CBCI
COLORADO BLOOD CANCER INSTITUTE

Rocky Mountain Hospital *for* Children
At Presbyterian/St. Luke's Health ONE

A Member of the Sarah Cannon Blood Cancer Network

High-Dose Immunosuppressive Therapy (HDIT) followed by Autologous Hematopoietic Cell Transplantation (HCT) for Opsoclonus Myoclonus Ataxia Syndrome

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Opsoclonus Myoclonus Ataxia Syndrome

- Clinical symptoms
  - Continuous, involuntary arrhythmic movements of the eyes
  - Myoclonus of the limbs, trunk, head
  - Ataxia
  - Irritability and sleep disturbance
  - Regression of motor and language skills
  - Can lead to long term cognitive impairment
- Diagnosis in pediatrics based on 3 of 4:
  - Opsoclonus
  - Myoclonus or ataxia
  - Behavioral changes or sleep disturbance
  - Neuroblastoma

Opsoclonus Myoclonus Ataxia Syndrome

- In pediatrics, around 50% associated with tumor
  - Neuroblastoma, ganglioneuroblastoma, ganglioneuroma
  - Nearly always associated with small, even difficult to find tumors
  - Tumor is often treatable with surgical resection alone
  - Usually not associated with the high risk neuroblastomas that require high dose chemotherapy followed by stem cell rescue for cure
  - Rarely associated with ovarian teratoma
- May also be associated with infections in pediatrics
- In adults, can be associated with infection, trauma, toxins, malignancy
  - Small cell lung carcinoma
  - Thyroid carcinoma
  - Breast carcinoma
  - Gynecologic tumors

Opsoclonus Myoclonus Ataxia Syndrome

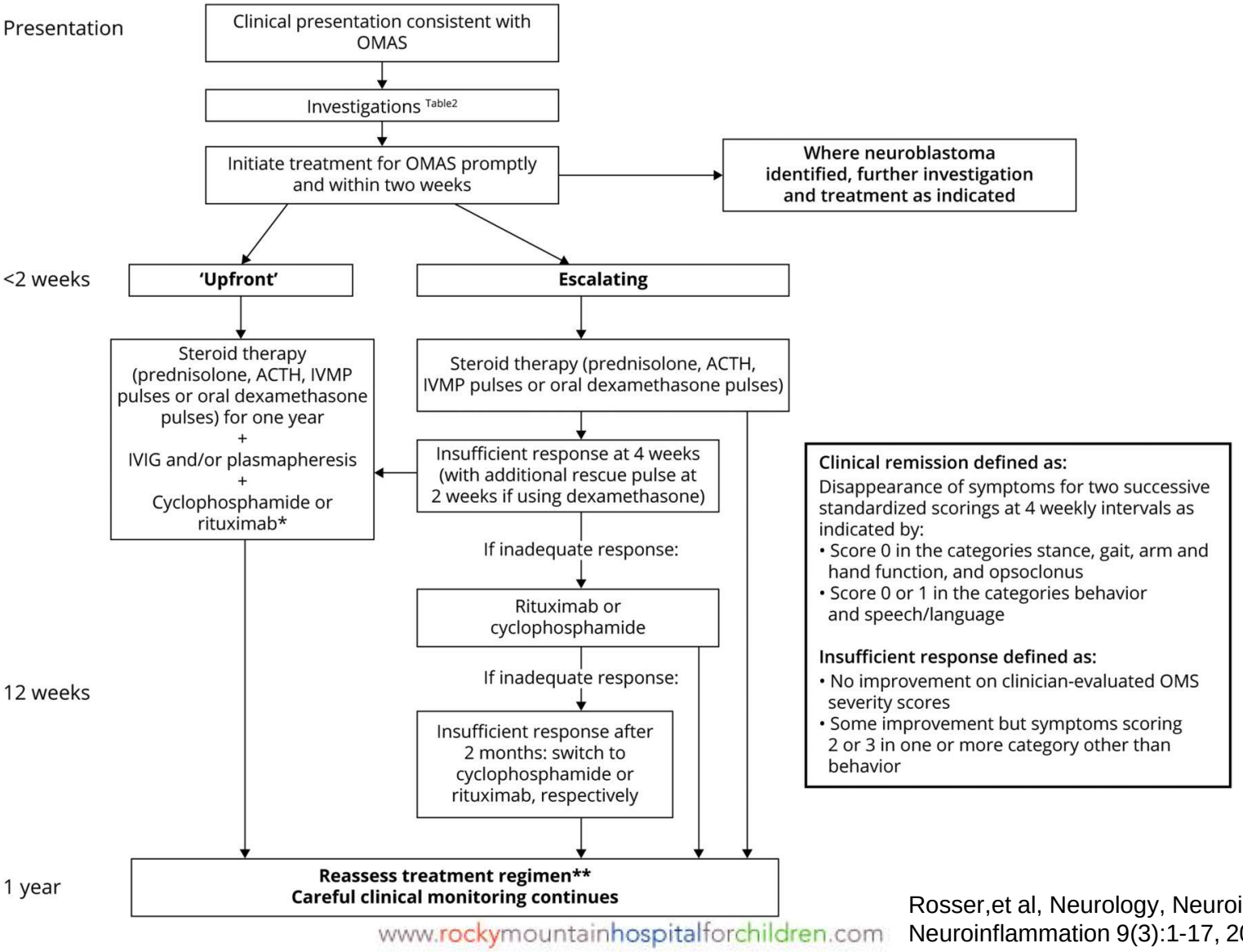
Table 1 Biomarkers in OMAS and Neuroblastoma

Biomarker	Significance	OMAS vs control	Research or clinical setting	Specificity	Reference
CSF immunology					
CSF B-cell expansion	Expansion of B cells in OMAS	Increased	Research	No	17,18
CSF oligoclonal bands	Clonal expansion of immunoglobulin G	Intrathecal synthesis in 58% of untreated OMAS	Clinical	No	19
CSF neopterin	Cellular immune activation biomarker	Increased in majority	Clinical (limited)	No	20
CSF cytokines and chemokines	Support involvement of B-cell, T-cell, and innate immune activation	Increased in OMAS, higher in severe disease, and reduce with treatment	Research	No	20-25
Neuronal damage					
Neurofilament	Evidence of neuronal damage marker	Elevated in the acute phase and correlates with outcome	Research	No	26
Peripheral neuroblastic tumor markers					
Neuroimaging (MRI, CT, and ultrasound)	Evidence of peripheral neuroblastic tumor	Present in ~50% of patients	Clinical	Yes	8
Urine catecholamine	Support presence of catecholamine-secreting tumor	Elevated in the minority of patients	Clinical	Yes	8

Abbreviation: OMAS = opsoclonus-myoclonus-ataxia syndrome.

Rosser,et al, Neurology, Neuroimmunology, Neuroinflammation 9(3):1-17, 2022

Opsoclonus Myoclonus Ataxia Syndrome



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Rosser,et al, Neurology, Neuroimmunology, Neuroinflammation 9(3):1-17, 2022

Hematopoietic Cell Transplantation for Autoimmune Disease

- Allogeneic HCT
  - Replace host autoreactive immune system with donor-derived immune system
  - Promote regulatory mechanisms that control autoimmune disease (e.g. mixed donor-host chimerism)
  - Higher morbidity and mortality rate with allogeneic HCT than with autologous HCT, although in recent years this has improved
  - Retrospective analysis of allogeneic HCT in MS patients with hematological malignancies showed that patients stabilized and CSF in many patients became negative for oligoclonal bands.

Hematopoietic Cell Transplantation for Autoimmune Disease

Allogeneic HSCT and Autoimmune Diseases in Humans: Literature Review

Autoimmune Disease	Hematologic Disease	Patients	Remission	Alive	Follow-up
Rheumatoid Arthritis	8 SAA 1 MDS	9	8	5	2 mos – 13 yrs
SLE	SAA	1	1 (ANA+)	1	15 yrs
Psoriatic Arthritis	AML, CML	4	3	3	1, 3, 5, 5 yrs
Ulcerative Colitis	AML	1	1	1	4 yrs
Crohn's Disease	AML, CML	5	4	5	4.5 – 15.3 yrs

Table from FHCRC2260 protocol

Baldwin et al, Arthritis &Rheumatism 20:1043-1048, 1977
Snowden et al, Arthritis Rheum 41:453-459, 1998
McKendry et al, Arthritis & Rheumatism 39:1246-1253, 1996
Jacobs et al, BMT 1:237-239, 1986
Gur-Lavi et al, Arthritis & Rheumatism 42: 1777,1999
Yin et al, BMT 9:31-33, 1992
Eedy et al, Br Med J 300:908, 1990
Slavin et al, Exp Hemtol 28:853-857, 2000
Lopez-Cubero et al, Gastroenterology 114:433-440. 1998

Hematopoietic Cell Transplantation for Autoimmune Disease

- High-dose immunosuppressive therapy (HDIT) and autologous hematopoietic cell transplantation (HCT)
  - Allows dose intensification of immunosuppressive therapy
  - Rapid reduction of the autoimmune effector cells
  - Sustained immunomodulatory effect: resetting of the immune system, establish tolerance to the autoimmune targets

High-Dose Immunosuppressive Therapy (HDIT) followed by Autologous Hematopoietic Cell Transplantation (HCT)

- Mobilization of stem cells using cyclophosphamide and filgrastim
  - Cyclophosphamide allows for collection of fewer mature T cell clones, richer CD34 early progenitor cell population
- High dose chemotherapy (conditioning regimen) causes in vivo ablation of T and B cell clones
- Use of ATG acts as in vivo T cell depletion
- Post-transplant, patients have a change in the effector cell population, hopefully with destruction of the problematic clones

HDIT with auto HCT

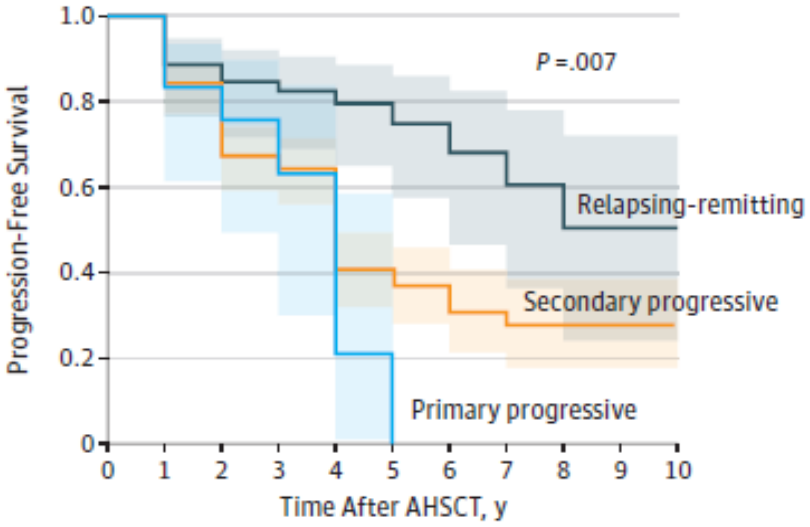
- Is the risk of the procedure justified based upon the risk of the disease?
  - These autoimmune neurologic diseases cause significant morbidity
    - Neurologic devastation from the disease itself
    - Long term sequelae of immunosuppressive treatments
  - Autologous hematopoietic stem cell transplantation
    - Mortality rate of <5% in breast cancer trials, registry data shows <1% mortality in previous MS trials
    - Low risk for long term complications such as infertility and secondary malignancy
    - Generally well tolerated
- Is there evidence to suggest that this strategy may be effective?

HDIT with auto HCT for Multiple Sclerosis

- Multiple sclerosis is a neurologic autoimmune disease
  - Migration of immune cells into the CNS
  - Production of inflammatory cytokines
  - Demyelination and neuronal damage
- Symptoms
  - Pain
  - Tremor
  - Involuntary movements, muscle paralysis, muscle rigidity
  - Poor balance, vertigo
  - Incontinence
  - Neuropathy
  - Visual changes or vision loss
  - Anxiety or mood swings
  - Difficulty with speech and/or swallowing

HDIT with auto HCT for Multiple Sclerosis

C By MS subtype at baseline

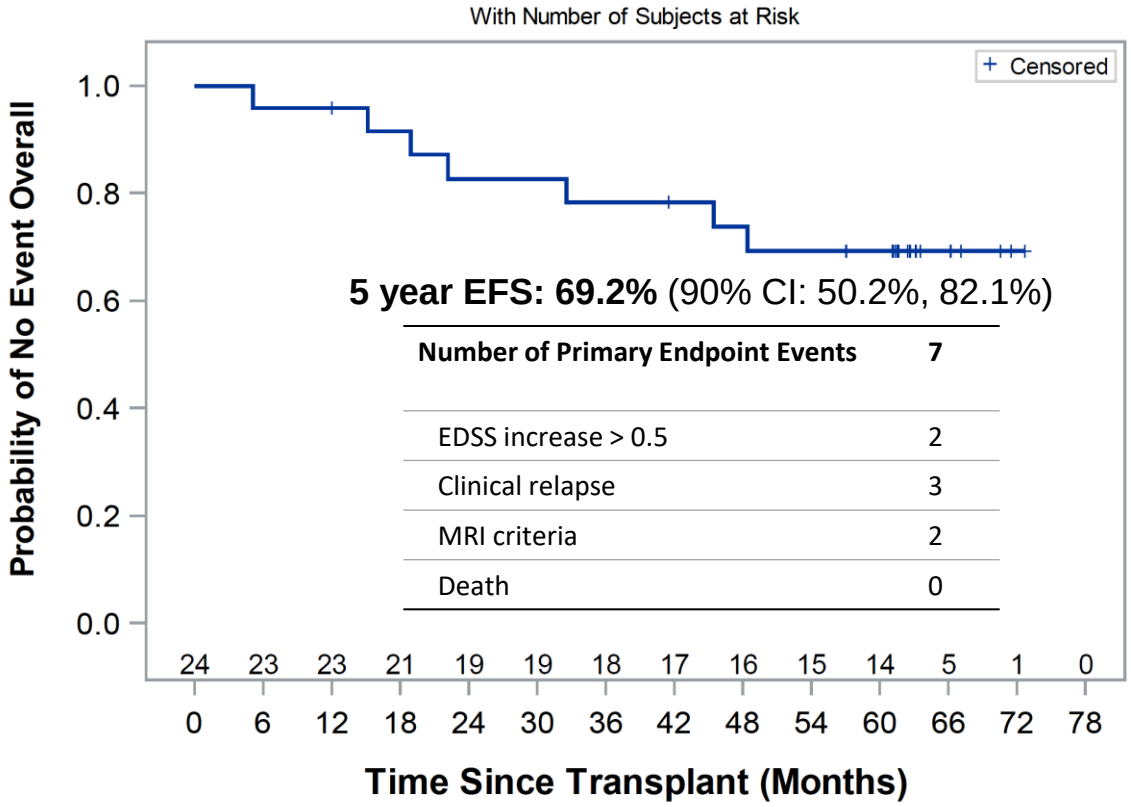


No. at risk

Relapsing-remitting	53	53	44	38	29	17	11	9	6	4	1
Secondary progressive	162	162	121	90	71	32	18	10	4	2	1
Primary progressive	24	24	11	6	3	1					

HDIT with auto HCT for Multiple Sclerosis

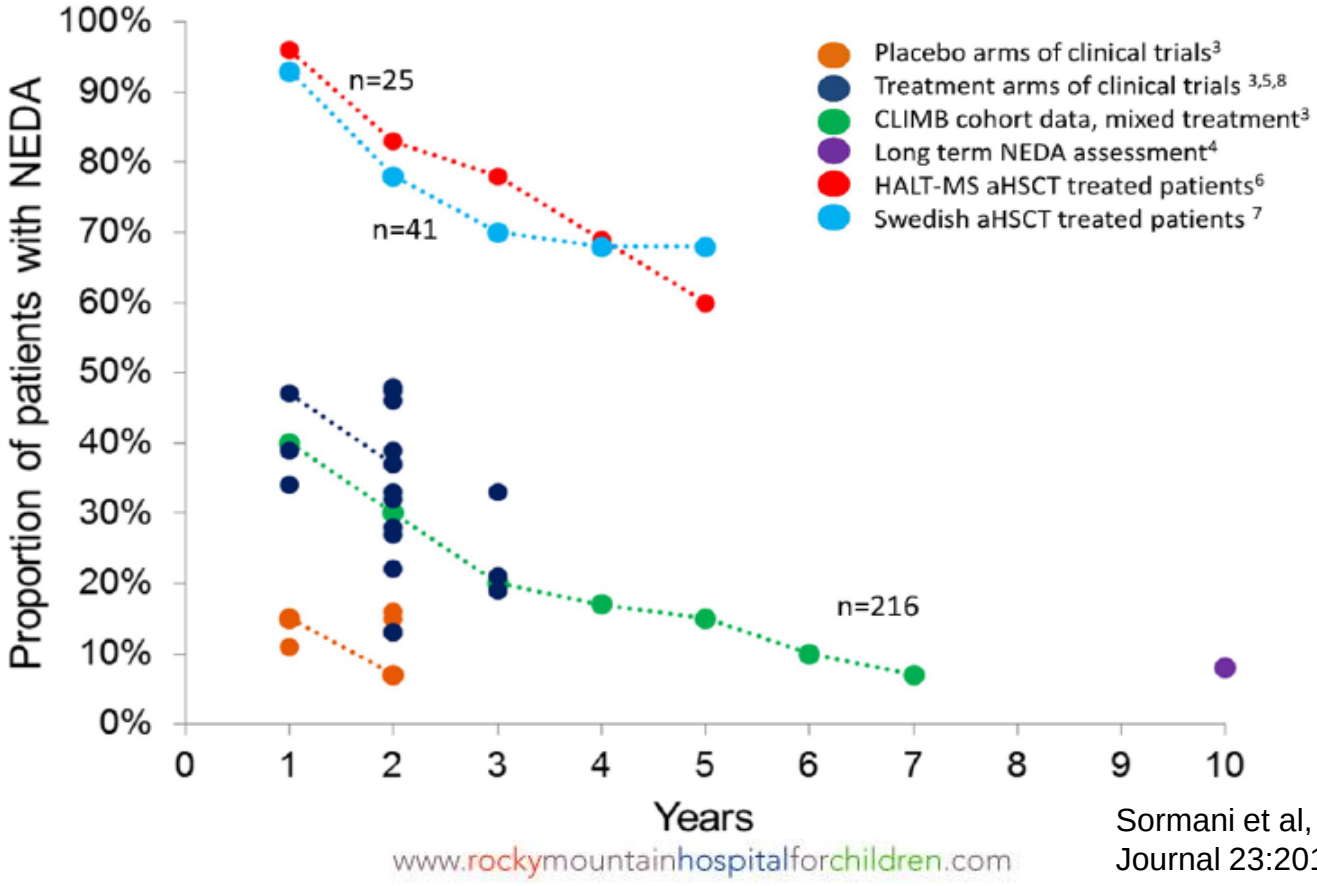
Primary Endpoint: Event-Free Survival (Relapsing Remitting)



Nash et al, Neurology 88:842-852, 2017

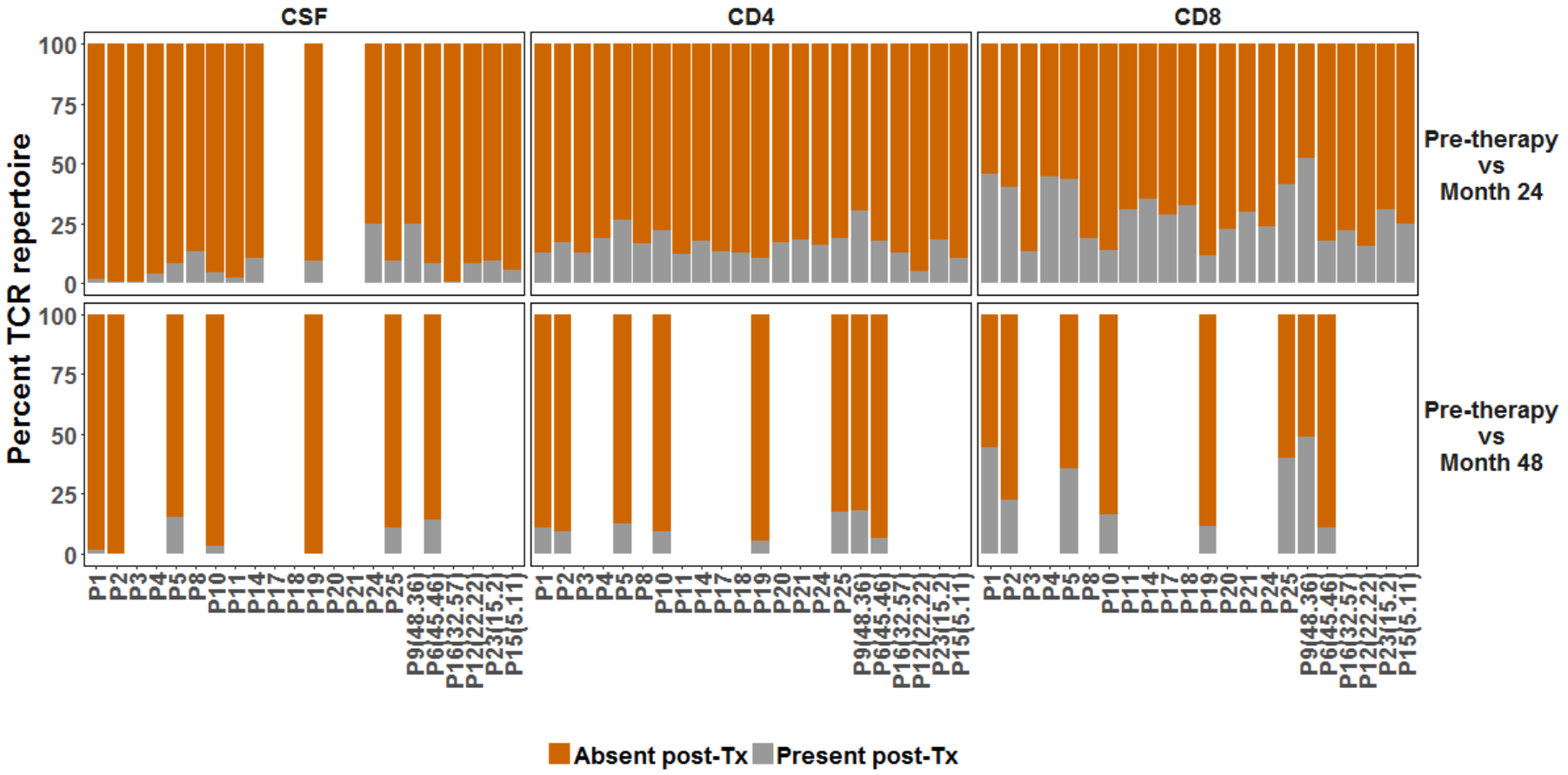
HDIT with auto HCT for Multiple Sclerosis

Conventional Treatment vs HDIT/HCT:
Maintenance of No Evidence of Disease Activity (NEDA)



Sormani et al, Multiple Sclerosis Journal 23:201-4,2017

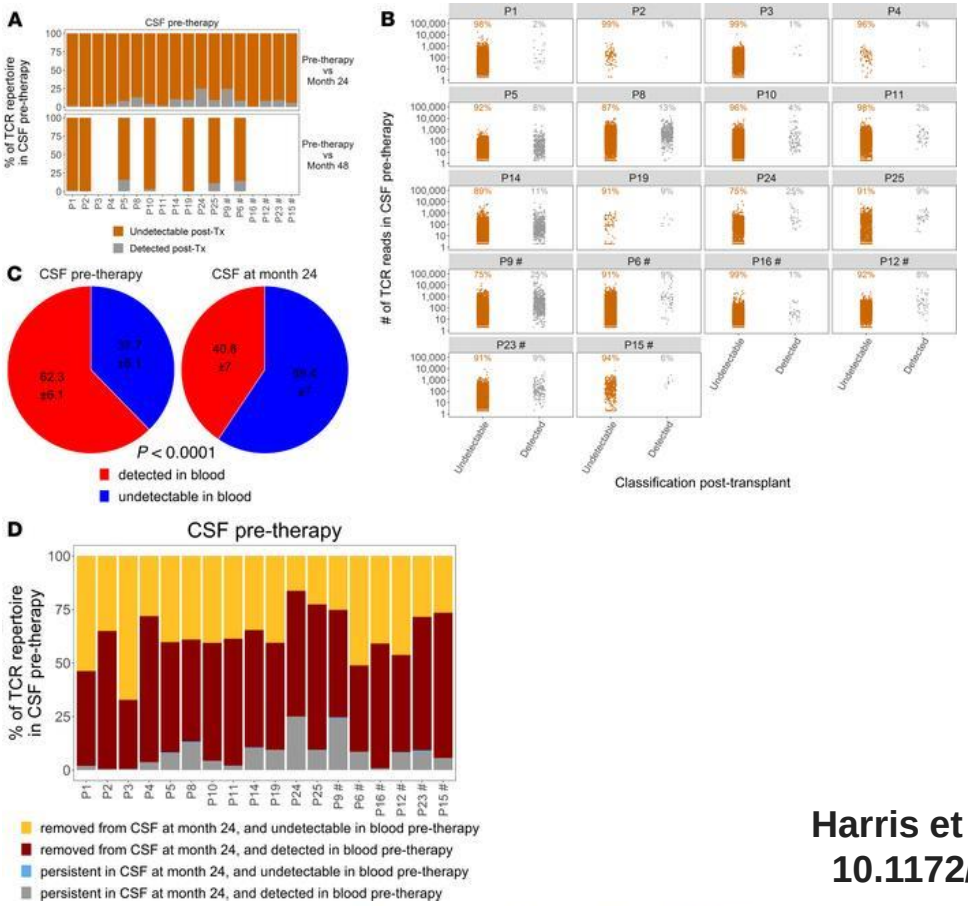
HDIT with auto HCT for Multiple Sclerosis



Harris et al, JCI Insight DOI: 10.1172/jci.insight.127655

HDIT with auto HCT for Multiple Sclerosis

Figure 2: Extensive intrathecal T cell renewal following hematopoietic transplantation for multiple sclerosis



Harris et al, JCI Insight DOI: 10.1172/jci.insight.127655

Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis: Recommendations of the National MS Society

- The National Multiple Sclerosis Society believes that AHSCT may be a useful treatment option for people with relapsing multiple sclerosis who demonstrate substantial breakthrough disease activity (ie, new inflammatory central nervous system lesions and/or clinical relapses) despite treatment with high-efficacy disease-modifying therapy or have contraindications to high-efficacy disease-modifying therapies.
- The best candidates are likely people younger than 50 years with shorter durations of disease (<10 years).
- The procedure should only be performed at centers with substantial experience and expertise.
- Ideally, recipients of the procedure should be entered into a single database, and further research is needed to establish ideal cell mobilization and immune-conditioning regimens.

Miller et al JAMA Neurology Oct, 2020

HDIT with auto HCT

- Based upon the success of HDIT for multiple sclerosis, FHCRC protocol 2260 trial opened for other autoimmune neurologic diseases of the central or peripheral nervous system
  - Myasthenia Gravis (n=1; 2 year follow-up completed)
  - Chronic Inflammatory Demyelinating Polyneuropathy (n=2)
  - Stiff Person Syndrome (n=9)
  - Neuromyelitis Optica (n=3; none recently)
  - Primary CNS Vasculitis
  - **Rasmussen's Encephalitis (n=2; returning for 1 year follow-up)**
  - Autoimmune Peripheral Neuropathy (anti-Hu [Anna-1], Anti-GM1 [GD1b], Anti-MAG, Anti-ganglioside, Anti-sulfatide)
  - Autoimmune Cerebellar Degeneration
  - Gait Ataxia with Late Age Onset Polyneuropathy (GALOP)
  - Lambert Eaton Myasthenic Syndrome
  - HTLV-1- Associated Myelopathy (HAM)/ Tropical Spastic Paraparesis (TSP)
  - **Opsoclonus/ Myoclonus (pediatric patient pending)**
  - Multiple Sclerosis
  - Other (n=1). Central or peripheral nervous system autoimmune diseases as approved by study neurologists and the FHCRC faculty at Patient Care Conference (PCC).

Myasthenia Gravis (MG)

- Antibody-mediated autoimmune disease of the neuromuscular junction.
- Autoantibodies - acetylcholine receptor (AChR - most common), muscle-specific kinase (MuSK), and lipoprotein-related protein 4
- Fluctuating fatigability and weakness of ocular, bulbar, and limb skeletal muscles.
- Refractory MG occurs in 10-20% (typically female, younger at disease onset, history of thymoma, MuSK antibody-positive).
- Pharmacotherapy: (1) promoting neuromuscular transmission (e.g. AChE inhibitors); (2) immunosuppression of the pathological immune processes.
- **Immunosuppression** through thymectomy or with medications including glucocorticoids, azathioprine, cyclosporine, methotrexate, MMF, tacrolimus, cyclophosphamide, monoclonal antibodies (Rituximab, eculizumab). .
- Intervention therapies including IVIg, plasmapheresis/plasma exchange are used in situations of imminent myasthenic crisis.

HDIT with auto HCT for Myasthenia Gravis (MG)

- Case series at the University of Ottawa
  - Years of transplant: 2001-2014.
  - Patients were described as persistent or life-threatening MG (n=7).
  - Cy mobilization and various high-dose therapy regimens before autologous HCT. CD34 selection.
  - Regimen well-tolerated and no TRM.
  - Median follow-up: 40 (29-149) months.
  - Last follow-up: all patients were in stable complete remission.
  - At 8 months after transplant, all patients were no longer on any immunosuppressive therapy and 6/7 patients had discontinued MG therapy.

(Bryant et al, JAMA Neurology 2017)

HDIT with auto HCT for Myasthenia Gravis (MG)

- MG Case from CBCI
  - 2006: Dx with MG at 20 yo. AChR ab positive. Tx- prednisone and pyridostigmine.
  - 2007: Thymectomy. MMF.
  - 2015: Worsened with pregnancy. MMF, IVIg, Rituximab, plasma exchange
  - 2017: Eculizumab.
  - 2018: Cyclophosphamide.
  - 2019: Placement of PEG for severe dysphagia and inability to eat.
  - 02/2020: Over the previous 2-3 years had been admitted to ICU more than 10 times and intubated x3. Presented in motorized wheelchair, spoke in whisper. AChR ab present but low titre. EMG c/w MG.
  - **03/19/2020: HDIT with auto HCT**.
  - 03/22/2020: Spoke with a normal tone of voice. Strength continued to improve.
  - 04/2020: AChR ab low titre unchanged. EMG was reported as unremarkable.
  - 05-07/2020: Able to ambulate independently, PEG tube removed, port for TPE removed
  - Pyridostigmine tapered. Patient returned to nursing school
  - **Follow-up in Denver at 1 and 2 years: complete remission of MG.**
  - Arranging for second pregnancy: embryos frozen before transplant.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- A peripheral nervous system disorder characterized by **demyelination** of **peripheral nerves and spinal roots.** The underlying pathogenesis is unknown but evidence supports that the disease is inflammatory and autoimmune mediated.
- Often manifests as symmetrical weakness of the proximal or distal limbs, loss of sensation and tendon reflexes (typical). Symptoms can be asymmetric as well (atypical).
- Diagnosis depends on the clinical features, cerebrospinal fluid protein analysis and electrodiagnostic studies. Nerve conduction studies show slow nerve conduction velocities. Imaging studies with ultrasound show that nerves are enlarged and MRI showed increased signal intensity on T2 weighted images.
- Current standard treatment: prednisone, plasma exchange, and IV immunoglobulin (IVIg).
- Most patients relapse after these treatments, making CIDP difficult to medically manage. Some patients are significantly debilitated and are refractory to therapy.

HDIT with auto HCT for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Review of worldwide cases treated with auto-HCT in Qin et al, Int J of Med Sci, 2020.
- In 1 study (Allen et al, 2013), drug-free remission was noted as 67% at 5 years. 2 deaths were observed from pre-existing conditions.
- In another study, sixty-six patients underwent HSCT for CIDP. Data on sixty patients with a mean follow-up of 4.5 years (range 2–5 years) was available for analysis (Burt et al, J of Neurology 2020).
  - Unselected peripheral blood stem cells were re-infused on day 0 after conditioning with cyclophosphamide 200 mg/kg/intravenously (IV), rATG (thymoglobulin) 5.5 mg/kg/IV, and rituximab 1000 mg/IV.
  - There were no treatment-related deaths, and overall survival was 97%.
  - Post-transplant immune medication-free remission was 80%, 78%, 76% 78%, and 80% at 1, 2, 3, 4, and 5 years.

Rasmussen's Encephalitis

- Autoimmune neurologic disease causing unilateral hemispheric atrophy, drug-resistant seizures, progressive neurological decline and cognitive deterioration.
- Characterized by frequent, severe seizures, progressive loss of neurological functions, paralysis on one side of the body, encephalitis, and mental deterioration
- Most common in children under 10, but affects teens and adults.
- Neurologic development at diagnosis is most often normal
  - The permanent effects stabilize within 8 to 12 months, but disease in teens/adults can continue to slowly progress.
  - Prodromal- infrequent seizures and mild hemiparesis.
  - Acute stage- experienced by all patients; frequent focal motor seizures. Untreated patients develop progressive hemiplegia, hemianopia, cognitive decline and behavioral changes.
  - Residual- less frequent seizures and persistent/stable neurological deficits.

Rasmussen's Encephalitis Therapy

- Antiepileptics are used, but despite the use of multiple agents, usually unable to completely control seizures.
- Some benefit seen with medications to control immune system response including steroids, IVIg, tacrolimus, plasma exchange, MMF, Rituximab, tocilizumab (humanized moclonal antibody against IL-6R), Adalimumab (Humira, recombinant anti-TNF mononclonal antibody)
- Surgical procedure with functional hemispherectomy
  - Definitive option to control seizures and stop neurological deterioration.
  - Timing of surgery influenced by age, severity and neurological deficit. It is recommended that younger patients be considered for early surgery for decreased long term sequelae.
  - Sequelae: homonymous hemianopia, hemiplegia, aphasia (if dominant side is involved).

HDIT with auto-SCT Rasmussen's encephalitis

- Adult patient in Seattle now >10 years post transplant, seizure-free.
- CBCI patient 16 years of age
  - Onset of seizures and right-sided weakness in 2017.
  - Intractable left hemispheric seizures, progressive speech deficit and mild right-sided weakness.
  - Progressive left hemispheric atrophy on MRI.
  - Seen by pediatric neurology and diagnosed Rasmussen's encephalitis
  - **Transplant date: 05/27/2021**.
  - Seizures early after transplant, slowly improved.
  - Day 30: Speech and right-sided weakness noted to be improved.
  - 2 partial seizures late 2021, remained on Felbamate, Levitiracetam, Phenobarbital.
  - **One year out from transplant: MRI stable** with asymmetric left cerebral volume loss most pronounced in left frontal lobe, perisylvian and insular regions.
  - **04/13/2022 EEG: persistent localized epileptiform waves** (subclinical) may be related to injury to brain prior to SCT
  - Has finished high school and is doing well.

HDIT with auto-SCT OMAS

- 10mo male INSS Stage IVS neuroblastoma (neck mass, positive marrow)
  - Intermediate risk
  - 8 cycles chemo (COG A3961)
  - After 7th cycle, developed OMAS
  - MRI no recurrent neuroblastoma, CSF normal
  - Treated for OMAS with IVIg, steroids, resection of residual tumor
  - Improved, treated with IVIg, steroids, cyclophosphamide
  - Worsened with steroid wean, course repeated x3 (5 total)
  - Unable to wean steroids
  - ACTH started 10 months into course, symptoms worsened with wean
  - Rituximab received 1 year into course, failed ACTH wean 6 months later
  - Rituximab received again 21 months into course, failed ACTH 6 months later
  - Started weekly methotrexate, failed ACTH wean 8 months later

Johnston et al, Pediatr Blood Cancer 65:e27110, 2018

HDIT with auto-SCT OMAS

- 10mo male INSS Stage IVS neuroblastoma (neck mass, positive marrow)
  - **At 6 yo underwent auto HCT**
  - Mobilization with cyclophosphamide/filgrastim, CD34 selection
  - Conditioning regimen with cyclophosphamide/ATG
  - Transplant course complicated by fever, mucositis
  - Engrafted on Day +15
  - **2 months after auto HCT, OMAS symptoms resolved** and methotrexate discontinued
  - Weaned off ACTH over the next 6 months
  - IVIg discontinued 1 year post transplant
  - **7 years from transplant, no recurrent OMAS, mild cognitive and learning deficits**

Johnston et al, Pediatr Blood Cancer 65:e27110, 2018

HDIT with auto-SCT OMAS

- 21mo female presented with ataxia, upper body unsteadiness, abnormal eye movements
  - Brain MRI normal, CSF normal
  - Abdominal imaging showed L suprarenal mass
  - Mass fully resected, INSS Stage 1, favorable biology neuroblastoma
  - Treated for OMAS with cyclophosphamide, prednisone, IVIg (COG ANBL00P3)
  - Symptoms improved but failed steroid wean
  - Changed treatment to monthly dexamethasone pulses with IVIg – no improvement
  - Rituximab at 31 months old - no improvement
  - Rituximab repeated x2 (3 courses total)
  - At 37 months old, new liver lesion noted on MRI, MIBG negative, biopsy inconclusive but suspected neuroblastoma recurrence.
  - Treated with 8 cycles of chemotherapy (COG A3961) with decrease in size of liver lesion
  - However, OMAS symptoms continued

Johnston et al, Pediatr Blood Cancer 65:e27110, 2018

HDIT with auto-SCT OMAS

- 21mo female presented with ataxia, upper body unsteadiness, abnormal eye movements
  - **At 4 years 3 months old, underwent auto-HCT**
  - Mobilization with cyclophosphamide/filgrastim
  - Conditioning regimen with cyclophosphamide/ATG
  - Transplant course complicated by Candida UTI and adenovirus reactivation
  - Engrafted on Day +14
  - **No significant improvement with HCT**
  - Ongoing therapy with IVIg, prednisone, MTX
  - Eye movements resolved but ongoing behavioral outbursts, sleep difficulties, intermittent ataxia

Johnston et al, Pediatr Blood Cancer 65:e27110, 2018

HDIT with auto HCT

- Excellent results in MS, promising results in several other diseases
- What is the strategy for HDIT with auto-HCT on FHCRC 2260?
- Mobilization regimen
  - Collection of hematopoietic stem cells
  - Initial FHCRC pilot study (p1164) for MS used filgrastim (granulocyte stimulation factor) alone
  - Some patients had an exacerbation in symptoms with filgrastim
  - Prednisone was used to treat flares
  - Changed strategy to cyclophosphamide/filgrastim
    - Decreases risk for flare of autoimmune disease
    - Increased chance of collecting a more pure CD34 product with fewer autoreactive cells

    BUT NOTE:
    - This requires hospitalization for chemo
    - Risk of infection during period of neutropenia

HDIT with auto HCT

- High-dose immunosuppressive therapy (conditioning regimen)
  - Initial FHCRC pilot study (p1164) used cyclophosphamide, total body irradiation (TBI), ATG
    - TBI carries risk for long term side effects of pulmonary fibrosis, cataracts, infertility, hypothyroidism, secondary malignancy
  - Italian study using auto-HCT for severe progressive MS used chemo alone (BEAM – BCNU, etoposide, ara-C, melphalan) , ATG
    - Outcomes were comparable to TBI based regimen with potential for fewer long term side effects
  - Retrospective analysis of studies through the EBMT also showed no benefit to TBI over chemo alone
  - BEAM regimen (without ATG) is commonly used and well tolerated regimen for relapsed Hodgkin and non-Hodgkin lymphoma
  - BEAM/ATG was chosen for conditioning regimen for FHCRC protocol 2260

Saccardi et al, Blood 105:2601-2607, 2005
Fassas et al, J Neurol,;249:1088-1097, 2002.

Autologous Transplant Timeline

Day -6 BCNU 300 mg/m2 IV

Day -5 VP-16 100 mg/m2 bid IV, Cytarabine 100 mg/m2 bid IV

Day -4 VP-16 100 mg/m2 bid IV, Cytarabine 100 mg/m2 bid IV

Day -3 VP-16 100 mg/m2 bid IV, Cytarabine 100 mg/m2 bid IV

Day -2 VP-16 100 mg/m2 bid IV, Cytarabine 100 mg/m2 bid IV, rATG 2.5 mg/kg IV

Day -1 Melphalan 140 mg/m2 IV, rATG 2.5 mg/kg IV

Day 0 STEM CELL INFUSION

Day +7 to Day +21 Prednisone 0.5 mg/kg (then taper over minimum of 2 weeks, may be longer in patients who have had a protracted course of steroids prior to transplant)

HDIT and auto HCT Course

- **Conditioning regimen**
  - Acute nausea, vomiting, fatigue.
  - Infusional reactions, anaphylaxis, serum sickness with rATG
- **Pre-engraftment**
  - Infectious risks (see next slide)
  - Mucositis
  - Sinusoidal obstruction syndrome (veno-occlusive disease)
  - Renal toxicity
  - Pulmonary toxicity
  - Cardiac toxicity
  - Bleeding complications, need for pRBC and platelet transfusions
- **Engraftment generally will occur between days 9-21**
  - Neutrophils first, then platelets and RBCs
  - Engraftment syndrome with flare of autoimmune symptoms
- **Post-engraftment – must stay <1 hour from transplant center for the first 60-100 days**
  - Still high infectious risk
  - pRBC and platelet transfusions
  - Electrolyte imbalance
  - Nausea/vomiting/anorexia/weight loss

HDIT and auto HCT Course

- Infectious risk
  - Bacterial prophylaxis until engraftment
  - PCP prophylaxis with pre-transplant cleanout then resumed at Day +30
  - Fungal prophylaxis until off steroids
  - Viral prophylaxis until Day +365
- Risk for infections after engraftment because cells are not yet fully competent
- This regimen includes rATG which causes prolonged T cell depletion.
- Increased risk in these patients for reactivation of CMV and EBV
  - Check CMV PCR weekly through Day 100 for all patients and continue to check every two weeks through Day 180 for those CMV antibody positive prior to transplant
  - Check EBV PCR weekly through Day 100, every two weeks through Day 180 for all patients (risk for EBV mediated PTLD)

HDIT and auto-HCT Course

- Study evaluations:
  - Pre-pheresis:
    - Study labs
    - Neuropsychiatric evaluation
    - Functional assessment appropriate for the specific disease
    - Expanded Disability Status Scale (EDSS)
  - Day +30:
    - Study labs
    - Neurological evaluation
    - Quality of life evaluation
    - MRI of the brain (for some diagnoses)
    - Functional assessment appropriate for the specific disease
    - EDSS
  - 6 months:
    - Neurologic evaluation and functional assessment by treating Neurologist
  - Evaluation yearly for years 1-5 post transplant
    - Same studies as Day 30
    - Also routine yearly post-transplant evaluation (echo/EKG, PFTs, TFTs, resume vaccinations)

HDIT and auto HCT for OMAS

- OMAS is a rare but neurologically devastating autoimmune disease
- This disease can be very difficult to treat with significant morbidity from symptoms
- Even once treated successfully, patients may suffer long–term neurological sequelae
- HDIT with auto HCT is a treatment strategy that has been used successfully in a number of autoimmune neurologic diseases, thus far most notably in MS
- Overall, HDIT with auto HCT has a low mortality rate and low risk for long term side effects
- There is very little data for HDIT with auto HCT for OMAS, but one published case report showed benefit for one of two patients treated
- Ongoing research is warranted and needed to determine the role of HDIT with auto HCT for OMAS

Thank you!

- To our patients and families who always push us to look for something better
- International Opsoclonus Myoclonus Syndrome Workshop for the invitation to share and to learn
- Dr. Richard Nash sharing his experience over more than 2 decades, sharing slides about the non-pediatric diseases he treats
- My parents and kids for taking care of each other while I am away!

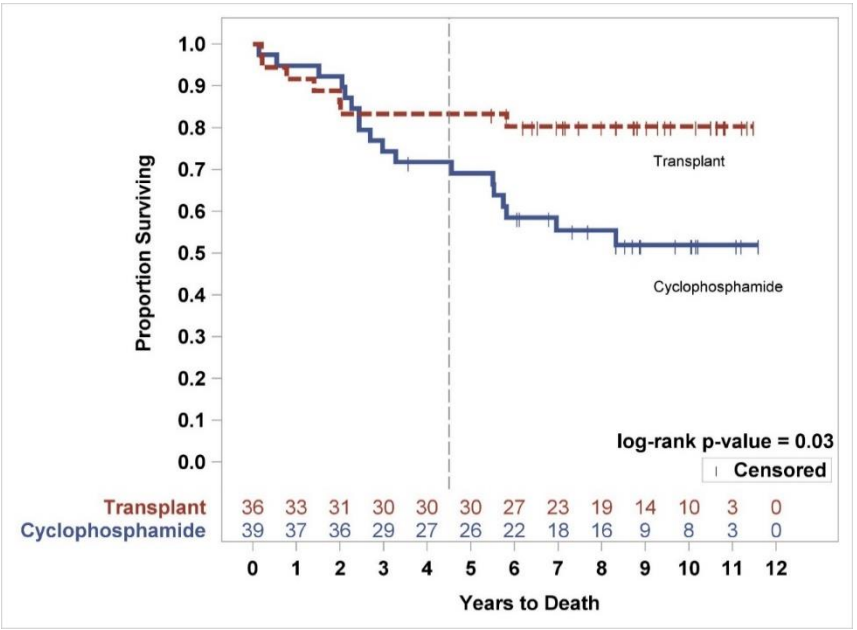
Systemic Sclerosis

- Wide spectrum of disease manifestations and organ involvement so the management of disease is tailored to the individual patient.
- Systemic immunosuppressive therapy
  - Diffuse skin involvement or severe inflammatory internal organ involvement.
  - MTX, MMF, pulse cyclophosphamide.
- Treatment of interstitial lung disease
  - MMF, cyclophosphamide, tocilizumab, azathioprine, nintedanib (TKI), Rituximab.
  - Lung transplantation for severe lung disease
- High-dose immunochemotherapy and autologous HCT

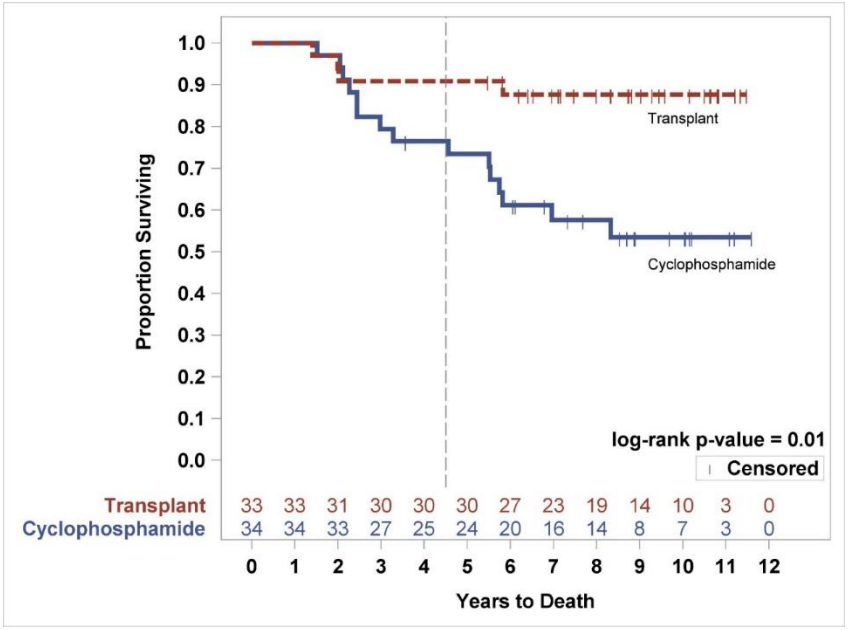
HDIT and auto HCT for Systemic Sclerosis

Overall Survival

Intention to Treat Population



Per Protocol Treated Population

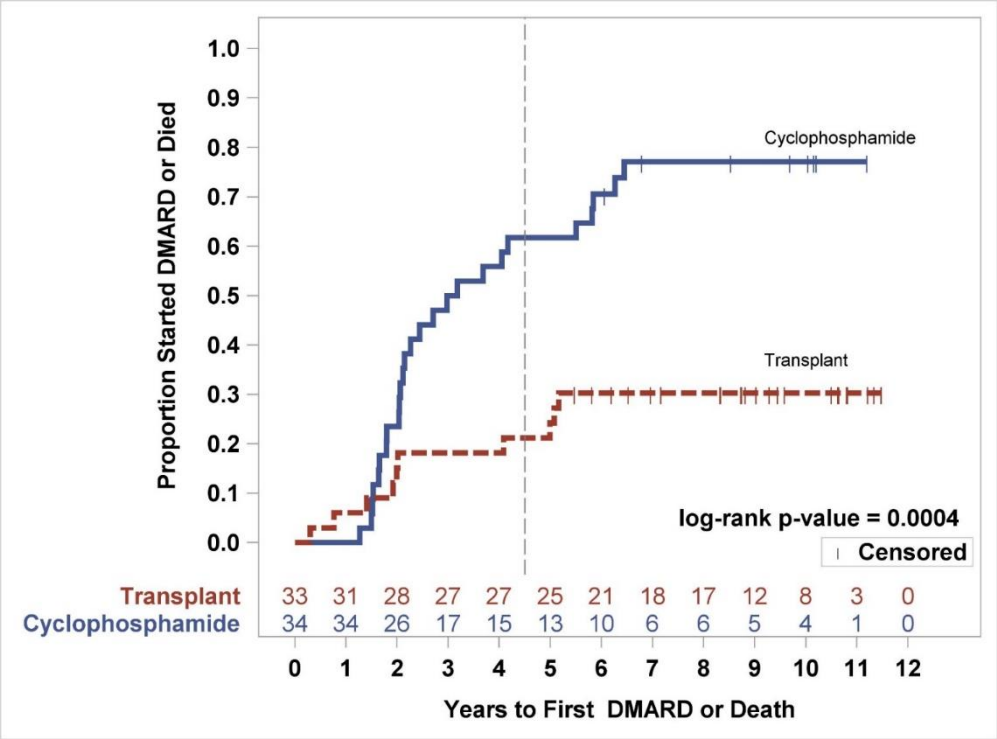


Sullivan et al, NEJM 2018

HDIT and auto HCT for Systemic Sclerosis

Time to First Disease-Modifying Anti-Rheumatic Drug (DMARD) or Death

(per protocol treated population)



Sullivan et al, NEJM 2018

HDIT with auto-HCT for Systemic Sclerosis
CBCI Experience

- Patient #1 doing well with improvement in the skin 8 months after transplant.
- Patient #2 doing well after transplant with marked reduction in scleroderma and pain. Lungs are stable 26 months after transplant.
- Patient #3 with worsening of pulmonary infiltrates early after transplant, transferred to nursing home after transplant.

HDIT with auto HCT

- Cyclophosphamide
  - Alkylating agent related to nitrogen mustard, inactive until metabolized by P450 isoenzymes in the liver to active compounds which produce interstrand DNA cross-linking
  - Anorexia, nausea, vomiting
  - Myelosuppression
  - Hemorrhagic cystitis
  - Nasal stuffiness with rapid administration (wasabi nose)
  - Arrhythmias with rapid infusion (rare)
  - SIADH (rare)
  - Cardiac toxicity with high dose (rare)
  - Infertility seen with dose with high dose
  - Secondary malignancy with high dose (rare)

HDIT with auto HCT

- Filgrastim
  - Recombinant human granulocyte colony-stimulating factor, a lineage specific colony-stimulating factor, which regulates the production of neutrophils, stimulates neutrophil activation
  - Bony pain
  - Low grade fever
  - Allergic reactions
  - Splenomegaly, risk for splenic rupture (rare)
  - ARDS (rare)
  - Hematologic malignancy (AML, MDS) with long term use (rare)

HDIT with auto HCT

- Apheresis
  - Risk of line placement including DVT/PE
  - Hypocalcemia
  - Hyper or hypotension
  - Bleeding complications from anticoagulant
  - Thrombocytopenia, anemia

HDIT with auto HCT

- **BCNU (bischloronitrosourea, carmustine)**
  - Alkylating agent (interferes with DNA synthesis and DNA-dependent RNA synthesis, can cause inhibition of enzymatic reactions required in the formation of DNA)
  - Nausea, vomiting, weight loss, anorexia
  - Metallic taste
  - Myelosuppression
  - Liver dysfunction (common), hepatic necrosis (rare)
  - Mucositis
  - Pulmonary fibrosis and/or infiltrates – pre-med with steroids decreases risk
    - 20-30% with high cumulative dose ≥ 1400 mg/m²
  - Cardiac toxicity (increased risk with older age and prior chest irradiation)
    - Risk with dose ≥600 mg/m²
  - Renal dysfunction, renal failure (rare)
  - Neurotoxicity including neuroretinitis (rare) and encephalopathy (rare)
  - Secondary malignancy (rare)

HDIT with auto HCT

- **Etoposide**
  - Binds to topoisomerase II and DNA causing single and double strand DNA breaks during S and G2 phase of the cell cycle.
  - Nausea, vomiting, anorexia
  - Myelosuppression
  - Diarrhea, abdominal pain
  - Mucositis
  - Transient hypotension during infusion (often resolves with slower infusion)
  - Anaphylaxis (rare)
  - Peripheral neuropathy (rare)
  - Hepatotoxicity (rare)
  - Congestive heart failure (rare)
  - Stevens-Johnson Syndrome, exfoliative dermatitis (rare)
  - Ovarian failure (rare -amenorrhea, anovulatory cycles, hypomenorrhea)
  - Secondary malignancy (rare)

HDIT with auto HCT

- **Cytarabine**
  - Inhibition of DNA polymerase, incorporated into both DNA and RNA, effective primarily in S-phase, may block progression of cells from G1 phase to S-phase
  - Nausea, vomiting, anorexia
  - Myelosuppression
  - Mucositis
  - Conjunctivitis (rare with low dose)
  - Capillary pulmonary leak syndrome (rare with low dose)
  - Flu like symptoms with fever and rash (rare with low dose)
  - Cardiomyopathy, vasculitis, pericarditis (rare even with high dose)
  - Cerebral and cerebellar dysfunction (rare even with high dose)
  - Hepatotoxicity including sinusoidal obstruction syndrome (rare)
  - Renal dysfunction (rare with low dose)
  - Asymptomatic nonoliguric rhabdomyolysis (rare even with high dose)

HDIT with auto HCT

- **Melphalan**
  - Nitrogen mustard, bifunctional alkylating agent forming covalent cross-links with DNA or DNA protein complexes causing cytotoxic, mutagenic, and carcinogenic effects. Results in misreading of the DNA code and inhibition of DNA, RNA, and protein synthesis in rapidly proliferating tumor cells, cell cycle non-specific.
  - Nausea, vomiting, anorexia
  - Hyponatremia
  - Myelosuppression
  - Mucositis
  - Diarrhea
  - Infertility (rare)
  - Anaphylaxis, hypotension (rare)
  - Atrial fibrillation (high dose, rare)
  - Hepatic toxicity (rare)
  - Pulmonary fibrosis, interstitial pneumonitis (rare)
  - Secondary malignancy (rare)

HDIT with auto HCT

- **Rabbit AntiThymocyte Globulin (rATG)**
  - Obtained by immunization of rabbits with human thymocytes resulting in cytotoxic antibodies directed against antigens expressed on human T-lymphocytes.
  - Infusion-associated reactions are common. Decreased with steroid premeds.
    - Fever, chills, rigors, dyspnea
    - Headache, myalgia, rash
    - Nausea/vomiting
  - Serum sickness – delayed reaction. Decreased with steroid premeds.
    - Glomerulonephritis
    - Fever, myalgia, arthralgia, rash
    - Peripheral edema, periorbital edema
  - Hypertension, hyperkalemia
  - Myelosuppression,
  - Increased risk of infection
  - Hepatic dysfunction (rare)
  - Hypersensitivity and anaphylactic reactions (rarely can be severe)