Bone Marrow Transplantation in Neurological Disease

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Objectives

- Understand the rationale for considering bone marrow transplantation (BMT) in the treatment of autoimmune neurological disease
- Review the differences in BMT regimens that might contribute to variable outcomes
- Review the results of the Canadian MS BMT Study
- Review the results of the other small studies treating other neurological autoimmune conditions
Types of BMT

- **Autologous**
  - Immunoablative immunosuppression
  - Rescue of haematopoietic system using patient’s own bone marrow derived haematopoietic stem cells

- **Allogeneic**
  - Sub-myeloablative immunosuppression
  - Transplantation of an HLA-matched donor’s haematopoietic stem cells
The Bone Marrow Niche: Source for Stem Cells
Types of “Conditioning”

- Myeloablative
  - Complete ablation of all elements of the hematopoietic system
    - Total Body Radiation (TBI)
    - Chemotherapy: High dose Busulphan, Mitoxantrone, Etoposide

- Lymphoablative
  - Non-ablative or neutrophil sparing
    - Chemotherapy: Fludarabine/cladribine, low dose Cyclophosphamide, mAb (e.g. Alemtuzumab)
Non-autoreactive T Cell

Autoreactive T Cell

Non-autoreactive T Cell
Conditioning Regimens Used for BMT

- Bu CTX ATG
- V Mel TBI
- CTX TBI ATG
- BEAM ATG
- CTX ATG
BMT for Autoimmune Neurological Disorders

- MS (n=42)
- Myasthenia (N=8)
- CIDP (n=6)
- NMO (n=4)
- SPS (n=3)
To establish if complete myeloablation followed by autologous stem cell transplantation (ASCT) will induce a long-lasting MS progression-free response in patients with active and progressive disease who have a poor prognosis.
Targeting Multiple Sclerosis as an Autoimmune disease with Intensive Immunoablative Therapy and Immunological Reconstitution – A Potential Curative Therapy for Patients with Predicted Poor Prognosis MS.

- 3 centers (Ottawa, Montreal, Toronto)
- 24 patients to undergo HSCT
- 8 patients to act as concurrent control with BAT
Procedures

• Mobilization
  – Cyclophosphamide: Single dose 4.5 g/m² i.v.
  – Filgrastim 1 μg/kg per day, s.c. x 10 days

• Conditioning
  – Busulfan (at first oral, then i.v.) with monitoring of 1st dose pharmacokinetics, q6 h for 16 doses
  – Cyclophosphamide: 50 mg/kg per day i.v. x 4 days
  – Rabbit anti-thymocyte globulin 1.25 mg/kg per day x 4 days

• Transplant
  – CD34-selected cells infused 48 hrs post last conditioning dose
  – Filgrastim 1 μg/kg per day, s.c.
16 pts (67%) developed febrile neutropenia,
3 pts (13%) with UTI.
Hospitalization and broad-spectrum antibiotics.
22 (92%) had 1 pheresis.
2 (8%) had 2 pheresis.
The Canadian BMT Study

• 24 patients treated in a non-randomized fashion with full immunoablation (Big BuCy) + ATG (reported in Lancet June 2016)
  – There were 2 controls undergoing “best medical treatment” who were followed alongside

• All grafts underwent CD34+ immunomagnetic selection

• Patients were followed systematically for >13 years

• A further 18 patients (reported at ECTRIMS 2016) treated with the same regimen and followed for a mean of 45 months
Experience to Date: Results

- There was no detectable ongoing inflammation in ANY patient for the full duration of follow-up (~18 years)
  - Inflammation was characterized by any clinical relapse or any MRI activity
- No patient required ongoing disease modifying medication
- There were no “treatment failures”
- Despite the absence of ongoing inflammation there was progression that seemed to continue from where it started before BMT
- The majority of patients either stabilized or many regressed and improved
- There were no clear baseline characteristics indicating which patients would do the best but younger patients with low latency between disease onset and BMT seemed to offer the greatest chance of benefit
MSBMT: Elimination of CNS Inflammation

Clinical Relapses

- 24 patients at risk
- 167 relapses
- 1.2 relapses/patient/year

After HSCT
- 23 patients at risk
- 0 relapses
- 0 relapses/patient/year

New or Enhancing Lesions

- Time to EDSS 3.0 or MRI scan performed
- Relapse or active MRI scan

Elimination of CNS Inflammation Reduces the Risk of Progression

A Time to sustained EDSS prior to aHSCT

B Time to EDSS progression after aHSCT

MSBMT: Recovery of Disabilities

A  EDSS improvement

% of patients with sustained improvement

Time after aHSCT (years)

# at risk 23 17 13 10 6 5 4

B  EDSS change at 1.5 years

Patient Better

Change in EDSS from prior to aHSCT

Patient Worse

C  EDSS change at 3 years

Patient Better

Change in EDSS from prior to aHSCT

Patient Worse

D  EDSS change at 6 years

Patient Better

Change in EDSS from prior to aHSCT

Patient Worse
KM outcomes (time to treatment failure) may depend on both the conditioning regimen and graft selection.

- BEAM-ATG + Selected HSCT
- CTX-ATG + Unselected HSCT
- Bu-CTX-ATG + Selected HSCT

Relapse, New MRI activity, Progression, MS related death

HALT-MS: Nash et al, JAMA Neurol; 2017, 88, 242

Progression

Burt et al, JAMA, 2015, 313(3), 275

### Late Effects
- Shingles
- Thyroid Disease
- ITP (2)
- Premature Menopause
- 2° Leukemia (1)

### Table

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<th>Total</th>
<th>Too Early</th>
<th>Disease Inactive</th>
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<tr>
<td>Total</td>
<td>53</td>
<td>11</td>
<td>35 (83%)</td>
<td>7 (17%)</td>
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Preliminary follow-up data of patients undergoing autoHSCT for a neurologic autoimmune disease

# death, loss to follow-up, active disease (progression or active)
8 patients between 2001-2016

- Class I: Ocular weakness
- Class II: Mild weakness
- Class III: Moderate weakness (N=3, 2 x III B, 1 x III A)
- Class IV: Severe weakness (N=3, 2 x IV B, 1 x IV A)
- Class V: Intubation (N=2)

- A: predominantly limb & axial muscles
- B: predominantly oropharyngeal & respiratory
  - IVB if feeding tube required.
• Complete Stable Remission:
  - No signs of MG for > 1 yr without therapy

• Pharmacologic Remission:
  - No signs of MG for >1 yr but needs some therapy other than cholinesterase inhibitors

• Minimal Manifestations
CSR – complete stable remission; PharmR – drug free remission
• 6 patients treated between 2007-2016 @ TOH
• 2 with MADSAM variant
  o 1 CSR, 1 PharmR
  o One rapid response, one developed over 2.5 yrs.
• 4 with distal motor neuropathy
  o 1 CSR, 1 unchanged, 2 too early to evaluate
• About 20 other cases reported in Pubmed.

Neuromyelitis Optica (NMO)

- N=16 (2001-2011)
- 3 yr OS 94% +/- 6%
- 3 yr PFS 48% +/- 13%
- 3 yr RFS 31% +/- 12%

Greco et al. Mult Scler J 2015;21(2):189-197
Neuromyelitis Optica (NMO)

TOH
- N=4 (2011-2016)
- 24 to 64 yr old.
- 1 death
  - mobilized with CTX/Rituximab $\rightarrow$ Bu/CTX/ATG/HSCT
- No further relapses
- No further progression
  - 12, 21, 49 mo. follow-up
  - 2 have improvement in function
  - 1 returned to work

EBMT:
- N=16 (2001-2011)
- 3 yr OS 94% +/- 6%
- 3 yr PFS 48% +/- 13%
- 3 yr RFS 31% +/- 12%

Greco et al. Mult Scler J 2015;21(2):189-197
Case Report/Case Series

Autologous Stem Cell Transplantation for Stiff Person Syndrome
Two Cases From the Ottawa Blood and Marrow Transplant Program

Sholagh Sanders, MD; Christopher Bredeson, MD; Isabelle Bence-Bruckler, MD; Linda Harnett, MD; Jason Tay, MD; Lothar Huebsch, MD; Harold L. Atkins, MD

IMPORTANCE Stiff person syndrome (SPS) is a functional disability for patients and poses a significant challenge for medical care. Autologous hematopoietic stem cell transplantation (HSCT) is an emerging therapy for SPS patients treated with auto-HSCT, a novel therapy.

OBSERVATIONS Two anti-glutamic acid decarboxylase (GAD) antibody-positive patients underwent autologous HSCT. Both patients exhibited marked improvement in symptoms and continued to improve 2.5 and 4.5 years after the procedure.

CONCLUSIONS AND RELEVANCE Stiff person syndrome is a type of autoimmune disorder. The resolution of clinical manifestations of SPS and the anti-glutamic acid decarboxylase antibody titers does not play a direct role in the pathogenesis of SPS. The treatment of SPS with HSCT is a promising approach for future studies.

Ingrid Stepan

This next step is my last ditch effort of having a life, of giving my husband back a wife and my kids a mom.

Ingrid Stepan
Indications for AutoHSCT (TOH Experience)

Total=99

Updated 5-June-2018
BMT for Neurologic Autoimmune Conditions

- 75 patients
- 95% long-term survival
- 1 early death from RRT (MS)
- 2 late deaths from disease (NHL, NMO)
Indications for AutoHSCT

Autologous HSCT for autoimmune indications

- Year: 1998 to 2018
- Patients (number)
Annual Activity in Autologous HSCT for Autoimmune Diseases

Autoimmune Indications for AutoHSCT

EBMT  n=900  
1996-2007

- Neurological: 46%
- Rheumatological: 38%
- Hematological: 4%
- Other: 2%

EBMT  n=900  
1996-2007

- Neurological: 46%
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Conclusions

- BMT is a reasonable treatment option for MS patients with early aggressive disease not controlled with DMT.
- BMT is also an option for other chronic disabling autoimmune neurological disorders resistant to other treatments.
- The option should be considered before exhausting all other therapies in the face of rapidly advancing and disabling disease.
- Patient selection is very important to maximize response to therapy as well as to minimize toxicity.
- Conditioning regimens are improving in terms of less morbidity/mortality but differ in their results.