, Neurology Feb 1, 2017
Nash RA et al,
Neurology
Feb 1, 2017
A. EDSS Score

EDSS Score Change from Baseline

Visit

Month 6 (n=24)
Year 1 (n=23)
Year 2 (n=21)
Year 3 (n=20)
Year 4 (n=18)
Year 5 (n=17)

p-value
p = 0.133
p = 0.003
p = 0.004
p = 0.007
p = 0.046
p = 0.001

Nash RA et al, Neurology Feb 1, 2017
Summary for HALT-MS Trial

• HDIT (BEAM + ATG) and autologous HSCT with CD34-selected cells was well-tolerated with few serious early complications.
• 3 deaths unrelated to transplant, after disease progression.
• HDIT was highly effective for inducing sustained remissions of highly active RRMS (EDSS 3.0-5.5) through year 5. No disease-modifying therapy was administered after transplant unless the patient experienced relapse or increase in EDSS.
• MRI lesions (T2) decreased.
• Brain volume stabilized at year 3 through year 5.

Nash RA et al, Neurology Feb 1, 2017
T cell repertoire after AHSCT for MS

Muraro PA et al
JCI 2014
Investigators (HALT MS; ITN033AI)

Neurology Investigators
• Jim Bowen - Swedish Neurosci. Inst.
• George Kraft - UW
• Annette Wundes - UW
• George Hutton - Baylor
• Michael Racke – OSU

Consultant Neurologists
• Paolo Muraro - Imperial College
• Harry Openshaw - COH
• Olaf Stuve - UTSW
• Doug Arnold - McGill

Transplant Physicians
• Richard Nash – UW/FHCRC
• Steve Devine – OSU
• Uday Popat - MD Anderson
• George Georges - UW/FHCRC

Study Monitors
• Linda Griffith - NIAID/NIH
• Peter Sayre – ITN

Statisticians
• Kaitlyn McConville – Rho
• James Rochon - Rho

Supported and conducted by Immune Tolerance Network (ITN), and sponsored by NIAID, NIH, Bethesda, MD USA
HDIT and Autologous HSCT


EBMT: Mancardi GL et al., Neurology v 84, 2015
HDIT and Autologous HSCT

Burt R.K. et al., JAMA v313(3), 2015
HDIT and Autologous HSCT

PFS after AHSCT for MS Subtypes

N=281 multi-center analysis

Muraro P et al., JAMA Neurology 2017
Which MS patients should be referred for transplant?
- RRMS
- EDSS between 2.5 to 5.0
- Failed one or two prior standard disease modifying treatments
- Advanced EDSS and age >50 has poorer outcome

Which transplant regimen?
- Outcomes in clinical trials of autologous HSCT are equivalent
- BEAM+ ATG is very well tolerated
- Total Body Irradiation/Cyclophosphamide
- Busulfan/Cyclophosphamide
- Cyclophosphamide 200 mg/kg + ATG

Is CD34+ selection necessary?
- Probably not
- Risk of infections, technology is not yet widely available
Comparison of autologous HSCT to mAb therapy

Corresponding EFS Curves:

Month-Free Survival

Months after start of treatment
Future Directions-- Stay Tuned!

- BEAT-MS: Randomized phase III clinical trial comparing HDIT and autologous HSCT to best available antibody therapy.
- Immune Tolerance Network, BMT-CTN, NIH.
- Autologous transplant is probably less expensive and very cost effective compared to biologic therapy.
- Phase 2 clinical trial of allogeneic HCT for primary progressive MS?
- Retrospective study showed after allogeneic HCT there was resolution of oligoclonal bands in the CSF.
Stiff Person Syndrome (SPS)

- Autoimmunity against gamma aminobutyric acid (GABA)-ergic neurons
- Excessive rigidity of the lumbar trunk, proximal limb muscles that cause sustained muscular contractions in agonist and antagonist muscles.
- “Frankenstein’s gait”
- Frequent falls (log tumbling down)
- Startle reflex, episodic muscle spasm
- Muscle hardening to board-like sensation
- Paroxysmal autonomic dysfunction (apnea, cyanosis)
Stiff Person Syndrome (SPS) cont’d

- Antibody to GAD-65 (glutamic acid decarboxylase, N-terminus)
- Electromyography (EMG) continuous motor unit activity with agonist and antagonist muscle group co-contraction
- Rule out paraneoplastic syndrome, progressive encephalopathy with rigidity and myoclonus (PERM).
- Neuropathology negative or possibly vacuolization of anterior horn cells, loss of $\alpha$-, $\gamma$- motor neurons
Standard Treatment of SPS

- Drugs designed to enhance GABA neurotransmission, such as diazepam provide mild to modest benefit.
- IVIG has demonstrated efficacy, but the duration of the beneficial effects vary.
- Immune suppressive agents (corticosteroids, MMF)
- Plasma exchange (PLEX)
- The anti-GAD65 antibody titer does not necessarily correlate with the severity of disease. The reduction in titer does not necessarily correlate with the degree of improvement in the patients' clinical condition.
Stiff Person Syndrome and AHSCT

- Case report showed improvement in 2 patients with SPS after HDIT and autologous HSCT (JAMA Neurology, 2015) Ottawa, Canada

- FHCRC #2260
  9 SPS patients transplanted since 2014 in Seattle and Denver. All 9 had clinical improvement (longer follow-up needed)

Rituximab + GCSF mobilization
BEAM + ATG conditioning
<table>
<thead>
<tr>
<th>Pt. #</th>
<th>Age</th>
<th>Sex</th>
<th>Years from Dx</th>
<th>Medications</th>
<th>Distribution of Stiffness Index</th>
<th>EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>F</td>
<td>1.0</td>
<td>PLEX, IVIG, Ritux., Aza., MMF, diazepam, IT baclofen</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>2.5</td>
<td>PLEX, IVIG, Ritux., Botox diazepam, IT baclo., pregaba</td>
<td>6</td>
<td>6.5</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>M</td>
<td>12.5</td>
<td>PLEX, IVIG, Ritux., Botox diazepam, IT baclo, gabapen</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>1.5</td>
<td>PLEX, IVIG, Ritux., Botox diazepam, baclo, gabapen</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>M</td>
<td>14.7</td>
<td>PLEX, IVIG, Ritux., Aza, Pred., diazepam, baclo, gabapen</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>F</td>
<td>4.2</td>
<td>PLEX, IVIG, Ritux. diazepam, tizanidine</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>F</td>
<td>1.4</td>
<td>PLEX, IVIG, Ritux., diazepam, tizanidine</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>4.3</td>
<td>PLEX, IVIG, Rituximab, diazepam, baclofen</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>F</td>
<td>5.7</td>
<td>IVIG, Rituximab, diazepam, baclofen</td>
<td>5</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Improved DSI and EDSS after AHSCT

n = 9
Protocol 2260
Preliminary Results
Stiff Person Syndrome: Case Study

- 27yo F, nurse with severe, refractory SPS dx’ed per neuro exam, anti-GAD 65+, onset 2013, rapidly progressive decline
- Progression despite prednisone, multiple courses of IVMP, plasma exchange 5 d. x 3, IVIG q2wk, 3 x IV rituximab, MMF x 15 mo.
- High dose diazepam (>210 mg/day) and po baclofen >40 mg/d
- IT baclofen pump 650 mcg/day
- Rescue meds (diazepam, hydromorphone, diphenhydramine)
- Severely disabled. Able to walk a few steps with assist, unable to propel, h/o multiple falls d/t startle response, multiple injuries d/t falls and joint dislocations for muscle spasms, hypoxia requiring oxygen during episodes
EMG 3/2014: abnormal co-contraction of agonists/antagonists + continued motor unit activity in many muscle groups

Hospital admission for 5 day PLEX and IVIG 3/2014

Autologous HSCT in 5/2014
SPS patient after transplant

8 months  12 months

With patient permission
Thank you!

FHCRC
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Anne Stevens MD
Michael Weiss, MD

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James Bowen MD

Colorado Blood Cancer Institute:

Richard Nash, MD
Peter McSweeney MD
Marie Provost, RN
Nicole Stephens, RN
Callee Redman, RN
Juli Murphy, RN