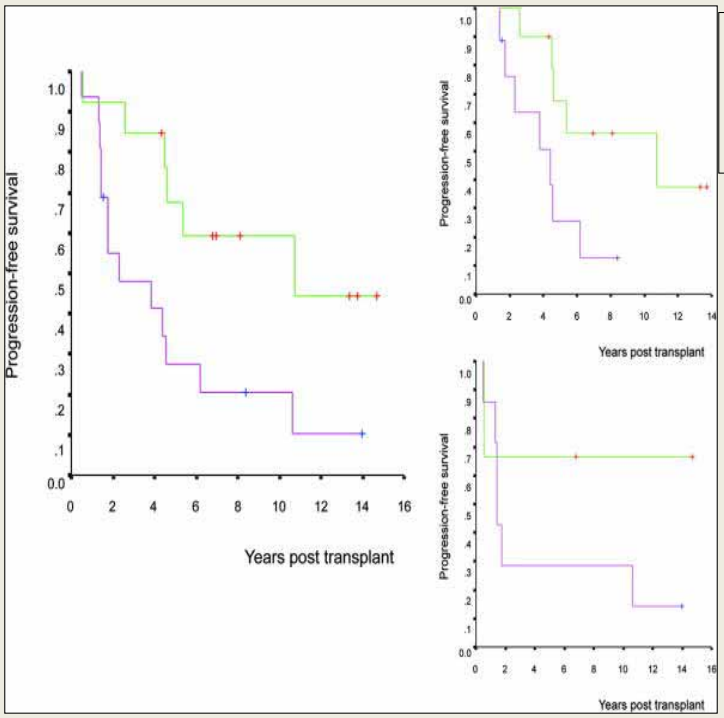
U.S. Experience and HALT MS Clinical Trial: 5-Year Follow-Up

Richard A. Nash, MD

06/02/2016

Consortium of MS Centers Annual Meeting
National Harbor, MD



Long-term results of stem cell transplantation for MS: a single-center experience.
Fassas A; Kimiskidis VK; Sakellari I; Kapinas K; Anagnostopoulos A; Tsimourtou V; Sotirakoglou K; Kazis A

Neurology. 76(12):1066-70, 2011 Mar 22.
DOI: 10.1212/WNL.0b013e318211c537

Figure 1 Progression-free survival by pretransplant MRI activity (presence of gadolinium-enhancing, new, or enlarging T2 lesions). Data were available in 20 patients with secondary progressive (n= 15) and relapsing (n= 5) multiple sclerosis (MS) types, and in 10 patients with primary progressive MS: 44% at 15 years for patients with active lesions on MRI vs 10% for those without; p= 0.01. The difference also appears significant for the group of secondary progressive/relapsing MS (upper right) but not for primary progressive disease (lower right).

HALT MS: Study Overview

- Hypothesis: Intensive immunosuppressive therapy supported by autologous hematopoietic 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 HCT. Interim analysis was done at 3 years.

Primary Endpoint

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 hrs

b) MRI abnormalities (>12 months post-tx)
   - ≥ 2 or more independent MS lesions

c) Progression in disability (> 6 months post-tx)
   - ≥ 1.0 EDSS confirmed > 3 months later

d) Mortality

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 or PRMS.
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.

Patient Characteristics (n=25)

Age at Mobilization (years), median (range)	37 (26 – 52)
Gender (F/M)	17/8
Baseline EDSS, median (range)	4.5 (3.0 – 5.5)
Disease Duration (years), median (range)	4.9 (0.6 – 12.0)
Prior therapy (n):	
Interferon Beta-1A	22
Interferon Beta-1B	1
Glatiramer Acetate	18
Mitoxantrone	8
Natalizumab	6
Other	11

High-Dose Immunosuppressive Therapy Regimen (BEAM + ATG)

HDIT

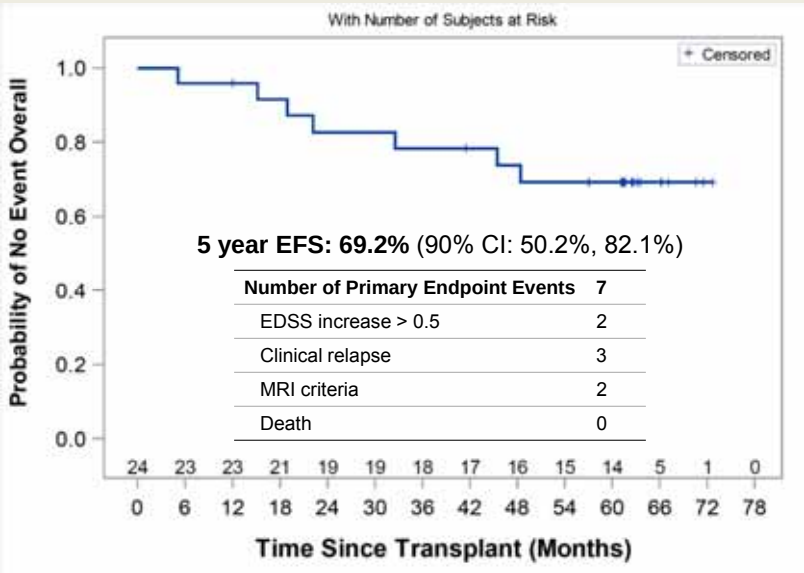
Day -6	BCNU 300 mg/m^2 IV
-5	VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-4	VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-3	VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV
-2	VP-16 100 mg/m^2 bid IV; Ara C 100 mg/m^2 bid IV rATG 2.5 mg/kg IV
-1	Melphalan 140 mg/m^2 IV; rATG 2.5 mg/kg IV
0	CD34+ HSC infusion

Post-transplant

G-CSF from Day +5 until ANC >500/uL.

Prednisone 0.5 mg/kg/day from Day +7-21 then taper over 2 weeks.

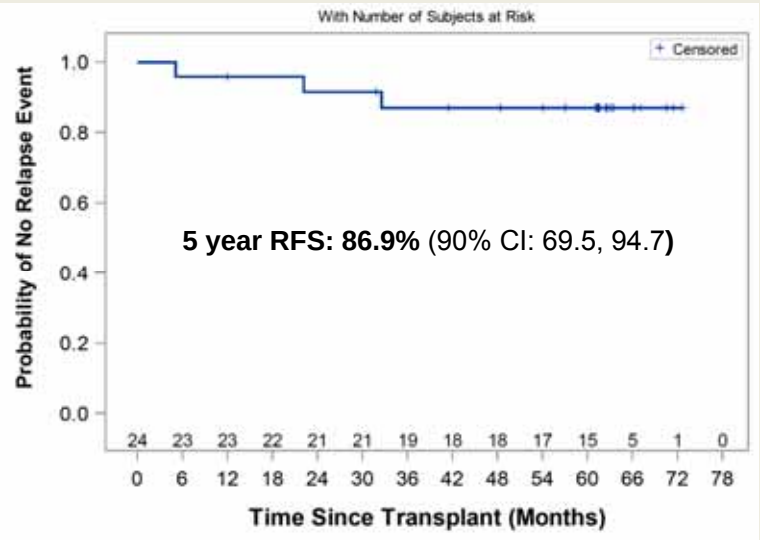
Primary Endpoint: Event-Free Survival



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

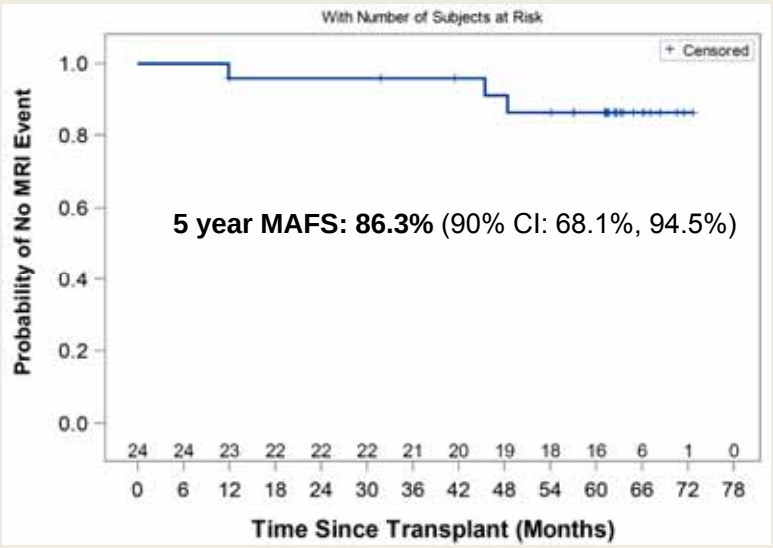
Number of Primary Endpoint Events	7
EDSS increase > 0.5	2
Clinical relapse	3
MRI criteria	2
Death	0

Relapse-Free Survival



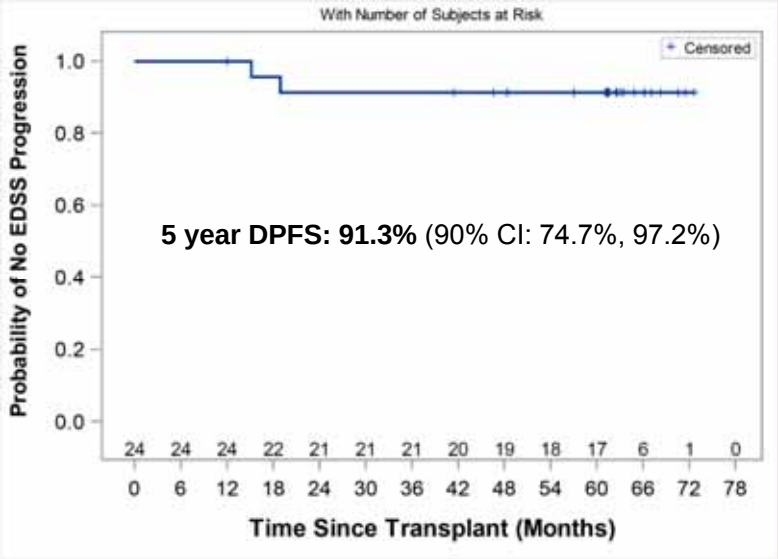
Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components.

MRI Activity-Free Survival



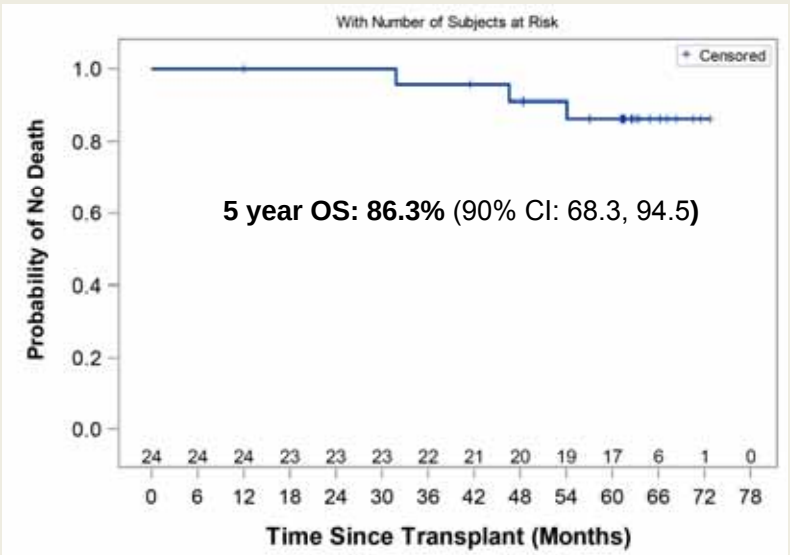
Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components. The MRI event that occurred at 11.9 months was not a primary endpoint event, but rather an event that occurred subsequently after the subject met primary endpoint via clinical relapse at 5.1 months

Disease Progression-Free Survival



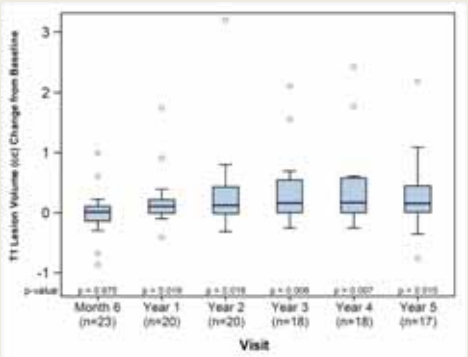
Note: Upon meeting primary endpoint, a participant is not censored from further events in the remaining components.

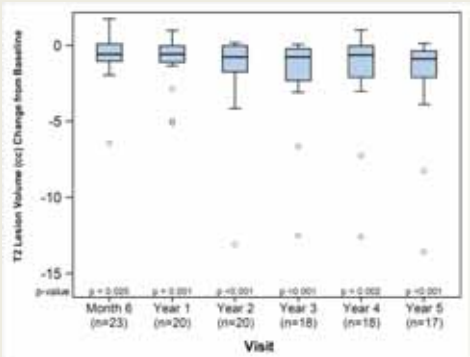
Overall Survival



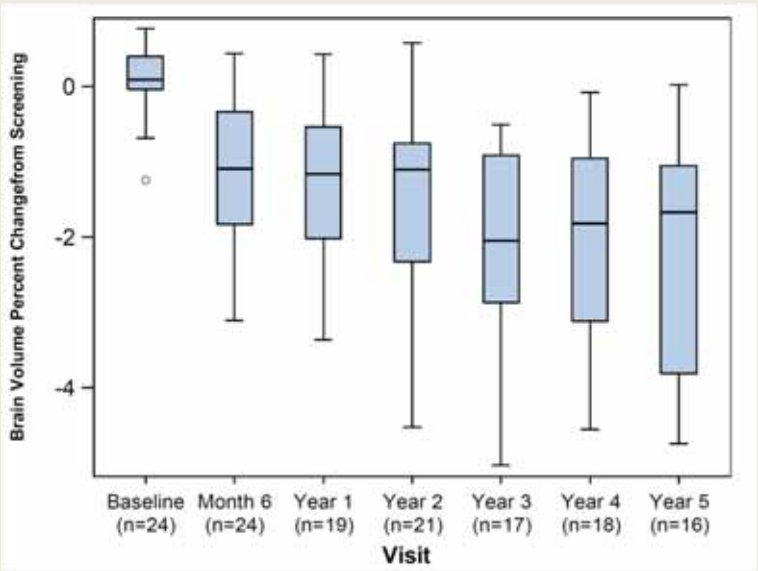
Note: Upon meeting the primary endpoint, a participant is not censored from further events in the remaining components. In each of the 3 deaths, the subject previously met primary endpoint via another criterion.

Change from Baseline in T1 and T2 Lesion Volume





Percent Change in Brain Volume from Screening



Summary

1. High-dose immunosuppressive therapy (BEAM + ATG) and autologous HCT with CD34-selected cells was well-tolerated with few serious early complications.

2. High-dose immunosuppressive therapy 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 subject experienced relapse or increase in EDSS.

3. MRI lesions reduced.

4. Brain volume stabilized at Year 3 through Year 5.

Investigators (HALT MS; ITN033AI)

Neurology Investigators
- Jim Bowen - Swedish Neuroscience 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
- 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

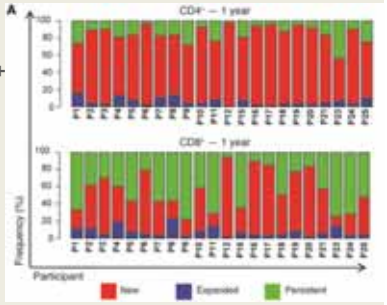
Immune Tolerance Network

NIAID
National Institute of Allergy & Infectious Diseases

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

T cell repertoire following autologous stem cell transplantation in multiple sclerosis

- High-throughput deep TCR sequencing used to assess millions of individual TCRs per patient sample (baseline, 2 months and 12 months)
- Found that HSCT has distinctive effects on CD4+ and CD8+ T cell repertoires.
- In CD4+ T cells, dominant TCR clones present before treatment were hard to detect following reconstitution, and patients largely developed a new repertoire.
- In contrast, dominant CD8+ clones were not effectively removed, and the reconstituted CD8+ T cell repertoire was created by clonal expansion of cells present before treatment.
- Patients who failed to respond to treatment had less diversity in their T cell repertoire early during the reconstitution process.



Muraro et al; JCI 2014

Association of Autologous HSCT with Neurological Disability in Patients with RRMS: Pretransplant patient characteristics (N=145)

Gender	Men	60 (41%)
	Women	85 (59%)
Type of MS	Relapsing-remitting	118 (81%)
	Secondary Progressive	27 (19%)
Age (years)	18-25	11 (8%)
	26-35	55 (38%)
	36-45	56 (38%)
	46-60	23 (16%)
# of treatments	2-3	86 (59%)
	4-5	52 (36%)
	>6	7 (5%)

Burt et al, JAMA. 2015;313(3):275-284.

Association of Autologous HSCT with Neurological Disability in Patients with RRMS: Pretransplant patient characteristics (N=145) (cont'd)

Relapses	0	31 (21%)
	1	32 (22%)
	2	57 (40%)
	>2	25 (17%)
Baseline disability	<4	66 (46%)
	4-6	61 (42%)
	>6	18 (12%)
Gad-enhancing lesions	0	61 (42%)
	1-2	40 (28%)
	3-4	16 (11%)
	>4	28 (19%)

Burt et al, JAMA. 2015;313(3):275-284.

Association of Autologous HSCT with Neurological Disability in Patients with RRMS

Treatment:

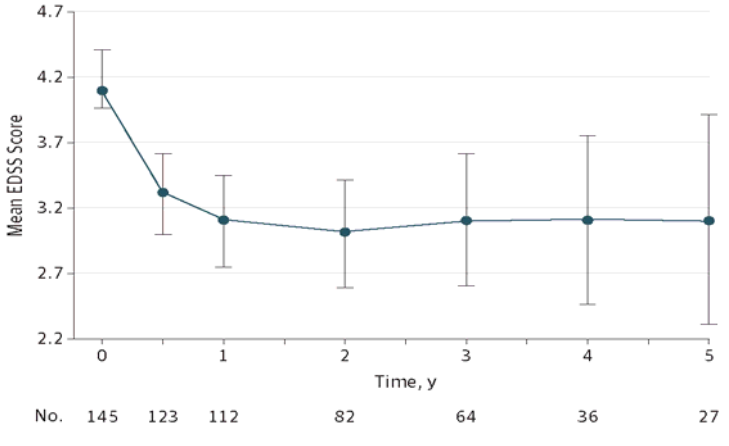
Mobilization: Cyclophosphamide 2 g/m2 + G-CSF
Conditioning: Cyclophosphamide 200 mg/kg
+
rATG (129 pts) or alemtuzumab (22 pts)

Alemtuzumab: 22.7% ITP/hypothyroidism/hyperthyroidism

Treatment related mortality: 0%

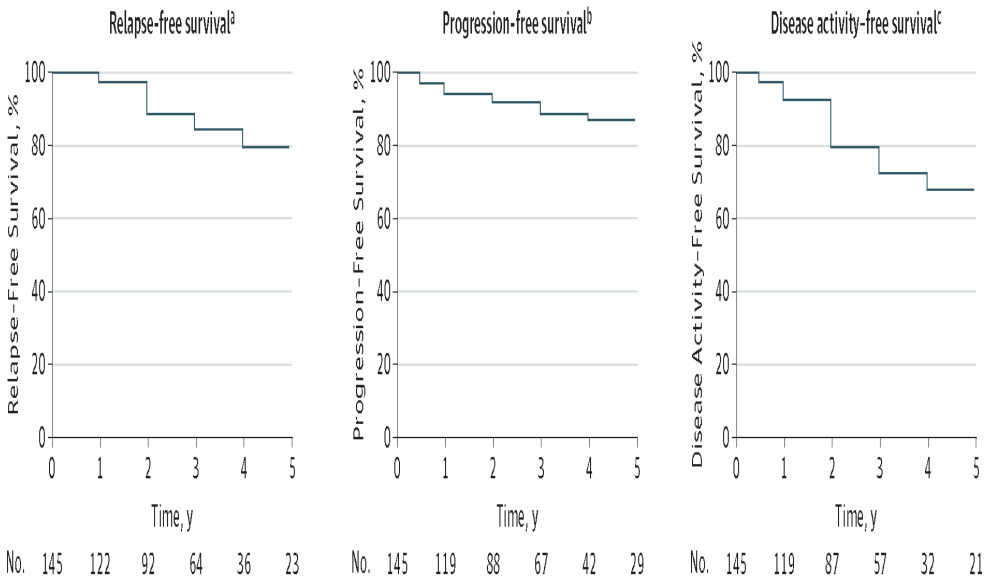
Burt et al, JAMA. 2015;313(3):275-284.

Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With RRMS: Neurological Disability Before and After Hematopoietic Stem Cell Transplantation



JAMA. 2015;313(3):275-284.

Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With RRMS: Survival



JAMA. 2015;313(3):275-284.

Conclusion

1. Long-term outcomes in relapsing-remitting MS patients after high-dose immunochemotherapy and autologous HCT was comparable in the North American studies (approx. 70% EFS).
2. Improvement in EDSS probably dependent on EDSS entering the study.
3. Effective suppression of relapses.
4. High-dose immunochemotherapy was well-tolerated.