Hematopoietic cell transplantation (HCT) for non-malignant disorders and uncommon malignancies

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Conflict of Interests (COI) Statement

• No COIs to be disclosed
Outline

• HCT overview
• HCT for non-malignant disorders
  – Hemoglobinopathy (sickle cell)
  – Autoimmune disorders
• HCT for uncommon solid tumors
  – Neuroblastoma
  – Sarcoma
  – Testicular cancer/germ cell tumor
**Hematopoietic Cell Transplantation (HCT)**

- **Components:**
  - [A] Conditioning regimen (chemo +/- radiation)
  - [B] Infusion of stem cells (hematopoietic progenitor cells)
    - To (potentially) cure underlying condition and restore normal hematopoiesis
    - Anti-”tumor” chemoradiotherapy + graft-versus-malignancy effect

- **Types of HCT:**
  - *Allogeneic* (=recipient and donor are different)
    - Donor type:
      - Sibling, unrelated (matched and mismatched), related haploidentical, umbilical cord
  - *Autologous* (=recipient and donor are the same)
    - Syngeneic (=if identical twin available)
Components of HCT

• **Conditioning regimen/therapy**
  – Chemotherapy ± total body irradiation (TBI)
  – Regimen intensity:
    • Myeloablative (MAC)
    • Reduced intensity conditioning (RIC)/non-myeloablative (NMA)

• **Graft (type)**
  – Bone marrow
  – Peripheral blood stem cells
    • 10 times higher T cell dose compared to BM: 30x10E7/kg vs. 3 x10E7/kg)
  – Umbilical cord blood (double cord transplant for adults)

• **Immunosuppression** (only applicable to allogeneic HCT)
  – Pharmacologic
  – Graft manipulation

• **Infection prophylaxis (antibiotics)**

• **Supportive care**
  – IV fluids, pain management, IV access, nursing care, nutrition
Myeloablative conditioning

GVHD: graft-versus-host disease

Bleakley *Nature Reviews Cancer* 2004
Methods of Stem Cell Collection

(A) Peripheral blood stem cell collection (apheresis)
Granulocyte-colony stimulating factor (G-CSF) mobilized


(B) Bone marrow harvest
HCT Indications in US (2016)

- Allogeneic (Total N=8,211)
- Autologous (Total N=12,831)

Outpatient HCT

Early Discharge Model

- Outpatient HCT at MCC:
  - Launched in 2014 (> 200 cases thus far) – Multidisciplinary team (MD, APP, treatment center RN/TNC, Pharmacists, SW, Dietician)

Total Outpatient Model

BLOOD & MARROW TRANSPLANTATION (BMT) PROGRAM

ASK US ABOUT OUR OUTPATIENT PROCEDURES

Moffitt’s BMT Program is committed to providing you with quality transplant care. With today’s ever-advancing technology, an increasing number of medical services previously delivered in the hospital now can be safely performed in an outpatient setting.

BENEFITS OF AN OUTPATIENT TRANSPLANT:
- Quicker recovery
- Minimal hospital stay
- Inpatient admission only if medically necessary during the recovery period
- Lower risk of infection

YOU MAY BE A CANDIDATE FOR AN OUTPATIENT TRANSPLANT IF:
- Diagnosed with myeloma or lymphoma
- In good health
- No cardiac issues or prednisone diabetes

TO DETERMINE IF YOU ARE A CANDIDATE, ASK YOUR NURSE OR PHYSICIAN FOR MORE INFORMATION.

We will also confirm coverage and availability with your insurance provider.

“The benefits for me were convenience, privacy and comfort because I was able to stay in a hotel rather than a hospital room.”

— Ted Hernandez, BMT Patient

Moffitt Cancer Center
Guidelines

American Society of Blood and Marrow Transplantation Guidelines for Training in Hematopoietic Progenitor Cell Transplantation

Shakila Khan, Mark B. Juckett, Krishna V. K. for the American Society of Blood and Marrow Transplantation

Advances in hematopoietic progenitor cell transplantations and a concomitant requirement for physicians undertaking HCT physicians were published in 2001; however, the medical knowledge and skill set that these physicians need are evolving. By recognizing the importance of education for transplantation professionals, the American Society of Blood and Marrow Transplantation established a Committee on Education to guide the development of educational programs. The guidelines presented here provide an extensive and detailed framework for planning, developing HCT training programs and evaluating and mentoring trainees.

B. Indications for HCT (adult and pediatric)
1. Acute and chronic leukemias
2. Myeloproliferative and myelodysplastic syndromes
3. Plasma cell dyscrasias
4. Lymphoproliferative diseases
5. Paroxysmal nocturnal hemoglobinuria
6. Aplastic anemia and other marrow failure states
7. Solid tumors
8. Autoimmune disorders
9. Hemoglobinopathies
10. Pediatric metabolic disorders
11. Pediatric primary immune deficiencies, including severe combined immunodeficiency and non–severe combined immunodeficiency forms

(Hemoglobinopathy)
Sickle Cell Disease
Sickle Cell Disease (SCD)

- A single nucleotide mutation in the 6\textsuperscript{th} position of beta-globin chain (glutamine to valine)
  - Confers resistance to malaria
- Hgb protein polymerizes when deoxygenated causing sickle-shaped red cells (veno-occlusion)
- Common in African, Mediterranean, Middle Eastern, Indian heritage
- Presentation:
  - Hemolytic anemia, pain crisis, acute chest syndrome, stroke, aplastic crisis (due to parvovirus infection), splenic sequestration, infection/osteomyelitis (Staph, Salmonella), cholelithiasis, leg ulcers, pulmonary HTN, hepatopathy, reduced QOL
- Multi-organ disease, reduced survival
Sickle Cell Disease (SCD)

- Increasing number of SCD adults are living with accumulating end-organ damage
- SCD therapy:
  - RBC (exchange) transfusions
  - Hydroxyurea (Hydrea™)
  - *(Newborn screening, PCN prophylaxis, supportive care)*
  - **Allogeneic hematopoietic cell transplantation (HCT)** remains the only immediate cure
- SCD Listed as one of the strategic research priorities by NIH/NHLBI (National Heart, Lung, and Blood Institute) and ASH (American Society of Hematology)
  - [https://www.nhlbi.nih.gov/about/strategic-vision](https://www.nhlbi.nih.gov/about/strategic-vision)
(Standard) Pre-HCT Workup

• Organ function assessment:
  – Echo, EKG, PFT, blood (& urine) test (hepatic, renal)

• Disease assessment
  – Imaging (CT/PET, x-ray), bone marrow aspirate/biopsy

• Infectious disease markers

• ID/cardiology/nephrology/dermatology - subspeciality consult

• Dental clearance

• Social work/psychology evaluation

• Pharmacy consult

• Clinical trial coordinator
Patient evaluation in SCD (pre-HCT)

• Neurological assessment (including neurocognition)
  – Brain MRI/MRA
    • May uncover unanticipated severe cerebral vasculopathy (“moyamoya”)
    • Potential increase in transplant-related mortality (TRM) and morbidity
  – Transcranial Doppler (TCD)
    • Effective in predicting the risk of stroke
    • To predict the severity of disease

• Iron overload/secondary hemosiderosis from RBC transfusion
• Alloimmunization from prior RBC transfusion
  – Increased risk of graft rejection
• Pulmonary hypertension/hepatopathy
NIH Indications for HCT in SCD (Patients > 16 years)

- Irreversible end-organ damage
- Stroke or clinically significant CNS event
- Elevated tricuspid regurgitant velocity > 2.6 m/s
- Stroke-related renal insufficiency
  - serum creatinine > 1.5 times the upper limit of normal or biopsy proven
- Sickle hepatopathy (including iron overload)
- Reversible sickle complication(s) not ameliorated by hydroxyurea
  - ≥ 2 vaso-occlusive crises requiring hospitalizations
  - Any acute chest syndrome while on hydroxyurea
HLA-matched sibling allo-HCT

• First successful HCT in SCD performed in 1984
  – A pediatric patient with coexisting acute myeloid leukemia (AML)

• Traditionally myeloablative regimens
  – Busulfan and cyclophosphamide (BuCy) conditioning
  – Bone marrow graft
  – Anti-thymocyte globulin (ATG) was added later to decrease the risk of graft rejection in those transfused heavily and alloimmunized

• Neurologic complications (seizures and intracranial hemorrhage) occurred in 7/21 patients
  – Need to maintaining PLT transfusion threshold of > 50,000/microL, hemogloin 9-11 g/dL, adding phenytoin prophylaxis and preventing hypertension and hypomagnesemia

HLA-matched sibling allo-HCT

• Only limited number of SCD patients (mostly <16 yo) received myeloablative HCT
  – > 70,000 patients with SCD in the US
• After myeloablative regimens, 10%-20% with mixed donor chimerism
• Mixed donor chimerism state sufficient to direct bone marrow to produce donor-type hemoglobin and red cells, revert the SCD phenotype, and minimize the risk of GVHD
  – Observation leading to non-myeloablative approach


• EBMT/CIBMTR sib allo HCT in SCD
• N=1000 from 1986-2013
• Median age 9
• MAC (87%)
Non-myeloablative (NMA) regimens/Tolerance induction

- NMA (e.g., Fludarabine/Cyclophosphamide) allows stable engraftment
- GVHD has no benefit to patients with SCD
- Complete eradication of host hematopoiesis not necessary in SCD
  - Low levels of donor chimerism sufficient to reverse the disease
- Tolerance induction with pharmacologic immunomodulation
  - **Sirolimus** does not block T-cell activation but blocks proliferation by binding to mTOR (making T cells anergic, promoting T cell tolerance)
  - Avoid worsening renal failure, posterior reversible encephalopathy syndrome (PRES), induce regulatory T cells
  - Alkylating agents may increase risk of veno-occlusive disease (VOD) in severe sickle hepatopathy
  - **Alemtuzumab** (anti-CD52: Campath™) may be superior GVHD prophylaxis
NMA MRD in Adult SCD from NIH

• N=30 (from 2004 – 2013), median age 28.5 (17 – 65)
  – HCT indications: 77% with vaso-occlusive crises/43% with Pulm HTN
• NMA: alemtuzumab (0.03 mg/kg day -7, 0.1 mg/kg day -6, 0.3 mg/kg day -5 to -3), total body irradiation (TBI) (300 cGy day -2)
• GVH prophy;axis: sirolimus
• PB graft from sib donors
• Hydroxyurea given until day -8, RBC exchange to target Hgb S < 30%, PLT maintained > 50K, Hgb 9-10, no G-CSF, PenV prophy BID until PNA vaccines completed
• Median survival 3.4 years, 87% long-term stable donor engraftment, mean donor T-cell chimerism 48%, 4 graft rejections, no acute/chronic GVH, no TRM
• Normalized hgb, no hemolysis among engrafted pts, stable brain MRI, reduction in pulm pressure, decreased narcotic usage

Hsieh et al. JAMA 2014;312(1):48-56
Other issues related to SCD HCT

• G-CSF mobilization in PB hematopoietic stem cells from sickle cell trait donors
  – Safe and can be done
  – Cryopreservation also has no negative impact

• Scarcity of HLA-matched sibling donors (14-20%)

• Not pursuing HLA-typing
  – Lack of available sibling, lack of financial/psychosocial support, parental refusal, physician refusal
Likelihood of finding an 8/8 HLA matched unrelated donor in the registry

Population-based genetic models for 21 racial/ethnic groups
- NMDP
- Cord blood

MUD HCT in SCD (BMT CTN 0601)

- Phase 2 (2008-2014)
- N=30 (ages 4-19)
- Alemtuzumab, fludarabine, melphalan conditioning, BM graft
- GVHD prophylaxis: CSA or TAC, MTX, methylprednisolone
- HCT indications:
  - Doppler velocity > 200 cm/s, vaso-occlusive crisis, acute chest syndrome
- Day 100 aGVHD: 28%, 1-yr cGVHD 62%

Shenoy et al. Blood 2016
Alternative donors

• Cord blood transplantation
  – First patient with SCD performed in 1996
  – Only 33 cases reported, mostly related donors
  – Very limited experience for unrelated cord transplant and double umbilical cord transplant

• Haploidentical transplant
  – More donor pool (probably) than cord options
  – Barriers – potentially greater risks for GVHD and graft rejection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>No. of patients (age)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raj (2004)</td>
<td>Flu 90 mg/m², 200 cGy TBI, CSA, MMF</td>
<td>1 (14 y)</td>
<td>Graft failure</td>
</tr>
<tr>
<td>Brodsky (2008)</td>
<td>Cy 29 mg/kg, Flu 150 mg/m², 200 cGy TBI, Cy 100 mg/kg, Tac, MMF</td>
<td>1 (33)</td>
<td>Patient with concomitant PNH</td>
</tr>
</tbody>
</table>
Post-transplant cyclophosphamide (PTCY)

Haploidentical BMT for SCD – Johns Hopkins

- Conditioning regimen
  - ATG, Cy 14.5 mg/kg x 2, Flu, TBI 200cGy (last 5 with 400cGy) with post-BMT Cy (PTCY)
- Sirolimus for GVHD prophylaxis to avoid PRES
- Median age 23 years; f/u 35 months (range, 1-93)
- 100% donor chimerism > D+60 with TBI 400cGy (N=5)

38 patients screened; 36 (95%) transplanted, 31 with haplo donor
22/31 with stable engraftment (71%) with 97% survival
Overall incidence of cGVHD is 5.8%.

# BMT CTN 1507 (RIC before HLA-haploidentical BMT in patients with symptomatic sickle cell disease)

<table>
<thead>
<tr>
<th>Day</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day –70 → –10</td>
<td>Hydroxyurea 30 mg/kg po daily</td>
</tr>
<tr>
<td>Day –9</td>
<td>Thymoglobulin 0.5 mg/kg</td>
</tr>
<tr>
<td>Day –8</td>
<td>Thymoglobulin 2 mg/kg</td>
</tr>
<tr>
<td>Day –7</td>
<td>Thymoglobulin 2 mg/kg, thiotepa 4 mg/kg IV q12 h</td>
</tr>
<tr>
<td>Day –6, -5</td>
<td>Fludarabine 30 mg/m² IV over 30-60 minutes, then</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 14.5 mg/kg IV over 1-2 hours *</td>
</tr>
<tr>
<td>Day –4 → -2</td>
<td>Fludarabine 30 mg/m² IV over 30-60 minutes</td>
</tr>
<tr>
<td>Day –1</td>
<td>TBI 200 cGy</td>
</tr>
<tr>
<td>Day 0</td>
<td>Non-T-cell depleted bone marrow</td>
</tr>
<tr>
<td>Days 3, 4</td>
<td>Cyclophosphamide 50 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>Mesna 40 mg/kg IV*</td>
</tr>
<tr>
<td>Day 5</td>
<td>Begin sirolimus, mycophenolate mofetil, and G-CSF</td>
</tr>
</tbody>
</table>

- Children <16 years of age with a cerebral infarction (clinically overt or silent)
- Adults 16-45 years of age with severe disease
HCT for SCD: Conclusions

- HCT for SCD, highly effective, but underused
- Achievement of mixed chimerism - minimum target
- Need future sophistication of immune tolerance induction (through GVHD research)
- SCD-specific regimens are needed
- Enrollment to clinical trials desirable and encouraged to answer questions on HCT for SCD patients
  - Especially in high-risk children and adults
- Ongoing trial: **BMT CTN 1507** - RIC haploidentical HCT in SCD (NCT03263559)
Autoimmune Diseases

• Affect 5% of the population
• Current systemic therapies rarely curative in the most severe, life-threatening forms
  • Biologic therapies – prolonged administration, cost
• In the past 2 decades, HCT has become an emerging cell therapy
  – A significant improvement in the safety of autologous HCT
  – Durable PFS of approximately 50% (with HCT) for those who failed multiple therapies
• Clinical effects of autologous HCT
  – A qualitative changes in the reconstituted immune repertoire rather than transient depletion of immune cells
  – Hypothesis: “resetting” of the immune system

Sullivan KM. BBMT 2010; Farge D. Haematologica 2010; Singh JA. Cochrane Database Syst Rev 2011
Autoimmune Diseases

- Since 1996, > 1300 cases in EBMT, almost 500 cases in CIBMTR
- Common indications for autologous HCT:
  - *Multiple sclerosis (MS)*
  - *Systemic sclerosis (SSc)*
    - Systemic lupus erythematosus (SLE)
    - Crohn’s disease
    - Type 1 diabetes mellitus
    - Juvenile idiopathic arthritis
- Majority (90%) - autologous HCT
- Allogeneic HCT still considered “too toxic” for use in autoimmune diseases, except for cases of immune cytopenias

Pavletic SZ. *Blood* 2011
Multiple Sclerosis
Multiple Sclerosis (MS)

- Inflammatory demyelinating and degenerative disease of the CNS

- **Relapsing-remitting (RR) MS:**
  - Recurrent localized acute inflammation in CNS

- **Secondary progressive (SP) MS:**
  - Accumulating damages caused by recurrent inflammatory events

- **Primary progressive (PP) MS:**
  - Without a preceding RR phase (occasional)

- **Treatment of RR MS:**
  - First-line: interferon-b, glatiramer acetate (Copaxone)
  - Second-line: natalizumab (Tysabri), fingolimod (Gilenya), mitoxantrone, cyclophosphamide
HCT in Multiple Sclerosis (MS)

- HCT conditioning eliminates the immune system harboring disease-associated cells and introduces healthy immune system
- Reduction of MS inflammatory events (on MRI) by immune system renewal
  - T cell pool gradually repopulated by thymus-derived naïve cells (restoration of a new and diverse TCR repertoire)
- HCT offered to rapidly deteriorating refractory forms of MS
- Prior studies enrolled progressive forms (PP or SP), hence the relapse rates of limited usefulness as an outcome measure
  - Quality of life (QOL) and disability - more relevant outcome measures

HCT in Multiple Sclerosis (MS)

• EBMT registry data
  – The largest, 178 patients, last updated in 2006
  – Progression-free survival (PFS) in 60% to 70% after 3 years
  – PFS 50% to 60% after 6 to 8 years

• Gradual resumption of progression over time

• Worsening of disability after HCT associated with preexisting chronic, severe disability (Expanded Disability Status Scale [EDSS] 6.0 and above = requiring assistance)
  – 0 = healthy vs. 10 = death

• Durable remissions and improvement of neurologic function seen in less advanced disability (EDSS ≤ 6) and RR phase before HCT

HCT in Multiple Sclerosis (MS)

- Reduced-intensity conditioning auto HCT
  - Cyclophosphamide IV 200 mg/kg + rabbit anti-thymocyte globulin (ATG) 6 mg/kg or alemtuzumab 30 mg
  - 21 RR MS patients with mild to moderate disability (EDSS 2.0 – 5.5)
  - PFS (no deterioration in EDSS score) 100% with 81% showing an improvement of neurological function after a median of 3 years of f/u
  - 25% experienced MS relapse following HCT (higher than more intensive conditioning regimen)

- Better transplant outcomes noted in short disease duration (<5 years from diagnosis) and younger age

- Younger patients with highly aggressive, rapidly evolving ("malignant") forms of MS likely benefit from HCT

Burt RK. *Lancet Neurol* 2009
MS: Patient Selection

• Candidates for HCT:
  – Evidence of inflammatory activity (ongoing relapses or activity on MRI) or “Malignant” MS

• Advanced disabilities (EDSS ≥ 6.5), PPMS or SPMS, accumulating disabilities without clear inflammatory activity less likely to benefit
  – Requiring bilateral aids to maintain mobility
  – Only able to walk for about 20 meters without rest

• Careful selection with MS specialists

• Less data available on variant MS
  – Neuromyelitis optica (“Devic’s disease”)
    • Autoantibodies against aquaporin 4
    • Optic neuritis and transverse myelitis
    • Severe visual impairment and severe restrictions on mobility
MS: HCT regimens/mobilization

- **Common low-intensity regimen:**
  - Cyclophosphamide + lymphocyte depleting antibody (e.g., anti-thymocyte globulin (ATG))

- **More intensive regimens:**
  - BEAM (BCNU, etoposide, cytarabine, melphalan) + ATG
  - Busulfan + cyclophosphamide + ATG

- **Stem cell mobilization regimens**
  - Granulocyte-colony stimulating factor (G-CSF) with steroids and cyclophosphamide
  - G-CSF alone
    - **G-CSF may induce MS relapse** (can be prevented by concurrent steroid or chemotherapy)

- **Cyclophosphamide mobilized grafts w/ lower immune cell load reducing the reintroduction of autoreactive cells during HCT**

MS: Complications after HCT

• Intensive conditioning regimens (e.g., ATG) and graft lymphocyte depletion (CD 34 selection) leading to infections
  – Urinary tract infections (UTIs) common in MS patients
  – Bladder dysfunction, frequent need for bladder catheterization
  – Epstein-Barr virus, HHV-6, and cytomegalovirus (CMV) reactivation

• Febrile neutropenia/infections may precipitate a pseudorelapse (transient worsening of MS symptoms)

• Greater risk of further loss of mobility due to chemotherapy-induced cachexia and myopathy
  – Physical therapy and rehabilitation

• Autoimmune phenomena not related to MS
  – Autoimmune thyroid disease (20%)
  – Autoimmune cytopenias (idiopathic thrombocytopenic purpura)

Hamerschlak N. BMT 2010; Nash RA. BBMT 2010; Daikeler T. Blood 2011
Phase 2 study in Canada

- 24 patients (median age 34, range 24-45) with EDSS3-6
- Autologous graft with cyclophosphamide and G-CSF
- Conditioning: Busulfan/Cyclophosphamide/rabbit ATG
- Primary outcome:
  - MS activity-free survival at 3 years 69.6% with 13 years of f/u
  - No relapses and no Gadolinium enhancing MRI lesions or no T2 lesions on 314 MRI scans (post HCT)
  - Rate of brain atrophy declined compared to the controls
  - One mortality (TRM – hepatic necrosis/SOS and klebsiella sepsis, 62 days post HCT) with 35% of patients with improved EDSS

HCT in MS: Future Directions

• Unclear best conditioning regimen to optimize risk/benefit ratio

• Currently open study:
  – Non-myeloablative (Cy + rATG) HCT vs. standard of care (e.g., interferon, glatiramer, or mitoxantrone) at Northwestern University (NCT00273364)

• Completed trials (closed for enrollment, results pending):
  – Randomized phase 2 Autologous Stem cell Transplantation International Multiple Sclerosis Trial (vs. control arm – mitoxantrone)
    • Conditioning: BEAM-ATG; Unmanipulated stem cell graft mobilized with cyclophosphamide (www.astim-s.org)
  – Multicenter US Phase 2 Trial of High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (NCT00288626)
Systemic Sclerosis
Systemic Sclerosis (SSc)

- Skin/organ fibrosis, vasculopathy, inflammation, autoimmunity
- (1) **Limited cutaneous SSc**
  - Benign in its clinical features, disease course, and prognosis
- (2) **Diffuse cutaneous SSc**
  - Can be life-threatening
- Overall survival improved in the past decade
  - ACE inhibitors to prevent “scleroderma renal crisis”
  - Immunosuppressive agents for joint disease and interstitial lung disease
  - Nutritional support, smoking cessation, lifestyle interventions (exercise therapy and physiotherapy aimed at preservation of functional ability)
**HCT in SSc**

- Early case reports: beneficial effects on skin thickening but also uncovered risks of HCT in SSc patients
- Registry analyses and phase 1/2 studies confirmed promising efficacy of HCT in SSc patients but with significant risks
- Earlier studies reported TRM of 8% - 23%
  - Challenges exist in SSc patients who undergo HCT
- Cardiopulmonary involvement of SSc:
  - Small vessel disease causing silent cardiac ischemia
  - Patchy fibrosis leading to ventricular arrhythmia
  - Pulmonary arterial hypertension with right ventricular diastolic dysfunction
  - SSc patients do not always tolerate hyperhydration
Autologous HCT in SSc

• Strict eligibility criteria needed (*traditional eligibility*):
  – Pulmonary artery pressure (PAP) < 50 mmHg
  – No cardiac involvement
  – No pulmonary fibrosis
  – Controlled hypertension

• Benefits:
  – Major regression of dermal fibrosis (confirmed with histologic analysis)
  – Improved functional status
  – Stabilization of lung function decline
  – Improved survival (not shown in Phase 3)
Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST)

• A single-center, controlled, open-label, randomized phase 2 trial, 19 patients (01/2006 – 11/2009)
• Mobilization: cyclophosphamide 2 g/m² + G-CSF
• Conditioning: cyclophosphamide 200 mg/kg + rabbit ATG 6.5 mg/kg
• Stem cell: unmanipulated autologous HCT
• Eligibility:
  – Age < 60 with diffuse SSc
  – Modified Rodnan skin score (mRSS: a validated measure of extent of skin thickening) > 14 (max score 51)
  – Internal organ involvement or restricted skin involvement (mRSS < 14) but coexisting pulmonary involvement
• Control: 1.0 g/m² IV cyclophosphamide monthly x 6 months

ASSIST

• Primary outcome: improvement at 12 months of decrease in mRSS (>25%) or an increase in FVC more than 10%
• Control group could switch to HCT with disease progression (i.e., >25% increase in mRSS or >10% decrease in FVC)
• Results:
  – Statistically significant improvements of the mRSS (p<0.0001) and FVC (p<0.03), as well as QOL by SF-36 at 2 years
  – Most control patients (7 of 9) who crossed over to the HCT arm due to disease progression also benefited from HCT
  – No death in either arm
  – F/U limited to assess survival and late effects

Phase 3 Trials

• Prospective, randomized, controlled phase 3 studies: ASTIS trial and SCOT trial (early dcSSc: Auto HCT vs. Cytoxan IV pulse)

• **ASTIS trial** (European)
  – Mobilization: cyclophosphamide 2 g/m$^2$ + G-CSF
  – Conditioning: Cyclophosphamide 200 mg/kg + rabbit ATG 7.5 mg/kg
  – Stem cell: CD34+ selected autologous HCT
  – Control: 12 monthly cycles of IV pulse cyclophosphamide 750 mg/m$^2$
  – 156 patients enrolled, a median F/U 5 years

• **SCOT trial** (North American)
  – Mobilization: G-CSF
  – Conditioning: cyclophosphamide 120 mg/kg, horse ATG 90 mg/kg, total body irradiation (TBI) 8 Gy with lung and kidney shielding (limiting to 200 cGy)
  – Stem cell: CD34+ selected HCT
SCOT Trial

- N = 36 (HCT) vs. 39 (Cy)
- Global rank composite score (GRCS: mortality, EFS, lung function, mRSS, Disability Index of Health assessment Questionnaire (HAQ-DI)) at 54 m: 67% (HCT) vs. 33% (p=0.01)
- Per-protocol population, EFS at 54 m: 79% (HCT) vs. 50% (p=0.02); OS at 72 m: 74% (HCT) vs. 47% (Cy) (p=0.03)

Soft tissue sarcoma/Ewing sarcoma
Ewing’s sarcoma family of tumors

- **Ewing’s sarcoma family of tumors (ESFT)**
  - Ewing’s sarcoma
  - Primitive neuroectodermal tumor (PNET)
  - Askin tumor
  - Peripheral neuroepithelioma

- The second most common type of malignant bone tumor (after osteosarcoma)
- Account for 25% of the bone sarcoma in the adolescent and young adult (AYA) population

- Chromosomal translocation:
  - t(11;22)(q24;q12)

- 25% present with overt metastases
  - Site of metastases: Lung (50%), bones (25%), bone marrow (20%)
HCT in Sarcoma

• High-risk ESFT (with metastatic or recurrent disease) - very poor prognosis
• EBMT registry data showed DFS of 21% for metastatic to bone or bone marrow who received HCT between 1982 to 1992
  – Results better with busulfan and melphalan (without TBI)
  – Updated report showed 5-year OS of 44% for busulfan-containing regimens, compared to 23% without busulfan
• The University of Washington offered HCT to responders to salvage therapy
  – Conditioning: busulfan, melphalan, and thiotepa (with or without total marrow irradiation)
  – 5-year OS for all metastatic with chemotherapy 23% vs. subgroup with lung only metastases (with received HCT) OS of 62%
  – HCT vs. no HCT (due to chemorefractory disease): PFS 61% vs. 21%; OS 77% vs. 21%

Neuroblastoma
Neuroblastoma

- Malignancy of young children derived from embryonic neural crest cells of the peripheral sympathetic nervous system
- Most common extracranial solid tumor of childhood
  - Approx. 650 new cases/year in the US (15% of cancer-related deaths in children)
- Able to secrete and store catecholamines
- Propensity to undergo differentiation (spontaneous vs. with stimuli)
- Nearly half of the children with neuroblastoma present after 1 year of age with metastatic disease
  - < 40% will survive more than 5 years
- Most common primary site: adrenal gland/abdominal sites (70%)
  - Mediastinal more common in infants than in older children
Clinical Presentation

High thoracic or cervical masses: unilateral ptosis, meiosis, and anhidrosis

Messes in the organ of Zuckerkandl (chromaffin body at the aortic bifurcation) in the pelvis: constipation, bladder dysfunction

Epidural or intradural extension (5%-16%): spinal cord compression

Respiratory compromise due to liver metastases (in neonates)

Metastatic disease: proptosis, periorbital ecchymoses, and bone pain

Paraneoplastic syndrome: water diarrhea from secretion of vasoactive intestinal peptide (VIP), or opsoclonus-myoclonus-ataxia syndrome (due to antineuronal antibodies that cross-react with normal brain tissue)

“Blueberry muffin” skin lesions (bluish hue)
International Neuroblastoma Staging System (INSS)

- INSS: Surgical staging
- **INSS 4S**: special designation
  - Unusually favorable course in infants <1 year of age w/ metastases limited to liver, skin and BM
  - Characterized by spontaneous differentiation and regression
  - May be treated (>50% of the time) with observation and supportive care
- Localized INSS stage (1, 2A, 2B) > 95% survival at 5 years
  - Primarily surgical treatment
- INSS stage 3 – survival 80%-90%
- **INSS stage 4**
  - 70% survival with infants (< 1 year of age)
    - Single copy of MYCN oncogene: > 90% EFS
    - **Amplified MYCN oncogene** [(chromosome 2q24), found in 25% of neuroblastoma]: 10% EFS
  - 40% survival with age > 1 year
Neuroblastoma: Therapy

- **Induction** chemotherapy: 5 - 6 cycles of combination chemotherapy (high-dose alkylators, a platinum derivative)
  - Cyclophosphamide, doxorubicin, etoposide, vincristine, ifosfamide
- **Surgery** to bulky tumor sites
- **Autologous hematopoietic cell transplantation (HCT)**
- **Maintenance**: anti-GD2 immunotherapy

- **Concerns**:
  - Risk of second malignancies
  - Acute/late toxicities
  - Quality of life
Three RCTs including 739 children. Favoring myeloablative therapy for EFS, HR 0.78 (95%CI, 0.67 – 0.90) but no OS benefit. Significantly higher incidences of renal effects, interstitial pneumonitis, and veno-occlusive disease (VOD).

Tandem Transplantation

• Dose-intensity correlates with outcomes
• Tandem HCT allows greater dose intensity in consolidation
• Early collection of peripheral blood stem cells and 2 sequential myeloablative regimens
  – HCT#1: carboplatin, etoposide, and cyclophosphamide
  – HCT#2: melphalan and TBI
  – 3-year EFS 55%
  – TRM 6%, 2 patients died of EBV PTLD
• Phase 3 COG trial (ANBL0532: NCT00567567) examined single vs. tandem HCT as consolidation for high-risk neuroblastoma
  – Tandem improved 3-yr EFS (61.4% w/ tandem vs. 48.4% with single, p=0.0081)

Grupp JCO 2000; Grupp Med Pediatr Oncol 2000; Kletzel JCO 2002 (tested 3 sequential HCTs); Powell BMT 2004; Park ASCO 2016
CEM vs. Bu/Mel

- Carboplatin/Etoposide/Melphalan (CEM) is the effective standard of care for neuroblastoma HCT in the US
  - Used in COG A3973 and COG ANBL0532 studies
- Busulfan/Melphalan (Bu/Mel) has been used by SIOPEN (International Society of Paediatric Oncology European Neuroblastoma Group) group (ASCO 2011)
  - 3-year EFS 48% (Bu/Mel) vs. 33% (CEM)
  - Rates of TRM similar
  - Bu/Mel better tolerated (except for VOD/SOSS)
    - Patient selection, immunotherapy, COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide) induction and interaction with HCT
    - Tolerability for XRT in thoracic neuroblastoma patients (undergoing Bu/Mel)
Targeted Radionuclides

• Neuroblastoma is a malignancy of sympathetic nervous system origin
  – Has the ability to concentrate, store, and secrete catecholamine metabolites
  – Increased level of urinary catecholamines including dopamine, homovanillic acid and/or vanillylmandelic acid (> 90% of cases)
• mIBG (metaiodobezylguanidine)
  – Norepinephrine analogue (developed for adrenal imaging)
  – Has the ability to concentrate in neural crest tissues and neuroblastoma via cell surface norepinephrine transport channels
  – Radiolabeled: $^{131}$I-mIBG, $^{123}$I-mIBG are licensed for scintigraphic imaging of neuroblastoma ($^{131}$I-mIBG used as a therapeutic modality)
**131I-mIBG Therapy**

- Initially used for palliation in refractory disease
- A dose-dependent response exists (8 to 21 mCi/kg)
- Toxicities: N/V, myelosuppression, hypothyroidism
- Stem cell rescue required if > 15 mCi/kg
- Incorporation of 131I-mIBG to transplant conditioning
  - 12 mCi/kg (MTD dosing) of 131I-mIBG on day -21, CEM chemotherapy from days -7 to -4
  - N=50; 3-yr EFS 20%, 3-yr OS 62% in refractory/progressive; 3-yr EFS 38%, 3-yr OS 75% in PR group
- Irinotecan, vincristine and 131I-mIBG (less epithelial injury than 131I-mIBG-CEM regimen) with stem cell rescue may be considered in a future COG trial

Yanik et al. *JCO* 2002; Matthay et al. *JCO* 2006; Yanik et al. BBMT 2015
Treatment of Minimal Residual Disease

• **13-cis-retinoic acid** (and all-**trans**-retinoic acid) causes decreased proliferation and differentiation in neuroblastoma cell lines
  – A phase 3 randomized trial by CCG showed 3-year EFS of 46% (with oral 13-cis-retinoic acid after autologous HCT) vs. 29% in no maintenance \((P=0.03)\)
    • Matthay et al. *NEJM* 1999

• Antibody-targeted therapy
  – Murine (3F8), chimeric (ch14.18), or humanized (hu14.18) (= **dinutuximab**), antibodies against the membrane disialoganglioside GD2 (almost uniformly expressed by neuroblastoma cells)
  – Activity may be enhanced by the co-administration of IL-2 and GM-CSF
Testicular Cancer/Germ cell tumor
Metastatic Germ Cell Tumor (GCT)

- 83% of men treated with standard first-line chemotherapy for metastatic GCT survive
- Incomplete response to first-line chemotherapy or platinum-refractory GCT – poor outcomes
  - Metastatic platinum-refractory GCT offered HCT
  - Disease-free survival after HCT: 60.4%
- Tandem HCT:
  - Conditioning regimen: carboplatin/etoposide (CE)
- Factors associated worse outcomes:
  - Second and later relapse, platinum-refractory, incomplete response to initial therapy

Germ Cell Tumor auto HCT (Indiana U)

- N=364 patients with GCT (341 with tandem auto HCT and 27 with single HCT due to toxicity or progressive dz) from 2004 to 2014
- Eligibility: Metastatic GCT progressing after one or more cisplatin/etoposide-base regimen
- Conditioning carbo 700 mg/m² and etoposide 750 mg/m² (each 3 consecutive days)

Adra et al. JCO 2016
Conclusions

• Hematopoietic cell transplantation (HCT) remains viable options for selected non-malignant hematologic conditions (hemoglobinopathy, autoimmune conditions) and uncommon solid tumors
• With introduction of reduced-intensity regimens, HCT has been expanded to large group of patients
• Haploidentical donor transplantation with post-transplant cyclophosphamide expanding donor availability
• Improved supportive care/GVHD prophylaxis improved survival
• More work needed to improve QOL and HCT-related toxicities
• Multidisciplinary approach necessary for successful and safe delivery of HCT
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Questions?

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