Stem Cell Transplantation for Autoimmune Disease

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Disclosures

- I have nothing to disclose.

Objectives

1. **Rationale for BMT in autoimmune disease (AID) – focus on autologous transplant (autoSCT)**
2. **Existing data for autoSCT in AID – focus on scleroderma**
3. **Challenges / Future directions**

Terminology

I generally prefer the term SCT (stem cell transplant) over BMT (bone marrow transplant)

- Reflects the source of stem cells (derived from bone marrow, but usually obtained through peripheral blood)

Allogeneic transplant – AlloSCT (someone else's stem cells)

Autologous transplant – AutoSCT(patient and donor same person)

In the Beginning…

Reports of AID being transferred via allogeneic stem cell transplant (alloSCT)

-AND-

Reports of AID cured after alloSCT when done for concurrent malignancy

Allogeneic vs. Autologous SCT

AlloSCT for AID makes sense theoretically

-BUT-

High morbidity / mortality of alloSCT makes specific use for AID difficult

What about autologous SCT (autoSCT)?

AutoSCT

AutoSCT leverages *dose-response* principle of cytotoxic chemotherapy

– If a little bit of chemotherapy is good, more chemotherapy is better!

Primarily used in lymphoma and myeloma where high-dose chemotherapy can induce prolonged remission or cure.

However - Chemotherapy / XRT at high doses are also the most powerful immunosuppressant.

AutoSCT for AID

Cartoon by Cynthia McKelvey, used with permission.

AutoSCT for AID

The theory is that autoSCT acts as a sort of “reset” button for AID.

– High-dose chemotherapy +/- radiation kills aberrant immune cells

– Infusion of stem cells with immune reconstitution eliminates autoimmune phenotype.

A lot of issues:

1) Lack of robust biomarker for AID
2) Incomplete knowledge regarding biology of AID.
3) Reinfusion of autoreactive cells?
4) Toxicity of autoSCT (organ toxicity, secondary malignancy)

Scleroderma

Highly morbid autoimmune disease affecting multiple organs (skin, heart, lungs, kidney, GI tract)

Age-matched mortality 3.5x overall

- 60% from pulmonary issues(PAH, pulmonary fibrosis)
- ~25-30% from cardiac issues (atherosclerosis, microvascular disease, cardiac fibrosis)
- Renal crisis mortality has decreased greatly with ACE inhibitors

Mortality correlates with age, male gender, active pulmonary disease, CHF, worsening skin score.

Scleroderma

Available treatments are poor, no true disease-modifying therapy

Lung – mycophenolate mofetil (MMF), cyclophosphamide (Cy - oral or pulsed IV) both with very modest benefits and require long-term use

Skin – methotrexate, MMF with very modest benefits, other topical / localized care

AutoSCT in Scleroderma

Three randomized trials of autoSCT in scleroderma (pulsed Cy control arm in all three) - **autoSCT superior in all three**

- ASTIS (Europe)
- ASSIST (Northwestern)
- SCOT (multicenter, US + Canada)

ASTIS

156 patients (HSCT = 79, monthly Cy = 77), accrual in Europe from 2001-2009

Adult patients with cutaneous disease, mRSS >= 15 and organ involvement

Exclusion: Pulmonary HTN, other serious comorbidities

Primary endpoint – EFS (event = death, persistent organ dysfunction)

Van Laar JM, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014 Jun 25;311(24):2490-8.

ASTIS

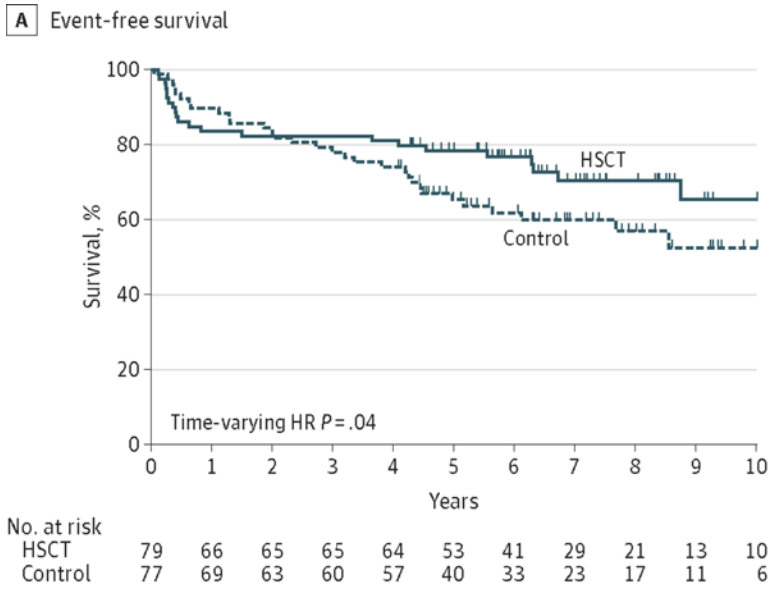
ASCT arm:

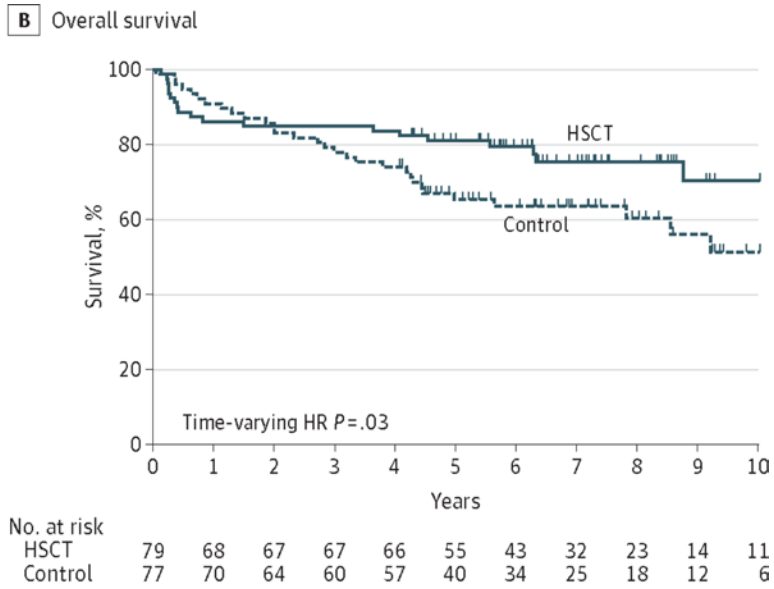
- PBSC mobilization with Cy 4 gm/m2 + G-CSF followed by CD34+ selection
- Conditioning:
    - Cy 200 mg/kg (50 mg/kg x 4), rabbit ATG 2.5 mg/kg daily x 3

Chemotherapy arm:

Cy 750 mg/m2 IV qmonth x 12

ASTIS





From: **Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis: A Randomized Clinical Trial**

JAMA. 2014;311(24):2490-2498. doi:10.1001/jama.2014.6368

ASTIS - Toxicity

HCT – 22 events (19 deaths, 3 organ failure)

Cy – 31 events (23 deaths, 8 organ failure)

More events with HCT in 1st year (13 vs. 8), but long-term EFS / OS better (trial not powered for OS)

- At two years, 14 vs. 14 events
- At four years, 15 vs. 20 events

HCT-associated 1-yr TRM – 8 (10%)

Secondary outcomes – improvement in mRSS, FVC, TLC in HCT, but worse kidney function

ASSIST

Single-center study at Northwestern University

Randomized phase 2 trial of ASCT vs. Cy, n = 19 (ASCT = 10, Cy = 9)

Inclusion: Age < 60, mRSS > 14, internal organ involvement. mRSS < 14 and pulmonary involvement was allowed too.

Exclusion: > 6 doses of Cy, TLC < 45%, EF < 40%, symptomatic cardiac disease, PAH

Primary endpoint: Improvement at 12 mo follow-up (either reduction in mRSS by > 25% or FVC increase by over 10%)

ASSIST

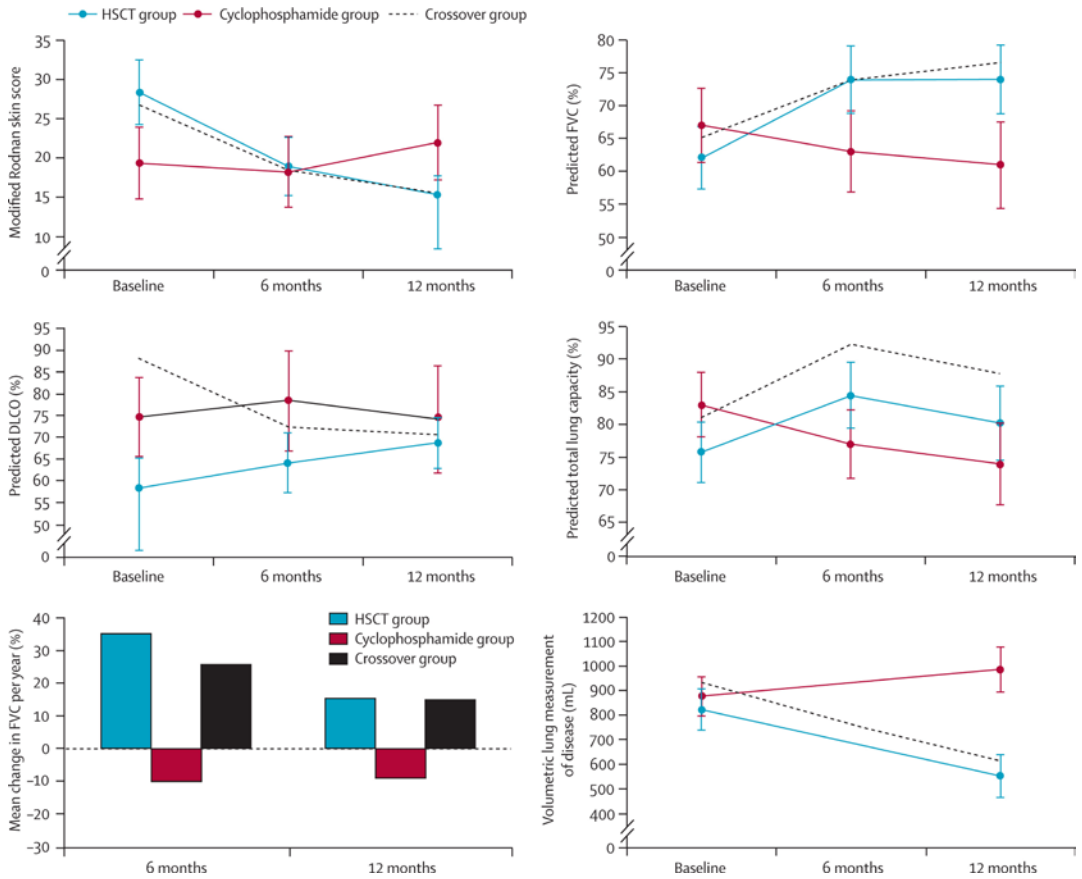
ASCT arm:

- PBSC mobilization with Cy 2 gm/m2 + G-CSF (no CD34+ selection)
- 50 mg/kg Cy D-5 to D-2
- rATG 0.5 mg/kg D-5, 1.5 mg/kg D-4 to D-1

Cy arm:

- 1 gm/m2 Cy qmonth x 6

ASSIST



Burt RK, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet. 2011 Aug 6;378(9790):498-506.

ASSIST

No TRM in HSCT

10/10 improvement in HSCT, 0/9 in Cy arm

7 patients in Cy arm switched to HSCT (1 did not progress, 1 was medically ineligible for HSCT), all 7 improved

Median mRSS in transplant arm from 28 to 15 in one year, DLCO 58 to 69%

SCOT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*

ABSTRACT

BACKGROUND

Despite current therapies, diffuse cutaneous systemic sclerosis (scleroderma) often has a devastating outcome. We compared myeloablative CD34+ selected autologous hematopoietic stem-cell transplantation with immunosuppression by means of 12 monthly infusions of cyclophosphamide in patients with scleroderma.

METHODS

We randomly assigned adults (18 to 69 years of age) with severe scleroderma to undergo myeloablative autologous stem-cell transplantation (36 participants) or to receive cyclophosphamide (39 participants). The primary end point was a global rank composite score comparing participants with each other on the basis of a hierarchy of disease features assessed at 54 months: death, event-free survival (survival without respiratory, renal, or cardiac failure), forced vital capacity, the score on the Disability Index of the Health Assessment Questionnaire, and the modified Rodnan skin score.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sullivan at the Cellular Therapy Program, Department of Medicine, Box 3961, Duke University Medical Center, Durham, NC 27710, or at keith.sullivan@duke.edu.

*A complete list of the SCOT study sites, collaborators, and personnel is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Goldmuntz and Keyes-Elstein contributed equally to this article.

N Engl J Med 2018;378:35-47.
DOI: 10.1056/NEJMoa1703327

SCOT

Multicenter randomized control trial of ASCT vs. Cy

75 patients (ASCT = 36, Cy = 39) – 3 did not receive transplant and died early but included in ITT analysis

Inclusion: 18-69yo, scleroderma duration of < 5y with pulmonary or renal involvement

Exclusion: active GAVE, DLCO < 60%, FVC < 45%, LVEF < 50%, CrCl < 40, PAH, more than 6 doses of Cy

Primary endpoint: Global rank composite score (GRCS) at 54 months

SCOT

ASCT arm:

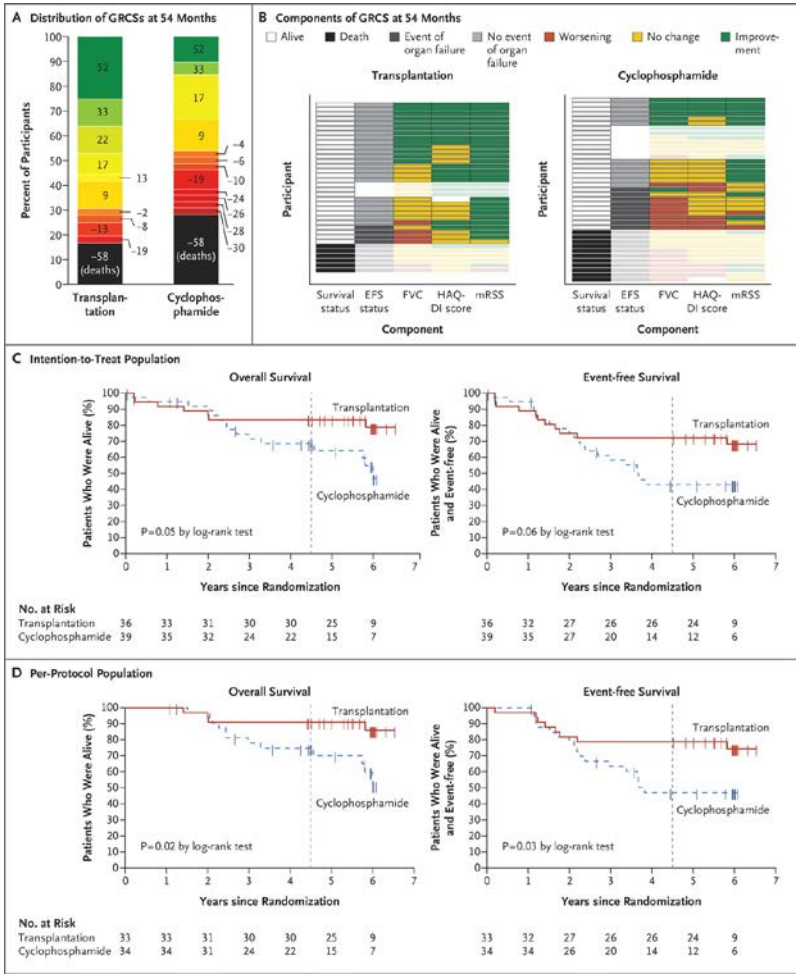
•PBSC mobilized with G-CSF alone with CD34+ selection

•TBI 800 cGy (lung and kidneys shielded to 200 cGy), cyclophosphamide 120 mg/kg + horse ATG 90 mg/kg.

Cy arm:

•Cy 500 mg/m2, then 750 mg/m2 q28 days

SCOT - Outcomes



Sullivan KM et al. N Engl J Med 2018;378:35-47

SCOT - Outcomes

		Transplant (N=36)	Cyclophosphamide (N=39)	p-value
Primary Endpoint:				
GRCS at Month 54 % of favorable pairwise comparisons	Median (min, max)	17 (-58, 52) 67.6	- 6 (-58, 52) 32.4	0.013
Secondary Endpoints:				
GRCS at Month 48	Median (min, max)	20 (-58, 55)	- 8 (-58, 55)	0.008
EFS at Months 48 & 54	n (%) failure	10 (28%)	20 (51%)	0.059
Mortality (all causes) at Months 48 & 54	n (%) deaths	6 (17%)	11 (28%)	0.28

SCOT - Outcomes

Table 3. Deaths during the 72-Month Trial Period (Intention-to-Treat Population).

Group and Time from Randomization to Death	Site-Reported Cause of Death	Completed Treatment
Cyclophosphamide group		
1.7 Mo	Pulmonary embolism	No (2 doses of cyclophosphamide)
6.6 Mo	Respiratory failure	No (5 doses of cyclophosphamide)
18.2 Mo	Scleroderma	Yes
24.5 Mo	Scleroderma*	Yes
25.4 Mo	Septic shock	Yes
27.2 Mo	Pulmonary hypertension	Yes
29.3 Mo	Respiratory*	Yes
29.3 Mo	Respiratory failure*	Yes
32.3 Mo	Unknown cause†	No (0 doses of cyclophosphamide)
35.7 Mo	Respiratory failure	Yes
39.4 Mo	Arrhythmia*	Yes
54.7 Mo‡	Infection*	Yes
68.9 Mo‡	Progression of systemic sclerosis*†	Yes
69.8 Mo‡	Sepsis*†	Yes
Transplantation group		
2.4 Mo	Unknown cause	No (no mobilization, conditioning, or transplantation)
2.6 Mo	Pulmonary alveolar hemorrhage	No (no conditioning or transplantation)
9.3 Mo	Unknown cause	No (no mobilization, conditioning, or transplantation)
16.9 Mo	Enterococcal meningitis§	Yes
23.9 Mo	Respiratory*	Yes
24.1 Mo	Metabolic*†	Yes
69.9 Mo‡	Acute myeloid leukemia§	Yes

* The participant had had an event of respiratory, renal, or cardiac failure before death.
† Death was identified through site contact or public records after participant withdrawal or trial completion.
‡ Deaths after 54 months were not counted in the primary end-point analyses.
§ Death occurred after a diagnosis of the myelodysplastic syndrome.

Sullivan KM et al. N Engl J Med 2018;378:35-47

SCOT - Outcomes

	HSCT (N=33)	CY (N=34)	P - value
Initiated DMARDs, n	3 (9%)	15 (44%)	0.001
Pulmonary artery hypertension, n	0	5 (15%)	0.022
Congestive heart failure*, n	0	4 (12%)	0.042

Abbreviations: CY, cyclophosphamide; DMARDS, Disease Modifying Anti-Rheumatic Drugs; HSCT, Hematopoietic Stem Cell Transplant

*** Requiring Treatment**

Summary of Randomized Trials

	ASSIST	ASTIS	SCOT
Treatment			
CY arm	CY 1000 mg/m^2/mo 1v x 6 (total 6 gm/m^2 over 6 mo)	CY 750mg/m^2/mo 1v x 12 (9 gm/m^2 over 12 mo)	CY 750mg/m^2/mo 1v x 12 (9 gm/m^2 over 12 mo)
HSCT arm	CY 200 mg/kg and ATG (rabbit) 6.5 mg/kg and mePrednisolone 5000mg	CY 200 mg/kg and ATG (rabbit) 7.5 mg/kg	CY 120 mg/kg, ATG (horse) 90 mg/kg, TBI 800 cGy (A)
Autologous cells	Unselected	CD34 selected	CD34 selected
Stem Cell mobilization	CY 2 gm/m^2 and G - CSF	CY 4 gm/m^2 and G-CSF	G-CSF only
Primary Endpoint	Improvement at 12 mo.	EFS at 24 mo.	GRCS at 54 mo.
Publication	Lancet 2011; 378:498	JAMA 2014; 311:2490	NEJM 2018; 378:35

Abbreviations: ATG, Antithmyocyte Globulin; CY, cyclophosphamide; EFS, event-free survival; G- CSF, Granulocyte Colony Stimulating Factor; GRCS, global rank composite score; HSCT, hematopoietic stem cell transplant; SSc, systemic sclerosis; TBI, total body irradiation

(A) Lung and Kidney shielded to 200 cGy transmission

Challenges in Scleroderma

Patient selection

Choice of conditioning regimen

Clinical experience – these patients get very sick, patient selection

Long-term morbidity (MDS/AML)

CD34+ selection? – Probably ok to use Cy mobilization without CD34+ selection

Rheumatologist comfort level

Payor coverage

Multiple Sclerosis

Global experience greater with MS than scleroderma.

Differences

- Effective therapy exists for MS
- Disease natural history more favorable (for relapsing-remitting)

As with scleroderma, main concern is toxicity. Also, **fever** poorly tolerated with MS.

Multiple regimens – high-dose cyclophosphamide, Bu/Cy, TBI-based regimens, BEAM.

Low TRM 0.7% from 2008 to 2016 (Muraro PA, et al. Nat Rev Neurol 2017)

Multiple Sclerosis

Retrospective analysis from CIBMTR / EBMT of 281 patients

PFS 46% at 5 years (82% for RRMS)

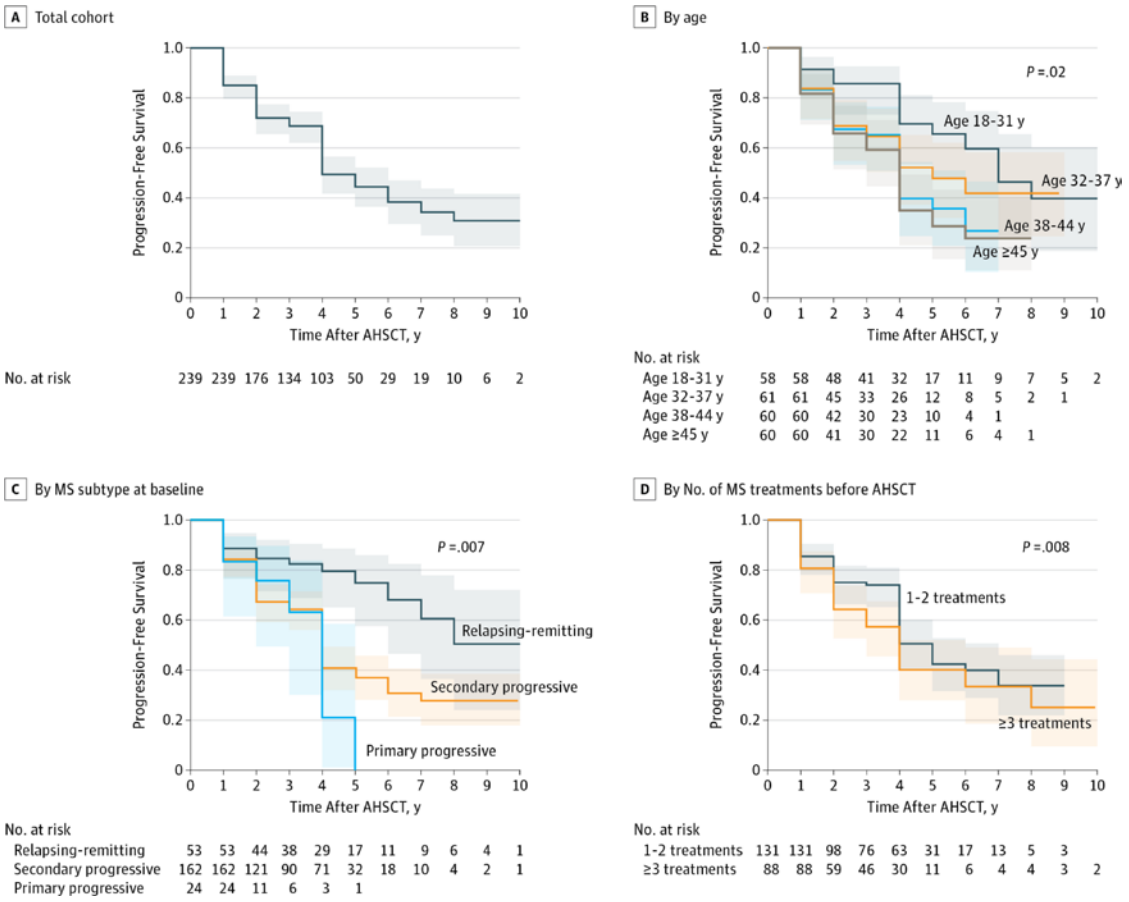
8 deaths (2.9%) within 100 days

Factors associated with disease progression:

1) Age
2) Progressive vs. relapsing disease (RRMS does best).
3) Number of prior therapies (3+ worse than 1-2)

9 secondary malignancies (tMDS in 3 patients)

Multiple Sclerosis



Muraro PA, Pasquini M, Atkins HL, et al. JAMA Neurol. 2017;74(4):459-469. doi:10.1001/jamaneurol.2016.5867

Multiple Sclerosis - MIST

Only randomized phase III trial of autoSCT vs. DMARD for relapsing / remitting MS (RRMS)

* DMARD arm did not include alemtuzumab or ocrelizumab.

110 patients (55 autoSCT, 55 DMARD).

Mobilization: Cy 2 gm/m2 + G-CSF

Conditioning: – Cy 200 mg/kg + rabbit ATG (6 mg/kg over 5 days)

Primary endpoint: Treatment failure (EDSS increase of >= 1 point sustained for 6 months) – met in 6% in autoSCT arm vs. 67% in DMARD arm.

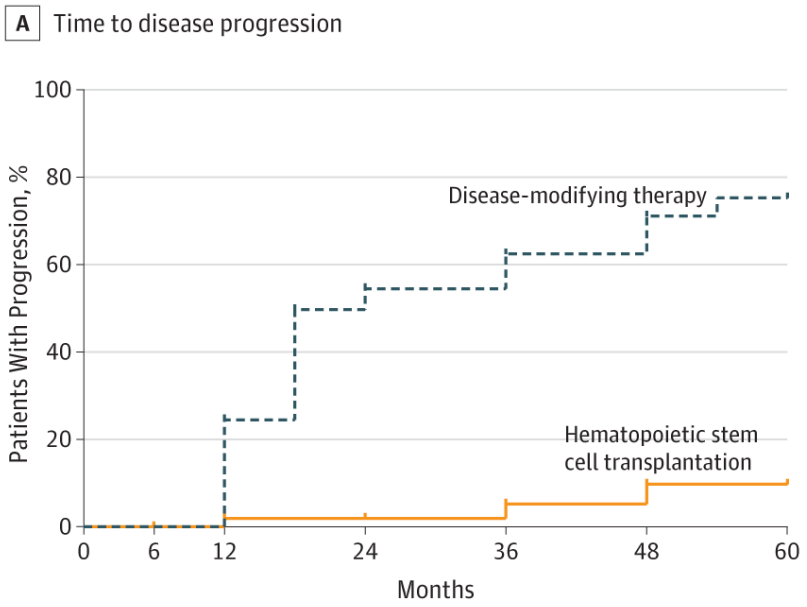
Multiple Sclerosis - MIST

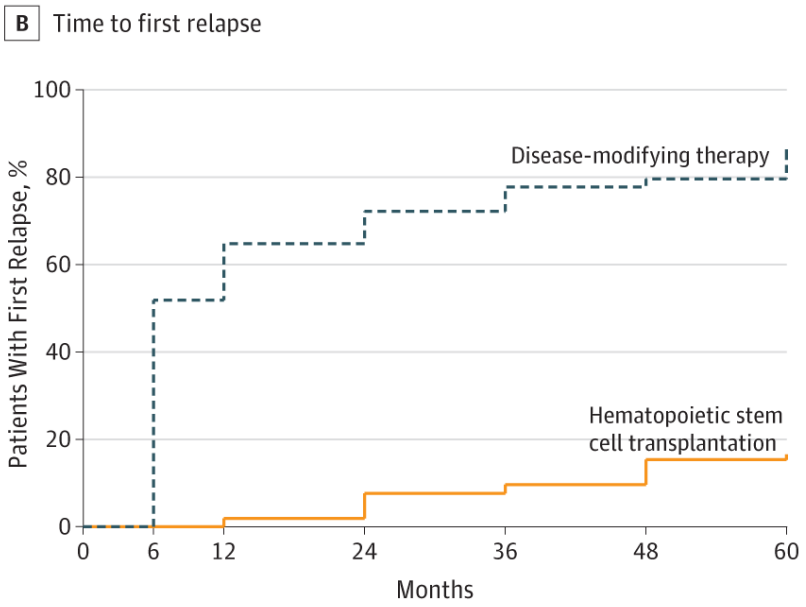
In autoSCT arm – mean EDSS improved from 3.38 to 2.36 at 1 year

In DMARD group – mean EDSS increased from 3.31 to 3.98 at 1 year.

TRM – 0!

Multiple Sclerosis - MIST





No. at risk

Hematopoietic stem cell transplantation	52	52	51	51	50	49	48
Disease-modifying therapy	54	54	43	30	26	24	23

Hematopoietic stem cell transplantation	53	53	52	49	48	45	45
Disease-modifying therapy	55	26	18	15	12	11	9

From Burt RK, Balabanov R, Burman J, et al. JAMA. 2019;321(2):165-174. doi:10.1001/jama.2018.18743

Future Directions

Scleroderma – Unlikely to be any more randomized trials

- Increasing awareness/advocacy
- Expertise in managing toxicities
- Payor coverage

BEAT-MS – randomized phase III trial of autoHCT with BEAM conditioning for RRMS (EDM 2-5) vs. best available antibody therapy

Further work on other diseases - TBA